

ENVIRONMENTAL SCAN

Policies to Prevent Harms from the Co-Prescribing of Opioids and Central Nervous System Depressant Drugs

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Background

Using opioids together with central nervous system (CNS) depressants like benzodiazepines happens frequently and is potentially harmful.¹ In North America, opioids such as oxycodone, fentanyl, hydromorphone, or morphine, are commonly prescribed for the management of acute pain, palliative care (in particular, for cancer pain), and chronic non-cancer pain.² Products containing opioids such as codeine are also used in the management of persistent cough. In addition, opioid agonists such as methadone or buprenorphine (in combination with naloxone) are used in the management of opioid use disorder (OUD).³ CNS depressants such as sedative hypnotics (e.g., benzodiazepines, z-drugs, and barbiturates) are commonly used in the management of insomnia and anxiety as well as in inducing sedation for surgical and other medical procedures, treatment of alcohol withdrawal, seizure control, and relaxation of skeletal muscles.⁴ Other CNS depressants include some antipsychotics as well as gabapentin, and pregabalin which are also used in managing various neurological conditions such as schizophrenia, seizures, and pain.¹

Harms Associated With Co-use of Opioids and CNS Depressants

Opioid and CNS depressants such as benzodiazepines continue to be prescribed at the same time in patients with various clinical conditions.⁵⁻⁹ However, concomitant use of opioids and CNS depressants like benzodiazepines is generally considered “low value care” and potentially dangerous.¹⁰ Both opioids and CNS depressants such as benzodiazepines depress the CNS, resulting in sedation, impaired thoughts, slowed response time, and more importantly slowed or difficult breathing and deaths.^{1,10} Evidence from various sources indicate that polysubstance use, such as concomitant use of opioids and benzodiazepines, is one of the most consistent predictors of problematic opioid use and associated harms, including overdose and death. Data from the Canadian provinces and territories indicate that 82% of 4,321 apparent opioid-related deaths between January 2016 and June 2017 also involved one or more types of non-opioid substances including benzodiazepines, alcohol, cocaine, and W-18.¹¹ According to a 2016 report from the Canadian Institute for Health Information (CIHI) titled *Hospitalizations and Emergency Department Visits Due to Opioid Poisoning in Canada*, the most common co-occurring poisoning with opioids involved benzodiazepines, presenting in one out of five hospitalizations due to opioid poisoning (19%).¹² According to the National Institute of Drug Abuse in the US, more than 30% of overdoses involving opioids also involve benzodiazepines.¹³ A study of individuals who died of opioid-related causes between January 1991 and December 2015, using data from the Office of the Chief Coroner for Ontario (OCCO), found that benzodiazepines were present in half of opioid-related deaths.¹⁴ Using administrative databases, a Canadian study found that the odds of an opioid-related death were at least 49% higher among individuals recently exposed to gabapentin and opioids compared with those exposed to opioids alone.¹⁵ Studies of patients on opioid maintenance therapy such as methadone have indicated that psychotropic drug use including benzodiazepines and antipsychotic drugs, was associated with up to two-fold increased risk of opioid-related death, and baseline benzodiazepine use is predictive of decreased retention in opioid agonist therapy.^{16,17} Similarly, several other studies indicate that concomitant use of opioids and CNS depressants — most prominently benzodiazepines — increase risk of harms such as cognitive disorder, accidental injuries including motor vehicle accidents, falls and fractures, substance use disorder, neonatal drug withdrawal, overdose, and death.^{1,18-33} Recognizing the negative health impact of concomitant use of opioids and benzodiazepines, in 2016, the US FDA released a “Black Box Warning” on the drug labelling of prescription opioid pain and prescription opioid cough medicines, as well as benzodiazepines, and issued a warning to patients and prescribers about the increasing risk of serious side effects and deaths when opioids and CNS

depressants such as benzodiazepines are used concomitantly.¹ Similarly, both the Center for Disease Control and Prevention's Guideline for Prescribing Opioids for Chronic Pain and the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain, have recommended that clinicians avoid prescribing opioids and benzodiazepines concurrently, whenever possible.^{34,35} Several other guidelines on prescribing opioids in the US and Canada, also recommend avoiding co-prescription of opioids and benzodiazepines when possible, and to exercise caution (including patient monitoring and dose reduction) when the drugs are prescribed concurrently.³⁶⁻⁴⁰ For patients on opioid maintenance therapy, guidelines and advisories from regulatory agencies such as the FDA recommend careful patient monitoring and dose reduction in patients who are also taking CNS depressant drugs such as benzodiazepines.⁴¹⁻⁴⁴

Prevalence of Use

Despite the knowledge of negative impact of opioids and CNS depressants and recommendations against their concomitant use, co-prescription of opioids and CNS depressants is common; the most notable being the co-prescription of opioids and benzodiazepines. The Ontario Drug Policy Network identified that the prevalence of concurrent use of opioids and benzodiazepines (defined as at least seven days of overlapping use) in residents of Ontario in 2016 was 14% among individuals dispensed opioids to treat pain and 17% among those dispensed opioids to treat addiction.⁴⁵ According to data provided by CIHI for this Environmental Scan, in 2016, 400,964 individuals claimed both an opioid and a benzodiazepine to a Canadian public drug program, representing 25% of all prescription opioid users (Appendix 2 for data sources and methods). A study of 315,428 privately insured persons in the US, 18 to 64 years of age, who filled at least one prescription of opioid medication found that 17% were also prescribed benzodiazepines in 2013, a rise from 9% in 2001. The same study also shows that the risk of overdose was 71% higher in chronic users who concurrently used a benzodiazepine compared with chronic users who did not (5.36% versus 3.13%).¹⁸ A study analyzing the laboratory test (urine test) results of all specimens from patients that were prescribed at least one opioid or benzodiazepine drug and tested for both opioids and benzodiazepines indicated concurrent use of opioids and benzodiazepines in more than 25% of patients (both prescribed and non-prescribed), and the positivity for prescribed benzodiazepines and prescribed opioids was found in 11.2% of all test results.⁴⁶ This result is consistent with a study by Hwang et al. examining the concomitant use patterns of opioids and benzodiazepines in 177 million individuals receiving opioids in a US outpatient retail setting between 2002 and 2014. The study found that the proportion of opioid recipients receiving a prescription for benzodiazepines increased by 41%, and approximately half of these patients received both prescriptions from the same prescriber on the same day. This translated to an increase of more than 2.5 million opioid users receiving concomitant benzodiazepines.⁷ Similarly, several other large-scale studies in the US, including studies in the veterans population and Medicare Part D enrollees, indicate that co-prescription of opioids and CNS depressants such as benzodiazepines is common, despite the increased risk of serious adverse events.^{8,26,28,47,48}

In the effort to reduce harms associated with concomitant use of opioids and CNS depressants, most prominently benzodiazepines, several policies have been recommended or established to better control the co-prescription of these drugs and thus prevent related harms. Such policies could include safety advisories and labelling on drugs warning about the risk; restriction on formulary reimbursement criteria; mandatory query on prescription drug monitoring programs before prescribing and dispensing; use of drug utilization reviews to monitor drug use in a population and implement policies accordingly; use of audit and feedback mechanisms to

educate prescribers about their potentially inappropriate prescribing practices; and other mechanisms. This Environmental Scan highlights policies that are aimed toward reducing harms from the concomitant use of prescription opioids and CNS depressants in outpatient settings. Policies that have been instituted in Canada, the US, Australia, New Zealand, and European countries are presented. Impact of these policies, as available, are also presented. Findings from this Environmental Scan may inform health care decision-makers to establish appropriate and effective policies that would help protect the population from potential drug-related harms.

