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Drug Shortages and Patient Harms

Key Messages

What Is the Issue?

- Drug shortages are a global issue with complex dynamics. Shortages can occur because of disruption at any point along the drug supply chain. Several strategies are used in Canada to prevent or alleviate the effects of drug shortages, including mandatory reporting by drug manufacturers.
- An understanding of the amount and types of real or potential harms caused to patients can inform policy decisions around drug shortage management and prevention.

What Did We Do?

- We searched for literature providing evidence on patient outcomes associated with supply chain disruptions of pharmaceuticals and vaccines. An information specialist conducted a search of peer-reviewed literature sources published between January 1, 2003, and September 13, 2023.
- Documents were excluded if the objective was to investigate the potential effects of a drug shortage in the absence of an actual drug shortage or if the outcomes were not direct patient harms.

What Did We Find?

- One scoping review and 33 nonrandomized studies were identified that evaluated patient outcomes associated with supply chain disruptions of pharmaceuticals and vaccines.
- We identified a wide variety of drug classes experiencing shortages. The most frequently reported shortages were anesthetics, oncology drugs, vaccines, drugs for the treatment of COVID-19, antimicrobials, and small-volume parenteral solutions.
- Most of the included primary studies concluded that the replacement drug or protocol was a safe or acceptable alternative to the shortage drug. The subset of primary studies that concluded that the replacement drug or protocol was not a safe or acceptable alternative to the shortage drug reported worse outcomes in health system use (including length of hospital stay), adverse events, disease progression, and mortality.

What Does This Mean?

- Drug shortages have the potential to cause harm to patients and some drug shortages may have a greater impact on patients than others. The

Key Messages

ability to predict which drugs could cause the greatest harm during a supply disruption would be a great benefit for future planning.

- The diversity of drugs experiencing shortages and their associated harms emphasizes that decision-makers may need to take a case-by-case approach when developing policies meant to lessen the impact of drug shortages.

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What Is the Problem?

Drug shortages are a global issue with complex dynamics. Between 2022 and 2023, more than 2,700 drug shortages were reported to Health Canada, lasting an average of 98 days.[1] Of these, 34 were considered high impact — shortages with the greatest potential consequences to people and health care systems (e.g., no therapeutic alternatives available).[1,2]

There are multiple steps along the drug supply chain, including:

- drug development and regulatory approval
- manufacturing
- purchase and distribution
- delivery to hospitals, pharmacies, and patients.[3]

Interruptions to any of these phases can cause a shortage. For example:

- good manufacturing practices noncompliance leading to recalls
- nonprofitable drugs leading to decisions to cease production
- stockpiling of medication
- external factors, such as a natural disaster.[3,4]

In addition, weak points in the supply chain, such as relying on the supply of drugs from a single source or not having protocols in place to respond to increases in demand, can also cause or worsen existing drug shortages.[3,4]

What Is the Current Practice?

Strategies currently used in Canada to attempt to prevent or alleviate drug shortages include:

- an expedited drug review process to accelerate Health Canada approval of substitute drugs in urgent circumstances
- drug manufacturing quality assurance protocols
- the development of ethical frameworks for resource allocation
- compounding drugs
- rationing protocols at the hospital and pharmacy level.[3]

Furthermore, mandated reporting of drug shortages went into effect in 2017,[2] Drug manufacturers are required to report anticipated shortages or discontinuations, ideally 6 months in advance, to allow time to put mitigation plans into place. Manufacturers are also required to report actual shortages as soon as they are aware of them.[2]

Why Is It Important to Do This Review?

People can experience clinical harm as a result of drug shortages. This can take several forms:

- inadequate treatment or management of health conditions
- withdrawal-related side effects
- adverse or safety events associated with replacement drugs
- medication errors.[4]

Some drugs have the potential for much greater patient harm if they become difficult to obtain. For example, shortages of drugs with life-saving benefits or strict dosing schedules might have more impact on patient outcomes, especially if there are no alternative options available.[2,4]

This report is the first in a series of CADTH-published initiatives that aims to emphasize potential priority medications and to ultimately support decision-making during drug shortages.

Objective

The purpose of this report is to summarize the evidence on patient outcomes associated with supply chain disruptions of pharmaceuticals and vaccines.

Research Question

What is the evidence on patient outcomes associated with supply chain disruptions of pharmaceuticals and vaccines?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources, including MEDLINE and the Cochrane Database of Systematic Reviews. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concept was drug shortages. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons; any types of clinical trials or observational studies; real-world evidence using routinely collected data; or to the context in Canada. The search was completed on September 13, 2023, and limited to documents published since January 1, 2003.

Selection Criteria and Summary Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1. Information from the relevant studies was extracted into summary tables and organized into broad clinical indication categories by 1 reviewer. Data were extracted on the study characteristics; shortage drug and its substitute, if applicable; findings that related to direct patient harms; and overall conclusion. Outcome results and their direction of effect were briefly summarized as reported by the study's authors and categorized into the following: no difference, worse, improved, or mixed between groups (e.g., in studies with multiple comparator groups, an outcome may improve in 1 group but worsen in another). No formal critical appraisal (e.g., risk of bias assessment) of the included studies was conducted.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2003.

Studies were excluded if:

- the natural effects of a drug shortage could not be observed because of the study design (e.g., randomized controlled trial)
- the shortage product was a multivitamin, supplement, homeopathic medication, or device
- the purpose of the study was to investigate the potential effects of a drug shortage in the absence of an actual drug shortage (e.g., anticipatory)
- the primary or secondary outcomes were not direct patient harms (e.g., studies that reported treatment delays without describing a direct measurable effect to patients were excluded).