Objective

The objective of this Environmental Scan is to identify policies established by the public sector in Canada, and internationally, to limit, monitor or take other actions on co-prescribing opioids and CNS depressants such as benzodiazepines, in outpatient settings. The scan also presents the impact of these identified policies, where available. This Environmental Scan aims to address the following research questions,

1. What policies (both within Canada and internationally) have been established to prevent harms from the co-prescription of opioids and CNS depressants such as benzodiazepines in outpatient settings?
2. What has been the impact of these policies on the concomitant use of prescription opioids and other CNS depressants and on other indicators of public health?

The Environmental Scan includes opioids that are used for acute or chronic pain including cancer pain (e.g., oxycodone, hydromorphone, methadone, fentanyl, tramadol, etc.), cough medicine containing opioids (e.g., codeine), both over-the-counter or prescription drugs, and opioid agonists used for the management of OUD (e.g., methadone, buprenorphine). CNS depressants included in this scan are benzodiazepines, z-drugs, antipsychotic drugs, gabapentin, pregabalin, barbiturates, and muscle relaxants such as baclofen, cyclobenzaprine, and methocarbamol. Policies established for outpatient settings (community settings), and those established by the public sector, such as those established by the government, regulatory agencies, public payers, or regulatory colleges are included in the scan. Policies established in Canada, the US, UK, and other European countries, Australia and New Zealand are included in the scan. When available, the impact of these policies on drug utilization, harms, health care utilization, quality of life, or other patient-centred outcomes will be presented.

Methods

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE with in-process records & daily updates through Ovid; the Cochrane Library through Wiley; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were CNS Depressants AND Opioids AND (Adverse events OR Policies).

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. The search was also limited to documents published between January 1, 2013 and December 8, 2017. Regular alerts were established to update the search until February 15, 2018. Conference abstracts were excluded from the search results.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the *Grey Matters* checklist (<https://www.cadth.ca/grey-matters>). Google

and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.

Closed stakeholder feedback was sought from members of the CADTH Optimal Use Working Group members on the draft report.

Findings

The section below presents policies established in Canada and internationally to limit harms from the concomitant use of prescription opioid and CNS depressants. Although, there are several policies that aim to impact appropriate prescribing of either opioids or CNS drugs separately, the policies identified below are only focused on those that aim to control how

Table 1: Summary of Identified Policies

Related Policies Identified	Jurisdiction Where Relevant Policies Are Identified and Examples	Studies on Impact of Policies
Safety Update or Advisory from a Regulatory Agency	<ul style="list-style-type: none"> US (FDA) UK (Medicines and Healthcare products Regulatory Agency) 	None
Product Labelling	<ul style="list-style-type: none"> Canada (Health Canada) US (FDA) 	None
Patient Lock-In Program	<ul style="list-style-type: none"> US (e.g., North Carolina Medicaid Recipient Management Lock-In Program) 	Yes (for North Carolina Medicaid Recipient Management Lock-In Program) ^{49,50}
Restriction or Prior Authorization	<ul style="list-style-type: none"> US (e.g., Medicaid program in Delaware, New York, Oregon, Virginia, Pennsylvania, Montana, Tennessee, Texas, Wyoming) 	None
Supply Limits	<ul style="list-style-type: none"> US (e.g., Hawaii) 	None
Requirement for Informed Consent and Treatment Agreement	<ul style="list-style-type: none"> US (e.g., Vermont, Delaware, Arizona, Hawaii) 	None
Drug Utilization Review	<ul style="list-style-type: none"> US (e.g., Connecticut, Delaware, Idaho, Indiana, Kentucky, Montana, New York, Oregon, Tennessee, Texas, Virginia, and Wyoming) 	None
Mandatory Prescription Drug Monitoring Program Query	<ul style="list-style-type: none"> US (e.g., State of Delaware, Virginia Department of Medical Assistance Services, Mississippi State Board of Dental Examiners) 	None
Audit and Feedback	<ul style="list-style-type: none"> US (Virginia Department of Medical Assistance Services, Medicaid in Indiana, Veterans Health Administration [VHA's] Opioid Safety Initiative [OSI]) 	Yes (for VHA's Opioid Safety Initiative) ⁵¹

Related Policies Identified	Jurisdiction Where Relevant Policies Are Identified and Examples	Studies on Impact of Policies
Standards of Practice	<ul style="list-style-type: none"> • Canada (The College of Physicians and Surgeons of Alberta, The College of Physicians, and Surgeons of British Columbia, The Prince Edward Island College of Pharmacists, The Newfoundland and Labrador Pharmacy Board) • US (see text) 	None
Harm Reduction Policies (e.g., Mandatory Co-Prescription of Naloxone)	<ul style="list-style-type: none"> • US (e.g., State of Vermont, State of Virginia) 	None

opioids and CNS depressants are prescribed together. The majority of policies identified were related to co-prescription of opioids and benzodiazepines as opposed to opioids and other CNS depressants such as antipsychotic drugs, pregabalin, gabapentin etc. In addition, the majority of the policies identified were from the US.

Regulatory Policies – Labelling on Product Monograph and Advisory from Regulatory Agencies

US

Based on the FDA's review of harms associated with concomitant use of opioids and benzodiazepines, and in response to the citizen petition from numerous local and state public health officials and other stakeholders, in August 2016 the FDA released a "Black Box Warning" on the drug labelling of prescription opioid pain and prescription opioid cough medicines, and benzodiazepines warning about the increasing risk of serious side effects and deaths when opioids and benzodiazepines are used concomitantly.⁵² The recommended text for the labelling is provided in Appendix 1.