Because of the large volume of potentially relevant articles identified for full-text review, those published before January 1, 2018, were excluded. A list of the articles published before 2018 that were identified for full-text review, but not screened for inclusion and exclusion criteria, can be found in Appendix 2.

Overall Summary

Quantity of Research Available

A total of 1,871 citations were identified in the literature search. Following screening of titles and abstracts, 1,742 citations were excluded and 129 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 95 publications were excluded for various reasons, and 34 publications met the inclusion criteria and were included in this report. These comprised 1 scoping review (SR) and 33 nonrandomized studies (NRSs).

Table 1: Selection Criteria

Criteria	Description
Population	General population
Concept	Supply chain disruptions of pharmaceuticals and vaccines
Outcomes	Patient harms (e.g., mortality, emergency department visits, hospitalization rates, adverse events)
Study designs	Health technology assessments, systematic reviews, scoping reviews, nonrandomized studies

Appendix 1 presents the PRISMA[5] flow chart of the study selection. Additional references of potential interest are provided in Appendix 2.

Summary of Study Characteristics

The SR by Phuong et al. (2019)[6] included 40 studies. Sixteen primary studies published between 2006 and 2017 met the inclusion criteria for this report. Of these, 3 were prospective cohort studies and 13 were retrospective cohort studies. The authors of the SR were from Australia.[6]

Of the 16 relevant primary studies in the SR, 4 were conducted in a surgical setting, 2 in a nonspecific hospital setting, 1 in the intensive care unit, 1 in an air medical setting, and 8 did not specify a setting.[6]

The 33 included primary clinical studies comprised 1 registry study,[7] 5 prospective cohort studies,[8-12] and 27 retrospective cohort studies.[13-39] Two studies were published as research letters.[8,30] The studies were published between 2018 and 2023. The primary clinical studies were conducted by authors from Australia,[11,12] Brazil,[23] Canada,[13,20,30,33] the Democratic Republic of the Congo,[38] France,[7,14,27] Japan,[8] the Netherlands,[39] and the US.[9,10,15-19,21,22,24-26,28,29,31,32,34-37]

Twenty of the included primary studies compared outcomes between the shortage drug and its substitute before and during a drug shortage period.[13-22,24,26,27,31-35,37,39] Of these, 3 studies had at least 1 substitute drug group that had a supply disruption and was further compared to an additional substitute drug group.[14,34,39] In Cole et al. (2021), the intervention and comparator groups flipped partway through when supply of the shortage drug resumed, and the substitute drug went into shortage.[10] In Li and Cimino (2020), the study occurred during the drug shortage period and compared patients who continued receiving the shortage drug to those who switched to a substitute drug.[28] In van Langenberg et al. (2020), for long-term outcomes, the intervention group was the substitute drug and was compared to patients who switched back to the shortage drug when supply resumed.[11] In this same study, there was no comparator group for short-term outcomes.[11] Nine studies did not have a comparator group.[8,9,12,23,25,29,30,36,38] The registry study aimed to identify adverse drug reactions related to drug shortages and describe the types of drugs and harms involved.[7]

Nine of the included primary studies were conducted in a nonspecific hospital setting,[13,18,22,24,25,29,35,36,39] 6 in the emergency department (ED),[10,15,26,32-34] 5 in the intensive care unit,[17,20,21,27,31] 5 in the community,[8,9,12,30,38] 3 in a surgical setting,[16,19,37] 3 in a hospital outpatient setting,[11,14,28] and 1 in dialysis clinics.[23]

Summary of Findings

The 16 relevant primary studies from the SR are summarized in Table 2. The registry study and 32 NRSs are summarized in Table 3.

There was considerable variability in the types of drugs experiencing shortages. Broadly defined categories by clinical indication were identified as follows:

- anesthetic, analgesic, or sedative medications (SR: 3 studies; NRS: 7 studies)[6,10,17-19,26,34,37]
- oncology drugs and drugs used in conjunction with oncology drugs (SR: 4 studies; NRS: 5 studies)[6,13,14,28,35,36]
- vaccines (NRS: 4 studies)[8,9,12,38]
- antimicrobials, including antibiotics and antivirals, and drugs used in conjunction with antimicrobials (SR: 3 studies; NRS: 3 studies)[6,22,31,33]
- drugs specific to the treatment or management of COVID-19 (NRS: 3 studies)[20,27,39]
- drugs that did not fit into the previously mentioned categories (SR: 6 studies; NRS: 6 studies)[6,11,16,21,23,30,32]
- nondrug, specifically, small-volume parenteral solutions, which are used to administer IV drugs (NRS: 4 studies).[15,24,25,29]

Strategies used to manage drug shortages:

- alternative drug (SR: 13 studies; NRS: 14 studies)[6,8-14,16,26,30-32,34,37]
- dose-sparing strategies (e.g., fixed dose) (SR: 1 study; NRS: 3 studies)[6,20,22,38]
- alternative route of administration (e.g., oral formulations) (NRS: 4 studies)[18,21,35,36]
- alternative method of administration (e.g., infusion technique) (SR: 1 study; NRS: 4 studies)[6,15,24,25,29]
- none (e.g., no suitable replacement available) (SR: 1 study; NRS: 2 studies)[6,23,33]
- a combination of the previously mentioned categories, either at the same time or in sequence (NRS: 5 studies).[17,19,27,28,39]

Outcomes related to patient harms and the direction of effect during a drug shortage period:

- Mortality: no difference (SR: 5 studies; NRS: 9 studies);[6,11,15-17,21,22,24,27,31] worse (SR: 1 study; NRS: 1 study);[6,20] improved (NRS: 1 study);[13] mixed results between groups (NRS: 1 study)[39]
- Hospital admission: no difference (NRS: 1 study);[30] worse (NRS: 1 study);[11] mixed results between groups (NRS: 1 study)[34]
- Intensive care unit (ICU) admission: no difference (SR: 1 study; NRS 1 study);[6,34] worse (NRS: 2 studies)[13,39]
- ED visit: no difference (NRS: 2 studies);[18,37] worse (NRS: 1 study)[30]
- Hospital readmission: no difference (NRS: 1 study);[33] improved (NRS: 2 studies)[18,24]
- Hospital length of stay (LOS): no difference (SR: 3 studies; NRS: 7 studies);[6,17,18,20,22,24,31,35] worse (NRS: 1 study);[13] mixed results between groups (NRS: 2 studies)[34,39]

- ICU LOS: no difference (NRS: 4 studies)[17,20,21,34]
- ED LOS: mixed results between groups (NRS: 2 studies)[10,34]
- Postanesthetic care unit LOS: worse (NRS: 1 study)[37]
- Adverse events: no difference (SR: 8 studies; NRS: 17 studies);[6,8,9,12,14-16,25-29,31,33-36,38] worse in at least 1 safety outcome (SR: 2 studies; NRS: 5 studies);[6,11,13,19,24,37] improved in at least 1 safety outcome (SR: 2 studies; NRS: 1 study);[6,32] mixed results between groups (NRS: 1 study)[10]
- Disease progression: no difference (SR: 1 study; NRS: 2 studies);[6,27,28] worse (SR: 2 studies; NRS: 3 studies);[6,11,23,31] improved (NRS: 1 study)[13]
- Duration of mechanical ventilation: no difference (SR: 1 study; NRS: 2 studies);[6,17,20] worse (SR: 1 study);[6] improved (NRS: 1 study)[21]
- Pain: no difference (NRS: 1 study)[17]

Primary study author's conclusions:

- The replacement drug or protocol was a **safe** or acceptable alternative to the shortage drug (NRS: 26 studies).[8-10,12-18,20-22,24-30,32-36,38]
- The replacement drug or protocol was considered **not safe** or at increased risk of harmful outcomes (NRS: 6 studies).[11,19,23,31,37,39] The shortage drug class differed for all 6 studies[11,19,23,31,37,39] and was compared to an alternative drug or protocol in 5 studies.[11,19,31,37,39] There was no suitable replacement therapy available in 1 study.[23] For these 6 studies, worsening direct patient harms were reported for the following outcome categories: health system use (3 studies),[11,37,39] adverse events (3 studies),[11,19,37] and disease progression (3 studies).[11,23,31] Swets et al. (2023) reported lower survival in 2 of the 3 replacement drug groups compared to the shortage drug.[39]

Context in Canada

Four primary studies investigated drug shortages occurring in Canada.[13,20,30,33] The shortage drugs were carmustine, tocilizumab, probenecid (in conjunction with an antibiotic), and generic valsartan.[13,20,30,33] Lachance et al. (2023) reported that the alternative drug, bendamustine, had worse outcomes in adverse events and ICU admissions and better outcomes in survival and disease progression.[13] Stukas et al. (2022) reported that the decreased dose of tocilizumab had worse outcomes in mortality, but no difference in hospital LOS, ICU LOS, or duration of mechanical ventilation.[20] Landry et al. (2019) reported that using the antibiotic without addition of the shortage drug had no difference in readmissions or adverse events.[33] McAlister and Youngson (2020) reported worse outcomes for ED and outpatient visits, but no difference in hospital admissions.[30] Three studies concluded that the replacement drug or protocol was an acceptable alternative to the shortage drug.[13,20,33] The fourth study concluded that there were no long-term adverse effects because of the shortage.[30]

Table 2: Summary of Included Scoping Review — Phuong et al. (2019)[6]

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
Anesthetics				
Romito B, et al. Hosp Pharm. 2015;50(9):798-805. US	**Study design:** retrospective cohort **Population:** NR **Setting:** surgery	**Drug class:** general anesthetic, systemic **Shortage:** propofol **Replacement:** alternative agents	Mortality	No difference
Price B, et al. Am J Emerg Med. 2013;31(7):1124-32. US	**Study design:** retrospective cohort **Population:** people requiring endotracheal intubation **Setting:** air medical	**Drug class:** general anesthetic, systemic **Shortage:** etomidate **Replacement:** ketamine	Adverse drug reaction	No difference
			Hemodynamics	No difference
Roberts R, et al. Crit Care Med. 2012;40(2):406-11. US	**Study design:** retrospective cohort **Population:** noncardiac patients in the ICU **Setting:** ICU	**Drug class:** general anesthetic, systemic **Shortage:** propofol **Replacement:** alternative anesthetic drugs	Duration of mechanical ventilation	Increased with alternative anesthetic drugs (NSS)
Oncology drugs and adjuncts				
Duan F, et al. Radiology. 2016;278(2):612-21. US	**Study design:** prospective cohort **Population:** people undergoing transcatheter arterial chemoembolization for hepatocellular carcinoma **Setting:** NR	**Drug class:** NR **Shortage:** NR **Replacement:** alternative vehicles of oncology medications	Adverse drug reaction	No difference
Berger JL, et al. Onco Targets Ther. 2014;7:1409-13. US	**Study design:** retrospective cohort **Population:** people with recurrent epithelial ovarian carcinoma **Setting:** NR	**Drug class:** antineoplastic **Shortage:** pegylated liposomal doxorubicin (Doxil) **Replacement:** non–FDA-approved second-generation liposomal doxorubicin	Treatment response	No patients had a complete or partial response with alternative therapy