At the same time, the FDA also issued a Drug Safety Communication warning patients, caregivers, and prescribers about the risk associated with concurrent use of opioids and benzodiazepines. In this Drug Safety Communication, "the agency also provides information for anyone who is taking, or who knows someone taking, either of these types of medications and encourages them to better understand the risks of taking them together; and, when it is medically necessary to take both drug types, for health care providers to be careful to prescribe them as directed, without increasing the dose or dosing frequency for either drug."^{1,52,53}

However, in September 2017, the FDA issued another Drug Safety Communication urging caution against withholding opioid addiction medications such as buprenorphine and methadone from patients taking benzodiazepines or other CNS depressant drugs. The FDA recommends careful medication management and patient monitoring, as the "combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks."⁴² The FDA will require that this information be added to the buprenorphine and methadone drug labels along with detailed recommendations for minimizing the use of medication-assisted treatment drugs and benzodiazepines together. As such, "expanded guidance will be added to the *Warnings and Precautions* section on how to manage patients in methadone treatment in Opioid Treatment

Programs (OTPs) who are also taking CNS depressants. For the buprenorphine products, an existing statement in the *Warnings and Precautions* section will be expanded and revised to provide more detailed guidance on managing patients in buprenorphine treatment who are also taking CNS depressants.⁴²

Canada

A search for the Canadian product monographs for opioid products shows that there is variation on how the risk of interaction and serious side effects of using opioids and CNS depressants is presented.

Some opioids products' product monograph has a section on "*Interactions with Central Nervous System Depressants (Including Alcohol)*" under the WARNING AND PRECAUTION section. This section warns about the interaction and serious risks with concomitant use of opioids and CNS depressants including sedative hypnotics such as benzodiazepines, antipsychotic drugs, tricyclic antidepressants, and other CNS depressants. It recommends that these drugs should be used with caution and in a reduced dosage when combined with CNS depressants.⁵⁴⁻⁵⁹ However, Product Monographs of some other opioid products also has a **boxed SERIOUS WARNINGS AND PRECAUTIONS** section that prominently highlights the interaction with other CNS depressants. The content of this section is similar to the one required by the FDA for RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS (see above and Appendix 1).⁶⁰⁻⁶²

Similar variation on how the information on the risk of serious side effects when combined with opioids was identified in the product monographs of drugs within the benzodiazepine or z-drugs drug class. Some product monographs of drugs within the benzodiazepine or z-drugs drug class have a section on Drug Interactions or Warnings and Precautions that discuss the drug interaction or the risk of side effects when combined with other drugs acting on the CNS.⁶³⁻⁶⁶ On the other hand, product monographs of other benzodiazepine drugs feature a boxed Warnings and Precautions section that specifically discuss the risk of serious side effects when combining benzodiazepines with opioids.⁶⁷

Product monographs of pregabalin, gabapentin, and baclofen mention the CNS side effects such as somnolence and respiratory depression when used with opiates.⁶⁸⁻⁷¹ However, only the product monographs of gabapentin and baclofen mention it under Warning and Precaution, and Drug Interaction section, respectively.^{70,71} Product Monographs of pregabalin only mention the CNS side effect with opiates under the Patient Counselling Information section, but special warnings are not issued.^{68,69} The product monographs of a sample of drugs within the antipsychotic drug class, barbiturate drug class, cyclobenzaprine, methocarbamol warn against the use with other CNS depressant drugs without specifically mentioning opioids.⁷²⁻⁷⁷

The reason for this variation in how the information on risks of concomitant use of opioid and CNS depressants is presented in the Canadian product monographs of these drugs is unknown.

It should be noted that only a sample of product monographs were searched. The above information above was not gathered from a comprehensive search of all the product monographs of the drugs within the opioid or other CNS depressant drug classes of interest.

Any advisory or safety communication to the public by Health Canada regarding the risk of serious side effects of opioids and CNS depressants, similar to the one issued by the FDA, was not identified.⁷⁸

UK

In 2008, the Medicines and Healthcare products Regulatory Agency in the UK issued safety updates regarding serious and fatal overdose of fentanyl patches, including warning about the increase in risk of adverse effects when used concomitantly with other CNS depressants such as sedatives and hypnotics.⁷⁹ In 2011, a safety update was issued by the agency regarding the risk of addiction when codeine and benzodiazepines are used together.⁸⁰ In October 2017, the agency issued a Drug Safety Update regarding the risk of concomitant use of gabapentin with opioids such as respiratory depression, and recommends that the dose of either gabapentin or the opioid should be reduced appropriately.⁸¹

Australia and New Zealand

Medicine Safety Updates on risk of opioids and CNS depressant drugs, issued by the Therapeutics Goods Administration of the Department of Health, Australian Government was not identified.⁸² Similarly, Safety Alerts on risk of opioids and CNS depressant drugs issued by the New Zealand Medicine and Medical Device Safety Authority was not identified.⁸³

Prescribing and Dispensing Policies

Canada

According to a 2015 CADTH report on Prescribing and Dispensing Policies to Address Harms Associated With Prescription Drug Abuse, there are several prescribing, dispensing, and reimbursing restrictions on opioids or benzodiazepines established by federal, provincial, and territorial drug plans in Canada as well as related authorities such as the regulatory colleges. These include quantity limit, dose limit, single prescriber or pharmacy designation, clinical criteria, special authorization, patient identification, or refill restriction.⁸⁴ Similar restrictions are applied for pregabalin, gabapentin, and other CNS depressants by some public drug plans (e.g., Non-Insured Health Benefits).⁸⁵ While these policies could still have an impact on concurrent use of the drugs, no policies were identified that established restriction on concomitant use of CNS drugs with opioids by any of the federal, provincial, or territorial public drug plans in Canada. Similarly, several provinces and territories in Canada have Prescription Drug Monitoring Programs (PDMP) in place. These PDMPs monitor the use of opioids or CNS depressants such as benzodiazepines, but none were identified that monitored their concurrent use.⁸⁴

Practice Guidance

In Canada the following Standards of Practice address the concurrent use of opioids and CNS depressants such as benzodiazepines.

- The College of Physicians and Surgeons of Alberta's (CSPA) Standard of Practice for Prescribing Drugs with Potential for Misuse and Diversion (including drugs such as opioids, benzodiazepines, sedatives) states that a regulated member who prescribes long-term opioid treatment (LTOT) for a patient with chronic pain, exclusive of treatment for active cancer, palliative or end-of-life care, **must** also evaluate and document risk factors for opioid-related harms and incorporate strategies to mitigate the risks, and at minimum, re-assess the patient within four weeks of initiating LTOT and every three months thereafter, among other requirements.⁸⁶ Based on this Standard of Practice, an

Advice To The Profession was issued in May 2017, to support physicians in implementing the College of Physicians and Surgeons of Alberta Standards of Practice. The document states the following:

- before initiating opioid therapy for acute or chronic pain, the physician is expected to not prescribe benzodiazepines, hypnotics, and/or sedatives concomitantly with opioids
- before initiating benzodiazepine therapy, the physician should not prescribe benzodiazepines concomitantly with opioids and/or sedatives.³⁶
- The College of Physicians and Surgeons of British Columbia’s Professional Standard for Safe Prescribing of drugs with potential for misuse/diversion, states that a physicians must not do the following:
 - prescribe benzodiazepines or sedative hypnotics to patients on LTOT, other than as a documented taper
 - prescribe combinations of opioids with benzodiazepines and/or sedative hypnotics.³⁸
- The Prince Edward Island College of Pharmacist’s Practice Directives for Community Pharmacies on Treatment of Opioid Dependence and the Newfoundland and Labrador Pharmacy Board Standards of Practice for Safe and Effective Provision of Medication for the Treatment of Opioid Dependence state the following:
 - a prescriber should base the initial dose of methadone on the patient’s underlying risk for methadone toxicity, including but not limited to, recent benzodiazepine use, or use of other sedating drugs, among other risk factors.^{39,40}

Additionally, the 2017 Canadian Guidelines for Opioids for Chronic Non-Cancer Pain which recommends caution for concomitant use of opioids and benzodiazepines, has been endorsed or adopted by authorities in Canada, such as the College of Physicians and Surgeons of Newfoundland and Labrador, the College of Physicians and Surgeons of Alberta, the Council of the College of Physicians and Surgeons of Nova Scotia, the Council of the College of Physicians and Surgeons of Saskatchewan.^{35,86-89} In 2016, the College of Physicians and Surgeons of British Columbia endorsed the Centers for Disease Control and Prevention (CDC) 2016 Guideline for Prescribing Opioids for Chronic Pain, which has similar recommendation against the concurrent use of opioids and benzodiazepines.^{34,90}

US

Lock-In Program

In general, US payers establish “lock-in” programs that typically restrict beneficiaries – who exhibit high-risk controlled substance seeking behaviour – to a single prescriber and/or pharmacy from which they may obtain controlled substance prescriptions covered by the payer, for a set period of time. Lock-in restrictions are intended to improve care coordination between providers, reduce nonmedical use behaviours, and limit costs stemming from nonmedical use and diversion, in particular for controlled substance such as opioids and benzodiazepines. Such policies are common in public payers in the US such as Medicaid managed care.^{91,92} Evidence suggests that lock-in programs decrease the utilization of controlled substances like opioids and benzodiazepines, and saves the program money.⁴⁹ The following section presents examples of US jurisdictions that have established lock-in programs that specifically target patients taking opioids and benzodiazepines concomitantly.

- In 2010, North Carolina Division of Medical Assistance (DMA) implemented the NC Medicaid Recipient Management Lock-In Program (NC MLIP). NC Medicaid beneficiaries identified for the lock-in program were limited to one prescriber and one pharmacy for benzodiazepine, opiate, and certain anxiolytic prescriptions. One of the criteria for the

MLIP was a history of receiving prescriptions for opioids and benzodiazepines from more than three providers in two consecutive months. In 2010 when the program was implemented, the plan was to enrol 200 additional patients each month, and the lock-in period was one year. Effective 2017, the lock-in program has been expanded to include all beneficiaries who qualify to be locked in, and the lock-in period was increased to two years.^{93,94} According to an analysis conducted by the DMA in 2012, there was a reduction in the number of pain pills (that is, opioids) and anti-anxiety medications (e.g., benzodiazepines) by 2.3 million in three months, and the program saved \$5.2 million during the first year of the policy being established.^{49,50}

A 2016 report based on a survey of Medicaid agencies in the US shows that a majority of the State Medicaid providers have established lock-in policies for their beneficiaries. Other than North Carolina, none of the other state policies specifically mention concomitant use of opioids and benzodiazepines as one of the criteria for beneficiaries to be recommended to a lock-in program. However, beneficiaries with prescriptions for multiple controlled substances, which could potentially include opioids and benzodiazepines, is one of the criteria that would make a beneficiary eligible to be recommended for the lock-in program in Medicaid administered care in various states including the District of Columbia, Georgia, Idaho, Massachusetts, Nevada, North Dakota, Tennessee, Texas, and Virginia.^{91,95} Patient-related outcomes of the lock-in programs have been studied, but no studies were identified that assessed the patient-related outcomes specific to concomitant use of opioids and benzodiazepines.^{49,96}

Prior Authorization or Claim Rejection

Prior authorization refers to the practice where the payer will not pay for beneficiaries' medication unless the provider has obtained permission before prescribing the drug. Many payers in the US have established prior authorization criteria for the concurrent use of opioids and benzodiazepines. Such claims are approved only when deemed medically appropriate. Following are some examples:

- In 2010, Delaware Medicaid & Medical Assistance (DMMA) program implemented a policy whereby any narcotic that already requires authorization will not be approved if the client is concomitantly using a benzodiazepine. This policy was implemented because most deaths attributed to benzodiazepine overdose in the US are in patients who are also taking narcotics, and there is no evidence that the use of benzodiazepines improves analgesic effects or makes a difference in the treatment of pain.⁹⁷
- As of December 2017, the New York State Medicaid Fee-For-Service Pharmacy Programs requires prior authorization for the following:
 - initiation of opioid therapy (both long- and short-acting opioids) in patients currently on benzodiazepine therapy
 - initiation of benzodiazepine therapy in patients currently on opioid or oral buprenorphine therapy
 - initiation of methadone therapy in patients currently on benzodiazepine therapy
 - initiation of clobazam therapy in patients currently on opioid or oral buprenorphine therapy.⁹⁸
- As of March 2016, the prior authorization policy of the Oregon Medicaid Pharmaceutical Services includes concurrent opioid use as criteria for potentially denying a request for long-term benzodiazepine (beyond four weeks) or sedative (z-drug) use, should the use be deemed medically inappropriate. If concurrent therapy is deemed medically appropriate, supplies are limited to only a fixed duration, e.g., six months for long-term benzodiazepines use.⁹⁹

- As of December 2016, all Medicaid Health plans in the State of Virginia have implemented prior authorization policy for concomitant use of benzodiazepines and opioids for new starts only.¹⁰⁰
- As of June 2017, all of Pennsylvania's Medical Assistance Programs providing services in the fee-for-service delivery system will require prior authorization for all prescription narcotic analgesics (long- or short-acting), except for one five-days' supply per beneficiary during a six-month period. Among other conditions, concurrent benzodiazepines could be a factor to reject the request for prior authorization unless the benzodiazepine or opioid is being tapered or the requested prescription is medically necessary.
- However, prior authorization of a prescription for a preferred analgesic, narcotic long- or short-acting will be automatically approved for a recorded diagnosis of active cancer, sickle cell with crisis, or newborn drug withdrawal syndrome for a beneficiary under 21 years of age, provided the short-acting narcotic analgesic does not contain codeine; or a recorded diagnosis of active cancer or sickle cell with crisis for an adult 21 years of age or older; provided the prescription is for more than a seven-day supply for short-acting narcotic analgesic.¹⁰¹
- The 2016 State Medicaid Drug Utilization Review Annual Reports highlights the following prior authorization criteria in the following US states' Medicaid Prescription Drug Fee-For-Service Programs, in addition to the above listed states.¹⁰²
 - **Montana:** limits benzodiazepines when used with methadone.
 - **Tennessee:** all benzodiazepine claimants require prior authorization, and requests are denied if enrollee is using chronic opioid or a buprenorphine-containing opioid addiction product.
 - **Texas:** Since 2013, for a combination of alprazolam, carisoprodol, and hydrocodone, claims with a 14-day overlap with each of the three drugs in the last 35 days is rejected. This edit is applied to clients of all age groups.
 - **Wyoming:** Prior authorization is required for concurrent use of opioids and benzodiazepines.