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
Nickel RS, et al. Pediatr Blood Cancer. 2014;61(5):810-4. US	**Study design:** retrospective cohort **Population:** people with newly diagnosed lymphoblastic leukemia and lymphoma **Setting:** hospital	**Drug class:** antineoplastic **Shortage:** daunorubicin **Replacement:** mitoxantrone	Mortality	No difference
			ICU admission	No difference
			Adverse events: fever, bacteremia, invasive fungal disease	No difference
			Hospital LOS	No difference
Trifilio S, et al. Leuk Res. 2013;37(8):868-71. US	**Study design:** retrospective cohort **Population:** people with acute myeloid leukemia **Setting:** NR	**Drug class:** antineoplastic **Shortage:** daunorubicin **Replacement:** idarubicin	Mortality	No difference
			Adverse drug reaction	No difference
			Complete remission	No difference
Antimicrobials and adjuncts				
McLaughlin MM, et al. Infect Dis Ther. 2017;6(2):259-64. US	**Study design:** retrospective cohort **Population:** NR **Setting:** NR	**Drug class:** antiviral **Shortage:** IV acyclovir **Replacement:** high-dose oral valacyclovir	Adverse drug reaction	40% of patients experienced at least 1 adverse drug reaction to high-dose oral valacyclovir
Dilworth TJ, et al. J Manag Care Pharm. 2014;20(12):1246-54. US	**Study design:** retrospective cohort **Population:** people with HIV *Pneumocystis jirovecii* pneumonia **Setting:** hospital	**Drug class:** sulfonamide **Shortage:** IV trimethoprim-sulfamethoxazole **Replacement:** alternative agents	Mortality	Equal number of deaths in both groups
			Clinical status	Worsened in the shortage group
			Treatment failure	No difference
			Adverse events	No difference

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
			Hospital LOS	No difference
Mendez MN, et al. Pharmacotherapy. 2006;26(1):61-7. US	**Study design:** retrospective cohort **Population:** NR **Setting:** NR	**Drug class:** penicillin; beta-lactamase inhibitor **Shortage:** piperacillin-tazobactam **Replacement:** alternative antimicrobials	Adverse drug reaction	• No difference in vancomycin-resistant enterococci rates • Decrease in *Clostridium difficile* infections with alternative antimicrobials
Other				
Vail E, et al. JAMA. 2017;317(14):1433-42. US	**Study design:** retrospective cohort **Population:** people with septic shock **Setting:** NR	**Drug class:** vasopressor **Shortage:** norepinephrine **Replacement:** alternative vasopressors	Mortality	Increased with alternative vasopressors
Blaine KP, et al. Clin Anesth. 2016;35:516-23. US	**Study design:** retrospective cohort **Population:** people undergoing cardiac surgery **Setting:** surgery	**Drug class:** antifibrinolytic **Shortage:** epsilon-aminocaproic acid **Replacement:** tranexamic acid	Adverse drug reaction	Decreased with tranexamic acid
Cho S, et al. nn Pharmacother. 2016;50(9):718-24. US	**Study design:** retrospective cohort **Population:** people with acute subarachnoid hemorrhage **Setting:** NR	**Drug class:** calcium channel blocker **Shortage:** nimodipine **Replacement:** shortened course of treatment	Mortality	No difference
			Adverse drug reaction	No difference
			Hospital LOS	No difference
			Duration of mechanical ventilation	No difference
			Neurologic outcomes	No difference

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
Malone C, et al. Ulster Med J. 2016;85(3):174-7. UK	**Study design:** prospective cohort **Population:** people undergoing nonemergent caesarean section **Setting:** surgery	**Drug class:** uterotonic **Shortage:** IV oxytocin **Replacement:** Syntometrine	Transfusions, blood loss	No difference
			Adverse drug reaction	Increased intraoperative antiemetics with Syntometrine
Ladha KS, et al. Anesth Analg. 2015;121(2):404-9. US	**Study design:** retrospective cohort **Population:** NR **Setting:** surgery	**Drug class:** vasopressor **Shortage:** pharmacy-prepared ephedrine syringes **Replacement:** alternative vasopressors	Hemodynamics	No difference
Goldblatt J, et al. Blood Cells Mol Dis. 2011;46(1):107-10. Australia	**Study design:** prospective cohort **Population:** people with Gaucher disease **Setting:** NR	**Drug class:** metabolic enzyme **Shortage:** imiglucerase **Replacement:** None	Clinical complications	Most patients had no significant clinical complications

ICU = intensive care unit; LOS = length of stay; NR = not reported; NSS = not statistically significant.

Table 3: Summary of Included Nonrandomized Studies by Clinical Indication

Study citation, location	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
General				
Borneau-Martin et al. (2023),[7] France	**Study design**: registry **Population**: drug shortage–related ADRs reported to a pharmacovigilance database (N = 462) **Setting:** any	**Drug class:** any **Most frequently reported:** nervous system drugs, cardiovascular drugs, anti-infectives for systemic use; replacement drug used in 96% of reported ADR cases	Number of ADR cases related to drug shortages	Increased at a greater rate than total reported ADRs over the study period
			ADRs	84% of cases related to drug shortages
			Serious ADRs: hospitalization, medically significant or life-threatening events, death	46% of cases related to drug shortages
			Death	2% of cases related to drug shortages
			Disease worsening	16% of cases related to drug shortages
			Medication errors	11% of cases related to drug shortages
Anesthetics, analgesics, and sedatives				
John et al. (2022),[17] US	**Study design**: retrospective cohort **Population**: adults receiving mechanical ventilation (N = 100) **Setting:** ICU	**Drug class:** opioid analgesic **Shortage:** IV opioids **Replacement:** oral opioids or alternative nonopioid drugs	Hospital LOS	No difference
			ICU LOS	No difference
			Mortality	No difference
			Duration of mechanical ventilation	No difference

Study citation, location	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
			Pain level	No difference
Katsivalis et al. (2022),[18] US	**Study design**: retrospective cohort **Population**: adults with sickle cell disease (N = 89) **Setting:** hospital	**Drug class:** opioid analgesic **Shortage:** IV opioid medications **Replacement:** oral opioids	Hospital LOS	No difference
			Readmission	Fewer 30-day readmissions during the shortage period
			ED visits	No difference
Rodriguez-Monguio et al. (2022),[19] US	**Study design**: retrospective cohort **Population**: adults with cancer (N = 3,906) **Setting:** surgery	**Drug class:** Opioid analgesic **Shortage:** any opioid analgesic in shortage during the study period **Replacement:** any, including drug substitutions, dose conversions, and alternative administration routes	Adverse event: post-operative hypoxemia	Increased in patients exposed to opioid shortages (NSS)
			Adverse event: post-operative hypoxemia reversed by IV naloxone	Increased in patients exposed to opioid shortages (NSS)
Cole et al. (2021),[10] US	**Study design**: prospective cohort **Population**: patients with acute agitation (N = 1,257) **Setting:** ED	**Drug class:** antipsychotic **Shortage:** droperidol; olanzapine **Replacement:** droperidol; olanzapine	ED LOS	Longer ED LOS in the olanzapine group
			Adverse event: extrapyramidal	Extrapyramidal adverse events were more common with droperidol
			Adverse events: cardiovascular, respiratory, intubation	No difference

Study citation, location	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
Farrell et al. (2020),[26] US	**Study design**: retrospective cohort **Population**: adults requiring rapid sequence intubation (N = 82) **Setting:** ED	**Drug class:** general anesthetic, systemic **Shortage:** etomidate **Replacement:** ketamine; methohexital	Complications: dental trauma, airway trauma, esophageal intubation, new onset seizures	No occurrences in either group
			Complications: aspiration	Two aspirations occurred in the etomidate group
Nelson et al. (2019),[34] US	**Study design**: retrospective cohort **Population**: adults with acute alcohol withdrawal syndrome (N = 300) **Setting:** ED	**Drug class:** benzodiazepine **Shortage:** IV diazepam; IV lorazepam **Replacement:** IV lorazepam with IV phenobarbital; IV phenobarbital alone	ICU admission	No difference
			Overall admission	• Increased admission rates with phenobarbital only compared to diazepam • No difference between the other groups
			LOS, total	LOS was shortest with lorazepam + phenobarbital compared to diazepam and phenobarbital only
			LOS, ED	ED LOS was shortest with diazepam compared to lorazepam + phenobarbital and phenobarbital only
			LOS, floor and ICU	No difference
			Intubation	No difference
Neff et al. (2018),[37] US	**Study design**: retrospective cohort **Population**: adults undergoing general	**Drug class:** general anesthetic, systemic **Shortage:** propofol	Postoperative nausea and vomiting	Greater incidence of postoperative nausea and vomiting during the propofol shortage period

Study citation, location	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
	anesthesia (N = 2,090) **Setting:** surgery	**Replacement:** inhaled volatile drugs		
			PACU LOS	Longer duration of stay in the PACU during the propofol shortage period
			Readmit to ED	No difference
Oncology drugs and adjuncts				
Lachance et al. (2023),[13] Canada	**Study design**: retrospective cohort **Population**: patients undergoing autologous stem cell transplant for relapsed-refractory lymphoma (N = 227) **Setting:** hospital	**Drug class:** antineoplastic **Shortage:** carmustine **Replacement:** bendamustine	Febrile neutropenia	No difference
			Mucositis	Increased development of grade ≥ 3 mucositis with bendamustine
			Toxicity: cardiac, pulmonary, liver	No difference
			Toxicity: renal	Increased with bendamustine
			ICU admission	Increased with bendamustine
			Transfusion	• Increased need for platelet transfusion with bendamustine • Decreased need for red blood cell transfusion with bendamustine
			Hospital LOS	Increased with bendamustine
			Mortality	• No early treatment-related deaths associated with bendamustine • Better overall survival with bendamustine

Study citation, location	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
			Disease progression	Better progression-free survival with bendamustine
Strobbe et al. (2023),[14] France	**Study design**: retrospective cohort **Population**: patients receiving paclitaxel-based chemotherapy (N = 831) **Setting:** outpatient	**Drug class:** H2A **Shortage:** ranitidine; famotidine **Replacement:** alternative H2A (famotidine); no H2A (H1A, corticosteroid, or combined H1A and corticosteroid)	Hypersensitivity reactions	No difference
Li and Cimino (2020),[28] US	**Study design**: retrospective cohort **Population**: patients receiving chemotherapy (N = 22) **Setting:** outpatient	**Drug class:** antineoplastic **Shortage:** etoposide injection **Replacement:** alternative therapy (e.g., oral etopisode or etopophos injection)	Adverse drug events	No difference
			Disease progression	No difference
			Medication errors	None recorded
Roy et al. (2019),[35] US	**Study design**: retrospective cohort **Population**: adults receiving HDTMX as inpatients (N = 18) **Setting:** hospital	**Drug class:** alkalinizing drugs **Shortage:** IV sodium bicarbonate and IV sodium acetate **Replacement:** oral sodium bicarbonate with oral or IV acetazolamide as needed	Hospital LOS	No difference
			Adverse events: acute kidney injury, hepatotoxicity, myelosuppression	No difference
			Adverse events: pneumonitis, mucositis, rash	No occurrences in either group
Visage et al. (2019),[36] US	**Study design**: retrospective cohort, uncontrolled **Population**: pediatric patients	**Drug class:** alkalinizing drug **Shortage:** IV sodium bicarbonate	GI side effects	The incidence of GI side effects was not drastically impacted by use of an oral alkalinizing drug