Supply Limits

The state of Hawaii limits initial concurrent prescriptions for opioids and benzodiazepines to a maximum of seven consecutive days, except for treatment of specified conditions. These exceptions include pain experienced in postoperative care; chronic pain and pain management; substance abuse or opioid or opiate dependence; cancer pain while the patient is in palliative care; or pain while the patient is in hospice care. For such co-prescriptions that last more than the seven-day supply of an opioid and benzodiazepine, the practitioner is required to document in the patient's medical record the condition for which the practitioner issued the prescription and that an alternative to the opioid and benzodiazepine was not an appropriate treatment for the condition. After an initial concurrent prescription for opioids and benzodiazepines has been made, a prescribing practitioner may authorize subsequent prescriptions through a telephone consultation with the patient if deemed medically necessary by the practitioner, for post-operative and pain management patients; provided that a prescribing practitioner consults with the patient in-person at least once every 90 days for the duration during which the practitioner concurrently prescribes opioids and benzodiazepines to the patient.¹⁰³

Requirement for Informed Consent, and Treatment Agreements

The health department of some US states have made laws that require prescribers to obtain informed consent from a patient when prescribing opioids. The informed consent requires that the patient is made aware of the risk associated with opioid use, including potentially fatal drug/drug interactions with drugs such as benzodiazepines. Additionally, some states

in US also require practitioners and patients to sign a treatment agreement. At the discretion of the practitioner, the treatment agreements could include requirements such as adherence to the dose and frequency of therapy; agreement to not misuse any medically unauthorized substances or medications; random fluid drug screens; requirement that all chronic pain management prescriptions are provided by a single practitioner or a limited, agreed-upon group of practitioners; or acknowledgement that a violation of the agreement may result in action as deemed appropriate by the prescribing practitioner such as a change in the treatment plan, a referral to a pain specialist, or referral to an addiction treatment program.

Criteria for informed consent in the states where it is mandatory are presented below, if they specifically mention that the informed consent includes risks associated with opioids and benzodiazepines. If any of these states also require treatment agreements, the criteria are also presented.

- **Delaware**^{104,105}:
 - Informed Consent: After the first-time outpatient prescription, or after the patient has been issued outpatient prescription(s) totalling up to a seven-day supply. before issuing a subsequent prescription for an opioid analgesic for Acute Pain.
 - Treatment agreement: For chronic patients.
- **Vermont**¹⁰⁶:
 - Informed Consent: Before writing a prescription for an opioid Schedule II, III, or IV Controlled Substance for the first time during a course of treatment to any patient, including initiating an opioid prescription for chronic pain, and during reevaluation of treatment; for prescription of extended-release hydrocodones and oxycodones without abuse deterrent opioid formulations; and for patients in hospice, palliative care at end-of-life, and end-of-life.
 - Treatment agreement: When initiating an opioid prescription for chronic pain, and during reevaluation of treatment (controlled substance treatment agreements for people receiving treatment for chronic pain shall be reviewed by the prescriber and patient no less frequently than once every 365 days to re-evaluate the patient); and for prescription of extended-release hydrocodones and oxycodones without abuse deterrent opioid formulations.
- **Arizona**¹⁰⁷:
 - Informed Consent: Before prescribing an opioid or ordering the administration of opioids. This requirement is not applicable to terminally ill patients.
- **Hawaii**¹⁰³:
 - Informed Consent: A patient requiring opioid treatment for more than three months; a patient who is prescribed benzodiazepines and opioids together; or a patient who is prescribed a dose of opioids that exceeds 90 morphine equivalent doses.

Authorities such as medical boards in several of the US states have established policies to obtain informed consent and treatment agreements when prescribing opioids. Examples include such as Florida Boards Of Medicine And Osteopathic Medicine; Alabama Board of Medical Examiners; Georgia Composite Medical Board; Kentucky Board of Medical Licensure; Minnesota Boards of Medical Practice, Nursing, and Pharmacy; South Carolina Board of Medical Examiners; among others. However, their policies do not specifically mention that the informed consent should include risks associated with opioids and benzodiazepines.^{37,108-113}

Drug Utilization Review

The 2016 State Medicaid Drug Utilization Review (DUR) Annual Reports for highlights that follow states in the US have audits in place to monitor opioids and benzodiazepines being used concurrently (in a prospective or retrospective DUR) in a state's Medicaid Prescription Drug Fee-For-Service Programs: Connecticut, Delaware, Idaho, Indiana, Kentucky, Montana, New York, Oregon, Tennessee, Texas, Virginia, and Wyoming. These DURs are utilized to implement policies such as prior authorization (see policies in sections entitled *Prior Authorization and Audit and Feedback*). However, some states such as Connecticut and Indiana have retrospective DUR, which cannot be utilized at the point of service.¹⁰²

Prescription Drug Monitoring Program

As of August 2017, 49 states in the US have an operational PDMP, and 36 states have laws in place to require the use of state PDMP. Typically, a query to the PDMP is required before controlled substances such as opioids or benzodiazepines are prescribed or dispensed.³⁷ However, the search conducted for this Environmental Scan did not identify any laws in these states that require prescribers or pharmacists to query the PDMP when opioids and benzodiazepines are used concurrently, except for Delaware. Delaware's new Opiate Regulations, started in May 2016, have made it mandatory for all prescribers statewide to query the Prescription Monitoring Program for Chronic Pain patients when they are prescribing opioids at least every six months, more frequently if clinically indicated, or whenever the patient is also being prescribed a benzodiazepine. This, is in addition to the requirement to obtain informed consent and treatment agreement (see above).^{104,105}

However, specific payers within these states may have established policies to make it mandatory to query PDMP when opioids and benzodiazepines are co-prescribed. For example, the Virginia Department of Medical Assistance Services (DMAS) requires checks of the Virginia Prescription Monitoring Program (PMP) for opioid prescriptions lasting more than 14 days from the dates of the last opioid and last benzodiazepine prescribed.¹¹⁴

Additionally, the boards of medicine or dentistry may also have requirements for members to query PDMP before co-prescribing opioids and benzodiazepines. For example, effective July 2017, the Mississippi State Board of Dental Examiners requires that every dentist licensed by the board run the Mississippi Prescription Monitoring Program (MPMP) at each patient encounter in which a Schedule II opioid and/or benzodiazepine prescription is written.¹¹⁵