Study citation, location	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
	receiving HDTMX (N = 102) (HDTMX cycles) **Setting:** hospital	**Replacement:** oral sodium bicarbonate and oral sodium citrate-citric acid		
Vaccines				
Miyazato et al. (2023),[8] Japan	**Study design**: prospective cohort, uncontrolled **Population**: people at risk of yellow fever (N = 1,1279) **Setting:** community	**Drug Class:** live vaccine, viral **Shortage:** YF-Vax **Replacement:** alternative 17D-204 yellow fever vaccine (Stamaril)	Adverse events	The alternative vaccination was shown to be generally safe
			Serious adverse events	Three participants developed serious adverse events that may have been related to vaccination
Rojas et al. (2023),[9] US	**Study design**: prospective cohort, uncontrolled **Population**: people at high risk of yellow fever (N = 627,079) **Setting:** community	**Drug class:** live vaccine, viral **Shortage:** YF-Vax **Replacement:** Stamaril	Adverse events	No safety issues were identified
			Serious adverse events	Serious adverse events were very rare and consistent with the known safety profile
Wong et al. (2020),[12] Australia	**Study design**: prospective cohort, uncontrolled **Population**: children (N = 6,779) **Setting:** community	**Drug class:** live vaccine, bacterial **Shortage:** Sanofi-Pasteur BCG strain **Replacement:** BCG-10 (derived from the Moreau strain)	Adverse events following immunization	BCG-10 had a similar safety profile to that reported for other BCG strains
Nzolo et al. (2018),[38] DRC	**Study design**: retrospective cohort, uncontrolled **Population**: people receiving preventative fractional dose yellow	**Drug class:** live vaccine, viral **Shortage:** 17DD yellow fever vaccine, full dose	Adverse events following immunization	Fractional dose vaccination had an acceptable safety profile

Study citation, location	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
	fever vaccination during an outbreak (N = 7,466,998) **Setting:** community	**Replacement:** 17DD yellow fever vaccine, fractional dose		
			Serious adverse events following immunization	Serious adverse events were reported by 5 individuals
Antimicrobials and adjuncts				
Haiduc et al. (2021),[22] US	**Study design**: retrospective cohort **Population**: adults in hospital with febrile neutropenia (N = 150) **Setting:** hospital	**Drug class:** cephalosporin **Shortage:** cefepime **Replacement:** cefepime (dose sparing)	Hospital LOS	No difference
			Mortality, all-cause, infection-related	No difference
Patel et al. (2020),[31] US	**Study design**: retrospective cohort **Population**: neonates (N = 101) **Setting:** neonatal ICU	**Drug class:** cephalosporin **Shortage:** cefotaxime **Replacement:** ceftazidime	Culture positive late-onset sepsis	Increased with the use of ceftazidime (NSS)
			Multidrug-resistant organism infection	Increased with the use of ceftazidime (NSS)
			Stage II to III necrotizing enterocolitis	Increased with the use of ceftazidime
			Urinary tract infection	No difference
			Mortality	No difference
			Hospital LOS	No difference
			Adverse events	No occurrences in either group
Landry et al. (2019),[33] Canada	**Study design**: retrospective cohort **Population**: adults with uncomplicated cellulitis requiring IV therapy (N = 203) **Setting:** ED	**Drug class:** uricosuric drug **Shortage:** probenecid (in combination with IV cefazolin) **Replacement:** IV cefazolin only, continuous infusion	Recurrence (admission or ED visit for cellulitis within 30 days of treatment end)	No difference

Study citation, location	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
			Adverse events: rash, nausea	No difference
COVID-19				
Swets et al. (2023),[39] the Netherlands	**Study design**: retrospective cohort **Population**: adults hospitalized for COVID-19 (N = 5,485) **Setting:** hospital	**Drug class:** monoclonal antibody (interleukin-6 inhibitor) **Shortage:** tocilizumab (IV) **Replacement:** tocilizumab (fixed dose and low dose); sarilumab	Mortality	• Lower survival with fixed-dose tocilizumab and sarilumab • No difference in survival with low-dose tocilizumab
			Hospital LOS	• Shorter LOS with low-dose tocilizumab and sarilumab • No difference in LOS with fixed-dose tocilizumab
			ICU admission or mortality	Higher ICU admissions or death with fixed-dose tocilizumab, low-dose tocilizumab, and sarilumab
Stukas et al. (2022),[20] Canada	**Study design**: retrospective cohort **Population**: adults with a diagnosis of pneumonia secondary to SARS-CoV-2 infection (N = 153) **Setting:** ICU	**Drug class:** monoclonal antibody (interleukin-6 inhibitor) **Shortage:** tocilizumab (IV), weight-based dose **Replacement:** tocilizumab (IV), fixed dose	Duration of mechanical ventilation	No difference
			ICU LOS	No difference
			Hospital LOS	No difference
			Mortality	Higher mortality in the fixed-dose group (NSS)
Lecronier et al. (2020),[27] France	**Study design**: retrospective cohort **Population**: patients with severe SARS-CoV-2 pneumonia (N = 80) **Setting:** ICU	**Drug class:** protease inhibitor **Shortage:** lopinavir-ritonavir **Replacement:** hydroxychloroquinine	Treatment escalation: intubation, ECMO, RRT	No difference
			Mortality	No difference