Audit and Feedback

Indiana's Medicaid system uses data collected from the retrospective DUR to send (by fax) a near real-time letter to the prescriber notifying them of the combination therapy (that is, opioids and benzodiazepines) and risks associated with this therapy.¹⁰²

Utilizing the mandatory PDMP query, the Virginia DMAS requires that educational letters are sent to prescribers for patients receiving benzodiazepines and opioids concomitantly. Letters include links to prescribing tools on the CDC website, Morphine Milligram Equivalent (MME) or Morphine Equivalent Dose (MED) calculators, and toolkits with suggested opioid tapers and benzodiazepine tapers.¹¹⁴

The Veterans Health Administration (VHA)'s OSI was implemented in October 2013, it included the dissemination of clinical practice guidelines for opioid therapy for the management of chronic pain, developed by the VHA. Additionally, a dashboard tool was provided that aggregates electronic medical record data to audit real-time opioid-related

prescribing and identifying a clinical leader at each facility to implement the tool and promote safer prescribing. Actions in response to the dashboard were developed at the discretion of the specific facilities, but could include notifying providers and providing feedback to promote safe prescribing.^{51,116}

Lin et al. examined changes associated with OSI implementation in October 2013 among all adult VHA patients who filled outpatient opioid prescriptions. Interrupted time series analyses controlled for baseline trends and examined data from October 2012 to September 2014 to determine the changes after OSI implementation in prescribing high-dosage opioid regimens (total daily dosages > 100 morphine equivalents [MEQ] and > 200 MEQ) and concurrent benzodiazepines. The study showed that in October 2012 (pre-OSI), 112,907 patients received benzodiazepines concurrently with opioids, which decreased to 89,564 patients by September 2014, i.e., post OSI (20.67% reduction overall and 0.86% per month). This study indicates potential effectiveness of large-scale interventions, and those that combine multiple interventions such as dissemination of guidelines, provision of tools to facilitate audit, and feedback to improve appropriate prescribing. However, the program design does not allow one to determine the effectiveness of specific elements of the intervention.⁵¹

Private payers, particularly in the US have established policies to better manage co-prescription of opioids and benzodiazepines. Some of these policies were shown to be effective in reducing concurrent use of opioids and benzodiazepines.^{117,118} However policies established by private payers were out of scope for the scan, and are therefore not discussed.

Practice Guidance

Several State governments or medical boards, associations of health care institutions, or associations of health care professionals across several states in the US recommend against the concurrent use of opioids and benzodiazepine. These include (but are not limited to) the Arizona Hospital and Healthcare Association; Arizona Nurses Association; Alabama Board of Medical Examiners; Hawaii Chapter of the American College of Emergency Physicians; Maine Legislature (for statute related to professional licensing); Massachusetts Board of Registration in Medicine; Minnesota Boards of Medical Practice, Nursing, and Pharmacy; New York City Department of Health and Mental Hygiene; Ohio Opiate Action Team (part of the Governor's cabinet); Ohio State Medical Board; Pennsylvania Board of Dentistry; Tennessee Department of Health; and Wisconsin Medical Examining Board.³⁷ These recommendation are consistent with the CDC's Guideline for Prescribing Opioids for Chronic Pain.³⁴ Additionally, payers such as the Virginia DMAS have developed policies for concurrent use of opioids and benzodiazepines (see other sections), to specifically align with the recommendations from the CDC guidelines.^{34,100}

Other Policies

Jurisdictions may establish laws that facilitate payers to establish additional policies or requirements that are specific to limiting concurrent prescription of opioids and benzodiazepines. For example:

- The State of Utah passed a bill in 2017 that authorizes commercial insurers, the state Medicaid program, workers' compensation insurers, and public employee insurers to implement policies to minimize the risk of opioid addiction and overdose from chronic co-prescription of opioids with benzodiazepines and other sedating substances.^{119,120}
- Arizona's Department of Health Services requires that a licensed health care institution establish, document, and implement policies and procedures for prescribing or ordering an opioid or administering an opioid as part of the treatment, for conditions that may contraindicate prescribing an opioid, or using an opioid in treatment that includes a concurrent use of a benzodiazepine.¹⁰⁷

Authorities or associations may develop measures to mandate or encourage monitoring concurrent use of opioids and benzodiazepines.

- The Centers for Medicare and Medicaid Services (CMS) encourages Part D sponsors to evaluate their claims data and use available drug utilization management tools to help address the concurrent use of opioids and benzodiazepines. Starting in October 2016, CMS added a concurrent opioid-benzodiazepine-use flag to the Outcome Measurement System (OMS) reports in an effort to assist Part D sponsors in addressing the issue of concurrent opioid and benzodiazepine use.^{121,122}
- State Medicaid fee-for-service agencies and managed care organizations are required to report annually to CMS their DUR program activities and processes to ensure appropriate drug utilization, including monitoring the concurrent use of opioids and benzodiazepines.¹²³
- In December 2016, the Pharmacy Quality Alliance (PQA) membership endorsed a new measure called “Concurrent Use of Opioids and Benzodiazepines.” This measure examines the percentage of individuals 18 years and older with concurrent use of prescription opioids and benzodiazepines. Patients in hospice care and those with a cancer diagnosis are excluded.¹²⁴ CMS has indicated that it may consider using this measure for future use in oversight or performance measurement.¹²²

Some jurisdictions mandate or encourage that patients who are prescribed opioids and benzodiazepines, also be co-prescribed naloxone, a drug that temporarily reverses potentially fatal opiate and benzodiazepine effects, such as respiratory depression.¹²⁵ Examples include the following:

- The state of Vermont requires that all prescribers statewide must co-prescribe naloxone for all patients receiving an opioid prescription if there is a concurrent prescription for benzodiazepines.¹⁰⁶
- The Regulations Governing Prescribing of Opioids and Buprenorphine in the state of Virginia requires that naloxone be prescribed for any patients taking opioids for acute or chronic pain when risk factors such as concomitant benzodiazepine use is present.¹²⁶
- Maryland Department of Health and Mental Hygiene encourages prescribers to provide prescriptions for naloxone to all patients who are at risk of an opioid overdose including anyone who uses opioids with antidepressants, benzodiazepines, alcohol, or other drugs.¹²⁷

Patients at High Risk

This Environmental Scan also explored if any of the policies identified patients who were at high risk of harms associated with the co-prescription of opioids and CNS depressants. Given that most of the policies were developed for safe prescribing and dispensing of opioids, concurrent use of opioids with benzodiazepines was considered high-risk use. No further distinction was made. However, some of the policies specifically focused on long-term opioid therapy (e.g., treatment lasting more than 14 days) or chronic pain or long-term benzodiazepine therapy (e.g., treatment lasting more than four weeks).^{99,102,104-106,114}

Limitations

This Environmental Scan does not provide a comprehensive review of all the policies established to limit co-prescription of opioids and CNS depressants in the jurisdictions of interest. Additionally, this scan is focused on policies that aim to manage concomitant prescription or dispensing rather than actual use of these drugs. Given that these drugs can be accessed through other means, such as illegal purchase, it should be noted that individuals may still use the drugs

concomitantly without a prescription or access to a pharmacy.^{46,128} Therefore, policies that do not specifically target concomitant prescription or dispensing of the drugs were excluded from the scan. Further, policies established by the private sector, such as those of the private insurers, are not included in the scan.

Policies established for in-patient settings such as in hospitals or critical care centres were excluded. Other topics excluded from the scan include the identification of conditions or patients groups in which co-prescription of opioids and one or more of the CNS depressants are appropriate, or the appropriate strategies to use these drugs concomitantly. Policies that are recommended but not established in any jurisdiction of interest were also excluded from the scan. Additionally, policies that address socio-economic aspects (e.g., housing, poverty alleviation) or law enforcement-related policies are outside the scope of this scan.

Success or failure of specific policies is context-dependent. Therefore, the impact of these policies, as presented in this Environmental Scan, should be interpreted in light of the health care system, culture, and other relevant related context of the jurisdiction in which the policy is established. This Environmental Scan does not make any recommendations as to whether or not the identified policies would be appropriate in the context of the Canadian health care system.

Conclusion

Concomitant use of opioids and CNS depressants like benzodiazepines is frequent and potentially harmful. However, they continue to be prescribed together in various clinical conditions. The negative health impact of concomitant use of opioids and CNS depressants has been widely recognized by authorities; and governments, regulators, public payers, and health care professionals' associations have established policies to limit, monitor, or take other actions with respect to the co-prescription of these drugs. This Environmental Scan highlights the policies that are established to reduce the concomitant prescription of opioids and CNS depressants in outpatient settings, in Canada and internationally. The scan also presents the impact of these identified policies, as available.

Most of the policies identified in this scan are focused on setting limits and parameters to the co-prescription of opioids and benzodiazepines, and other sedative hypnotics, as opposed to the other CNS depressants of interest (i.e., antipsychotic drugs, gabapentin, pregabalin, barbiturates, and muscle relaxants). Furthermore, the majority of the identified policies were established in US jurisdictions. These policies were established after 2012. In terms of the public payer policies, most of the identified policies, were the ones established by the Medicaid.

In terms of the regulatory policies, the US FDA has released a "black box" on product labelling of prescription opioid pain and prescription opioid cough medicines as well as benzodiazepines, warning about the risk associated with concurrent use of opioids and benzodiazepines. In Canada, product monographs of opioids and CNS depressants drugs like benzodiazepines, z-drugs, antipsychotic drugs, pregabalin, gabapentin, and baclofen warn about the side effects of concurrent use of opioids and CNS depressants. Some product monographs of opioids, benzodiazepines, and z-drugs have listed these risks in a **boxed** Warning and Precaution section.

The FDA also issued a Drug Safety Communication warning against the co-prescription of opioids and benzodiazepines. The exception was for opioid addiction medications such as buprenorphine and methadone, where careful medication management and patient monitoring was recommended rather than withholding the opioid addiction medication for patients taking

benzodiazepines or other CNS depressant drugs. Some safety warnings regarding the risk of concomitant use of opioids and certain CNS depressants were also issued by Medicines and Healthcare products Regulatory Agency in the UK.

Prescribing or dispensing policies, established by public payers in Canada, specific to co-prescription of opioids and CNS depressants were not identified. Some standards of practice for health care professionals were identified in Canada, which directed physicians to not prescribe opioids and benzodiazepines concurrently. Similar guidelines or directives were also identified in the US.

Public payers in the US states have implemented policies such as lock-in programs, whereby patients are limited to single or a pre-determined group of prescribers or pharmacists for their therapy with controlled substances such as opioids and benzodiazepines. Several public payers in the US also restrict the co-prescription of opioids and benzodiazepines by establishing prior authorization criteria, whereby claims are approved only if concomitant use of the drugs is deemed medically appropriate. The scan identified one US state which limits the duration of the supply of the opioids and benzodiazepines when they are prescribed concurrently. Some states in the US require prescribers to obtain informed consent from patients prior to co-prescribing opioids and benzodiazepines, and complete a signed treatment agreement form. This step allows the prescriber and patient to have a discussion regarding the risks associated with concurrent use of opioids and benzodiazepines.

Use of a DUR, querying prescription drug monitoring programs, or systems for audit and feedback are common for controlled substances in the US and Canada. In the US, DURs are used to monitor and implement policies specific to concurrent use of opioids and benzodiazepines. Although use of PDMP is becoming increasingly common in US states and Canada, the scan only identified one US state that had a regulation to query the state's PDMP program specifically for concomitant use of opioids and benzodiazepines. However, public payers or medical or dentistry boards within some US states may require that the PDMP program be queried for concomitant use. Audit and feedback is another aspect of the monitoring-related policies. A study has indicated the effectiveness of VHA's policy related to audit and feedback, a part of VHA's OSI, that also included guideline dissemination.

Other policies or measures in the US relevant to concurrent use of opioids and benzodiazepines were laws that facilitated payers to establish additional policies or requirements; development of outcome measures by authorities or associations to mandate or encourage monitoring concurrent use with and benzodiazepines; and mandatory co-prescription of naloxone to patients who are prescribed opioid and benzodiazepines concurrently.

Although most of the policies did not make a distinction of subgroups of patients, some policies specifically focused on long-term opioid therapy, chronic pain, or long-term benzodiazepine therapy.

As harms associated with concurrent use of opioids and CNS depressants are becoming widely recognized, regulators and payers, particularly in the US, have established policies to limit the co-prescription of these drugs. Further research is needed to ascertain the effectiveness of these policies within a given context, to enable policy improvement and to assist other jurisdictions in developing effective policies for ensuring population safety and optimal care.

Appendix 1: Examples of the Labelling Changes as Required by the FDA

Example: Opioid Analgesic Safety Labelling Change¹²⁹

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions (5.X)*, *Drug Interactions (7.X)*].

- Reserve concomitant prescribing of [TRADENAME] and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation

Example: Opioid Cough Medication Safety Labelling Change¹³⁰

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.1)*]. Avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol.

Example: Benzodiazepine Safety Labelling Change.¹³¹

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.X)*].

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

Appendix 2: Canadian Drug Utilization Methodology

CADTH requested aggregate claims data from CIHI regarding concomitant use of opioids and benzodiazepines in all provinces (except Quebec) and the Yukon, for the 2016 calendar year.

Only accepted claims, where at least part of the claim was accepted by the public plan/program, either toward a deductible (if applicable) or for payment are included in this analysis.