Study citation, location	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
			Safety and tolerance outcomes: neutropenia, anemia, thrombocytopenia, increased ASP and ALT, acute renal failure, prolonged QT interval	No difference
Other				
Dannemiller et al. (2022),[16] US	**Study design**: retrospective cohort **Population**: adults undergoing cardiac surgery (N = 1,544) **Setting:** surgery	**Drug class:** antifibrinolytic drug **Shortage:** epsilon-aminocaproic acid **Replacement:** tranexamic acid	Safety events: mortality, cardiovascular, renal, seizure	No difference
Freeman et al. (2021),[21] US	**Study design**: retrospective cohort **Population**: adults who qualified for general or continuous renal replacement therapy electrolyte replacement protocol (N = 288) **Setting:** ICU	**Drug class:** electrolytes **Shortage:** IV electrolyte replacement products **Replacement:** enteral electrolyte replacement	ICU LOS	No difference
			Mortality	No difference
			Duration of mechanical ventilation	Decreased in the shortage period group
Neto et al. (2021),[23] Brazil	**Study design**: retrospective cohort, uncontrolled **Population**: patients with atypical hemolytic uremic syndrome (N = 24) **Setting:** dialysis clinic	**Drug class:** monoclonal antibody **Shortage:** eculizumab **Replacement:** None	Disease relapse	Increased after unplanned eculizumab interruption
McAlister and Youngson (2020),[30] Canada	**Study design**: retrospective cohort, uncontrolled **Population**: adults dispensed any of the recalled valsartan products	**Drug class:** angiotensin receptor blocker **Shortage:** generic valsartan **Replacement:** alternative angiotensin receptor blocker; brand name valsartan	Outpatient visits	Increased immediately after generic valsartan recall

Study citation, location	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
	(N = 34,726) **Setting:** community			
			ED visits	Increased immediately after generic valsartan recall (older patients only)
			ED visits, hospitalizations for stroke or TIA	No difference
van Langenberg et al. (2020),[11] Australia	**Study design**: prospective cohort **Population**: people with mild to moderate ulcerative colitis (N = 31) **Setting:** outpatient	**Drug class:** 5-ASA **Shortage:** balsalazide **Replacement:** alternative 5-ASA formulations (e.g., multimatrix mesalazine)	Clinical activity	Higher than expected proportion of patients with worsening disease with alternative 5-ASA
			Adverse events	Higher than expected proportion of patients with significant side effects with alternative 5-ASA
			Remission	No difference
			Treatment escalation	No difference
			Mortality	No difference
			Flares requiring hospitalization	Increased with alternative 5-ASA
Yang et al. (2020),[32] US	**Study design**: retrospective cohort **Population**: adult patients with hyperkalemia receiving IV insulin (N = 134) **Setting:** ED	**Drug class:** glucose-elevating drug **Shortage:** dextrose 50% **Replacement:** dextrose 10%	Symptomatic hypoglycemia	Lower incidence in the dextrose 10% group (NSS)
			Adverse events, including extravasation	No occurrences in either group

Study citation, location	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
Non-drug				
Acadamia et al. (2022),[15] US	**Study design**: retrospective cohort **Population**: adults (N = 696) **Setting:** ED	**Drug class:** small-volume parenteral solutions **Shortage:** IV piggyback administration of penicillins and carbapenems **Replacement:** IV push administration of penicillins and carbapenems	Drug-related adverse events	No difference
			Mortality	No difference
Tschumper et al. (2021),[24] US	**Study design**: retrospective cohort **Population**: adults (N = 90) **Setting:** hospital	**Drug class:** small-volume parenteral solutions **Shortage:** prolonged infusion (4 hour) of piperacillin-tazaobactam **Replacement:** continuous infusion of piperacillin-tazobactam	Hospital LOS	No difference
			Mortality	No difference
			Safety: thrombocytopenia	Higher incidence with continuous infusion (NSS)
			Safety: *Clostridioides difficile* infection, acute renal failure	No difference
			Safety: seizure	No occurrences in either group
			Readmission	Fewer readmissions with continuous infusion (NSS)
Blair and Covington (2020),[25] US	**Study design**: retrospective cohort, uncontrolled **Population**: adults (N = 120) **Setting:** hospital	**Drug class:** small-volume parenteral solutions **Shortage:** 4-hour extended infusion of piperacillin--	Acute kidney injury	Incidence with continuous infusion similar to previously reported results with extended infusion

Study citation, location	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
		tazobactam **Replacement:** continuous infusion of piperacillin-tazobactam		
Marsh et al. (2020),[29] US	**Study design**: retrospective cohort, uncontrolled **Population**: adults (N = 1,000) **Setting:** hospital	**Drug class:** small-volume parenteral solutions **Shortage:** IV piggyback administration of beta-lactam antibiotics **Replacement:** IV push administration of beta-lactam antibiotics	Adverse events	Safety of IV push administration similar to previously reported results with IV piggyback administration

5-ASA = 5-aminosalicylate; ADR = adverse drug reaction; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCG = Bacillus Calmette-Guérin; DRC = Democratic Republic of the Congo; ECMO = extracorporeal membrane oxygenation; ED = emergency department; GI = gastrointestinal; H1A = histamine-1 antagonist; H2A = histamine-2 antagonists; HDTMX = high-dose methotrexate; ICU = intensive care unit; LOS = length of stay; NSS = not statistically significant; PACU = post-anesthetic care unit; RRT = renal replacement therapy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TIA = transient ischemic attack.