The chemicals in this analysis, provided by the requestor, are to be identified by the following World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) codes:

ATC Code	ATC Description	ATC Code	ATC Description
Benzodiazepines/Z-drugs			
N05BA ^a	Benzodiazepine derivatives (Anxiolytics)	N05CF	Benzodiazepine-related drugs
N05CD	Benzodiazepine derivatives (Sedatives and hypnotics)	N03AE01	Clonazepam
Opioids			
A03ED	Antispasmodics in combination with other drugs	N02BA51 ^b	ASA, comb excl psycholeptics
A07DA02	Opium	N02BA71 ^b	ASA, comb with psycholeptics
M03BB53 ^b	Chlorzoxazone, combinations excl psycholeptics	N02BE51 ^b	Acetaminophen, comb excl. psycholeptics
N01AH01	Fentanyl	R05DA	Opium alkaloids and derivatives
N01AH51	Fentanyl, combinations	R02DA20 ^b	Combinations (Opium alkaloids and derivatives)
N01BB51	Bupivacaine, combinations	R05FA02 ^b	Opium derivatives and expectorants
N02A	Opioids	R05FB02 ^b	Cough suppressants and expectorants

^a Excluding code N05BA09, which is primarily used for epileptic seizures.

^b Excluding products that do not have a schedule of narcotic as reported in the Health Canada Drug Product Database.

Please also note that due to the design of public drug programs in Canada (i.e., seniors and low income families/individuals are the only populations covered in all jurisdictions), data for non-seniors (with the exception of British Columbia, Saskatchewan and Manitoba) are limited. See the jurisdiction-specific notes section for more information.

The National Prescription Drug Utilization Information System (NPDUIS) Database does not include information regarding:

- 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
- diagnoses or conditions for which prescriptions were written.

Data Elements

Calendar Year	The calendar year during which a claim was dispensed.
Number of Concurrent Users	The number of people from whom the public drug plan/program has accepted at least part of at least one claim for an opioid drug and at least one claim for a benzo/Z-drug either toward a deductible (if applicable) or for payment, in a given calendar year.
Total Number of Opioid Users	The number of people from whom the public plan/program has accepted at least part of at least one claim for an opioid, either toward a deductible (if applicable) or for payment.

Plans and Programs in the NPDUIS Database:

The NPDUIS Database contains claims data from the following drug plans/programs for the requested time:

Jurisdiction	Plan/Program Code – Description
Alberta	Non-Group
	Seniors
	Palliative Care
British Columbia	Permanent Residents of Licensed Residential Care Facilities
	Recipients of British Columbia Income Assistance
	Cystic Fibrosis
	Children in the At Home Program
	No-Charge Psychiatric Medication Program
	Fair PharmaCare
	Palliative Care
	Smoking Cessation
Manitoba	Employment and Income Assistance Program
	Palliative Care
	Pharmacare
	Personal Home Care/Nursing Homes

Jurisdiction	Plan/Program Code – Description
New Brunswick	New Brunswick Prescription Drug Program <ul style="list-style-type: none"> • Seniors • Nursing Home Residents • Social Development clients • Individuals in Licensed Residential Facilities • Children in Care of the Minister Social Development and Children with Disabilities • Multiple Sclerosis • HIV/AIDS • Cystic Fibrosis • Organ Transplant Recipients • Growth Hormone Deficiency
	New Brunswick Drug Plan
Newfoundland and Labrador	Select Needs/Cystic Fibrosis Plan
	Select Needs/Growth Hormone Plan
	The Foundation Plan
	The Assurance Plan
	The Access Plan
	The 65Plus Plan
Nova Scotia	Drug Assistance for Cancer patients
	Diabetic Assistance Pharmacare Program
	Pharmacare Long-Term Care (Under 65)
	Palliative Drug Care Program
	Seniors' Pharmacare Program
	Family Pharmacare Program
Ontario	Ministry of Community Services (MCSS)
	Ministry of Health and Long-Term Care (MOHLTC) Ontario Drug Benefit Program (ODB)

Jurisdiction	Plan/Program Code – Description
Prince Edward Island	Diabetes Control
	Family Health Benefit
	Immunization Program
	High Cost Drugs Program
	Nursing Home
	Catastrophic Drug Program
	Seniors Drug Cost Assistance Program
	Children-In-Care/Financial Assistance
	Sexually Transmitted Diseases (STD)
	Quit Smoking Program
Saskatchewan	Universal Program
Yukon	Children’s Drug and Optical Plan
	Chronic Disease Program
	Pharmacare

Common to all provinces submitting claims data to the NPDUIS Database, people covered by provincial workers’ compensation boards or federal drug programs are not eligible for provincial public coverage. Federal drug programs include those delivered by:

- Correctional Service of Canada
- Veterans Affairs Canada
- First Nations and Inuit Health Branch (FNIHB).*

* This excludes individuals in Ontario who also have coverage through FNIHB. These individuals have their drug claims covered first by the Ontario Drug Benefit program and any remaining drug costs are covered by FNIHB.

Further information about public drug programs in Canada can be found in the [NPDUIS Plan Information Document](#).

Below contains jurisdiction-specific notes for claims data housed in NPDUIS Database:

Jurisdiction	Notes
Alberta	<ul style="list-style-type: none"> • Claims financed through the Income Support, Alberta Adult Health Benefit, Assured Income for the Severely Handicapped, and Alberta Child Health Benefit programs, are not submitted. • Claims financed to residents of long-term care facilities are not submitted.
Manitoba	<ul style="list-style-type: none"> • Includes accepted claims for people who are eligible for coverage under a provincial drug program but have not submitted an application and, therefore, do not have a defined deductible.
Nova Scotia	<ul style="list-style-type: none"> • Claims dispensed through the Department of Community Services Drug Programs are not submitted.
Prince Edward Island	<ul style="list-style-type: none"> • Claims dispensed through the Child in Care/Financial Assistance, Seniors Cost Assistance, Diabetes Control, Family Health Benefits, High Cost Drugs, Nursing Home, Quit Smoking, and Sexually Transmitted Diseases programs are included. Claims for all other plans are not submitted. For a list of all Prince Edward Island drug plans, please see the NPDUIS Plan Information Document. • Residents of privately owned nursing homes for whom care is publicly subsidized are eligible for drug coverage through the Nursing Home Program. Residents of privately owned nursing homes for whom care is not publicly subsidized are not covered through the Nursing Home Program, but may be eligible for coverage through another plan (e.g., the Seniors Cost Assistance Program). Residents of government manors (i.e., publicly owned nursing homes) are covered through the Institutional Pharmacy Program; claims for these residents are not submitted to the NPDUIS Database.
Saskatchewan	<ul style="list-style-type: none"> • Claims for non-published DINs (DINs not listed on the Saskatchewan Health Drug Plan Formulary) are not submitted. • Claims dispensed through special programs, such as the Saskatchewan Cancer Agency, are not submitted. • Claims dispensed through SAIL (Saskatchewan Aids to Independent Living) and Supplementary Health are only included if the DINs are published on the Saskatchewan Health Drug Plan Formulary.

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