Conclusions

The development of a preventive approach could possibly help mitigate the impacts of drug shortages. To achieve this, first, drugs that are potentially the highest impact need to be identified. Anticipating which drugs are likely to be most impactful during a shortage involves identifying those most at risk of supply chain disruptions and those most likely to cause patient harm. Ranking drugs based on their risk of shortage and their risk of harm during a shortage can help decision-makers put into place pre-emptive strategies. This report supports this objective by summarizing types of harms that may occur during drug shortages, and, although not the primary intent of this report, by identifying the types of drugs experiencing shortages studied in the literature. Most of the published trials examined the effectiveness and safety of alternative drugs during drug shortages. The harms outcomes that were most frequently reported were adverse events or safety-related outcomes and health system use, including length of stay, mortality, and disease progression. Similarly, a French registry study described the types of adverse drug reactions related to drug shortages as reported to a pharmacovigilance database.[7] The authors described harms from adverse drug reactions; serious adverse drug reactions, including hospitalization, life-threatening events, or death; and disease progression.[7] The primary studies that concluded that the examined drug shortage had negative consequences reported health system use, adverse events, disease progression, and mortality as harms outcomes.[11,19,23,31,37,39]

This report summarizes the available evidence on the effect of drug shortages on patient outcomes and will be used in combination with other CADTH work to support future decision-making regarding drug shortages, including:

- an environmental scan of existing clinical tools or scoring systems available for drug shortage or supply chain disruptions
- facilitation of a Delphi panel to support the identification of high-priority drugs based on their supply chain risk and clinical risk.

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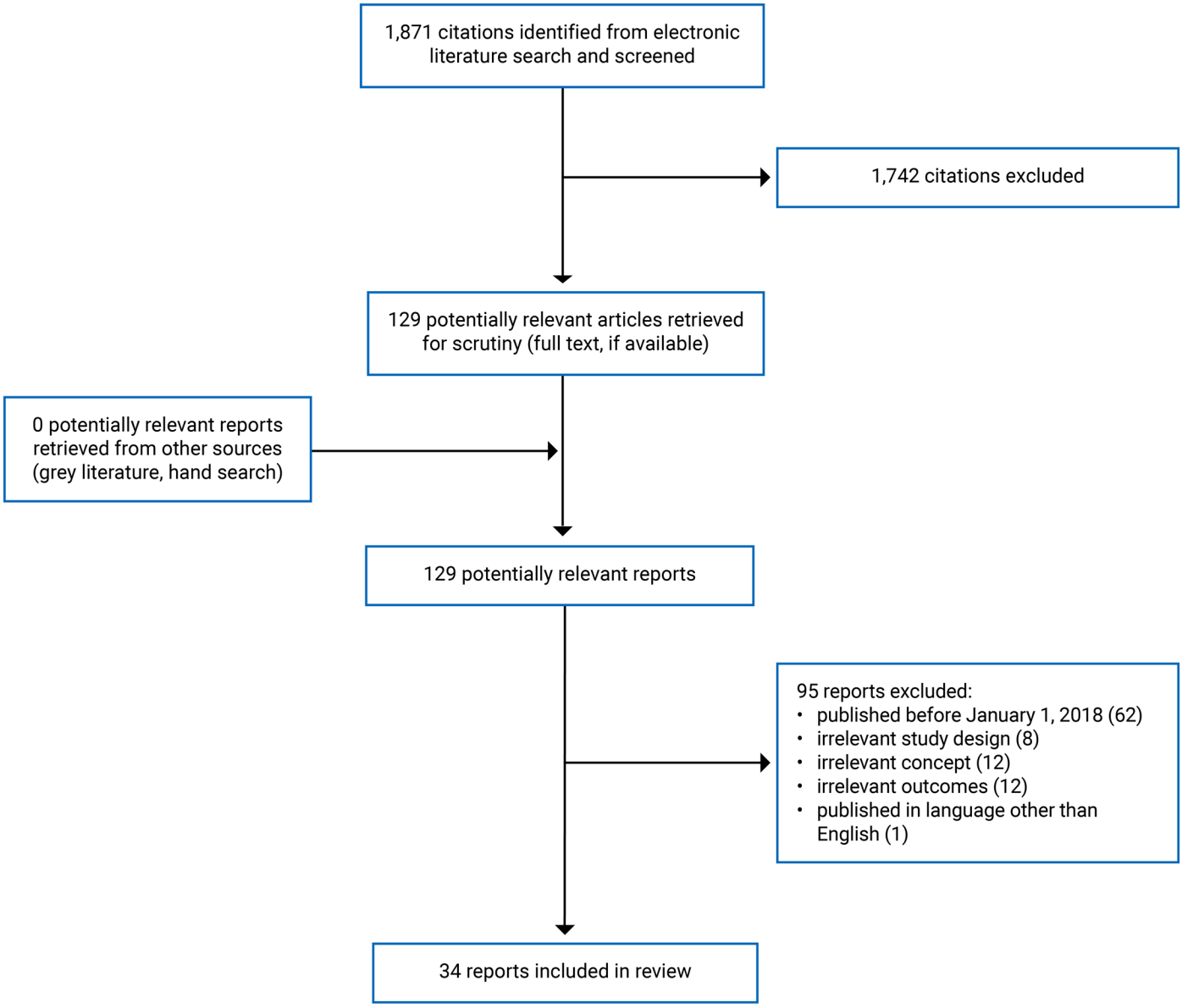
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: References of Potential Interest

Scoping Reviews

Unclear Outcomes

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Not Direct Patient Harm Outcomes

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