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Health Policy Analysis

Do Reimbursement Recommendations by the Canadian Agency for Drugs and Technology in Health Translate Into Coverage Decisions for Orphan Drugs in the Canadian Province of Ontario?

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ABSTRACT

Objectives: Unlike other high-income countries, Canada has no national policy for drugs treating rare diseases (orphan drugs). Nevertheless, in 2022, the Canadian government committed to creating a national strategy to make access to these drugs more consistent. Our aim was to study whether recommendations made by the Canadian Agency for Drugs and Technology in Health (CADTH) translated into coverage decisions for orphan drugs in Ontario, the largest Canadian province. This study is the first to look at this question for orphan drugs, which are at the center of policy attention.

Methods: We included 155 orphan drug-indication pairs approved and marketed in Canada between October 2002 and April 2022. Cohen's kappa was used to test the agreement across health technology assessment (HTA) recommendations and coverage decisions in Ontario. Logistic regression was used to test which factors, relevant to decision-makers, might be associated with funding in Ontario.

Results: We found only fair agreement between CADTH's recommendations and coverage decisions in Ontario. Although a positive and statistically significant association between favorable HTA recommendations and coverage was found, more than half of the drugs with a negative HTA recommendation were available in Ontario, predominately through specialized funds. Successful pan-Canadian pricing negotiations were a strong predictor of coverage in Ontario.

Conclusions: Despite efforts to harmonize access to drugs across Canada, considerable room for improvement remains. Introducing a national strategy for orphan drugs could help increase transparency, consistency, promote collaborations, and make access to orphan drugs a national priority.

Keywords: Canada, funding, health technology assessment, orphan drugs, rare diseases.

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Introduction

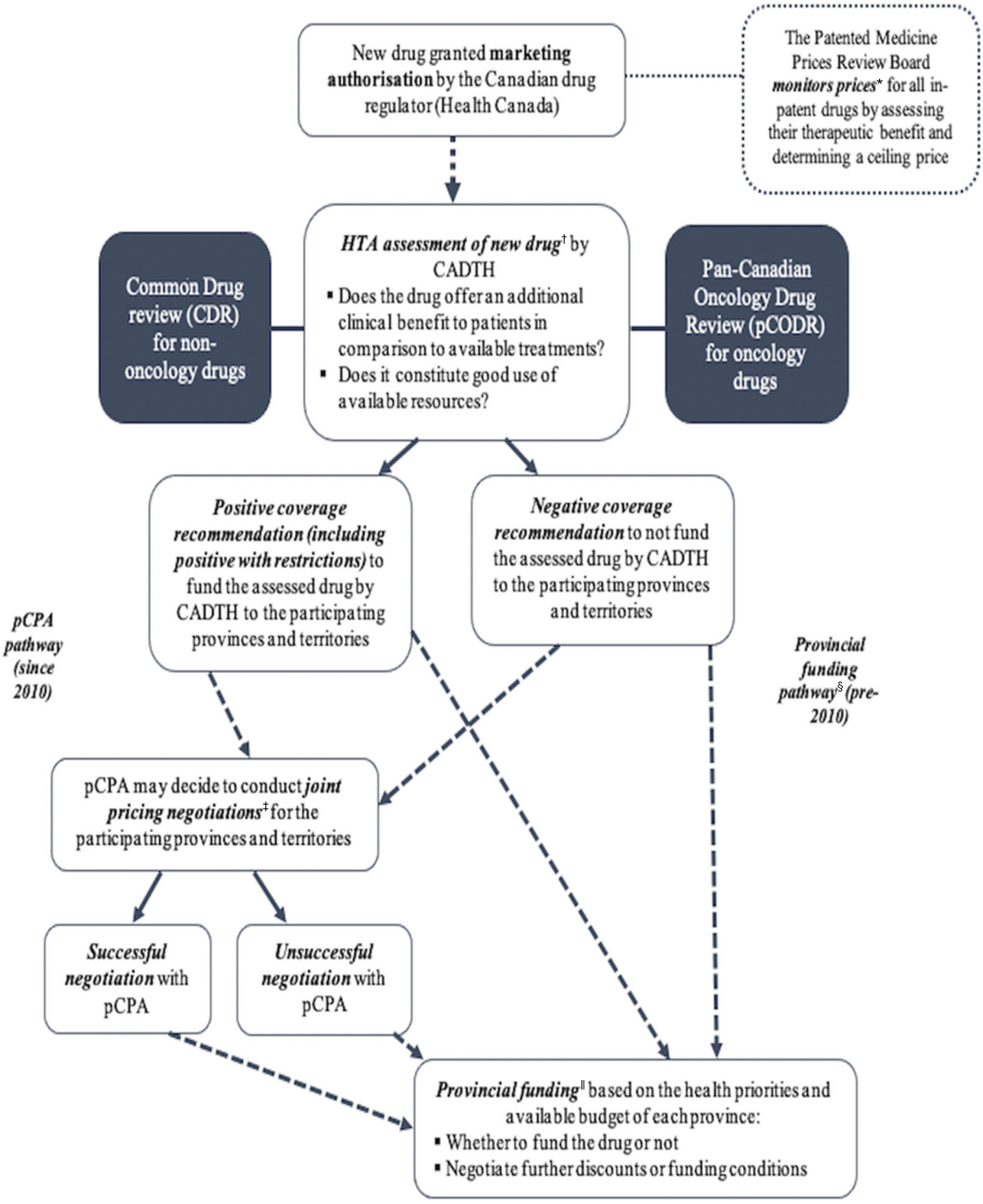
Allocating resources in the context of limited budgets is one of the biggest challenges facing healthcare systems globally. Increases in pharmaceutical prices and the associated expenditure further strain finite budgets, leaving decision-makers with tough coverage decisions.[1] In Canada, pharmaceutical expenditure has increased by approximately CAD1 billion annually over the last decade.[2] To optimize drug expenditure, health technology assessment (HTA) is conducted through Canada's Drug and Health Technology Agency (CADTH). Since the early 2000s,[3] CADTH has assessed newly approved drugs and provided coverage recommendations to the Canadian provinces and territories (apart from Quebec, which has its own HTA body). Nevertheless, funding decisions remain a provincial competency.

There have been both national and provincial efforts to harmonize access to drugs across Canada: in August 2010, the pan-Canadian Pharmaceutical Alliance (pCPA) was established to perform joint pricing negotiations with manufacturers on behalf of participating provinces/territories, aiming to achieve a single drug price across Canada.[4,5] In 2016, a collaboration between CADTH and the pCPA was initiated to formally engage the pCPA during CADTH's assessments and ensure timely information exchange.[6] Since April 2016, drugs assessed by CADTH are no longer required to undergo routine review by the Committee to Evaluate Drugs (CED) of the Ontario Ministry of Health.[7,8]

Figure 1[4,5,9-17] summarizes the pricing and reimbursement process for new drugs in Canada (excluding Quebec).

Evidence has shown that the degree of alignment between CADTH's recommendations and coverage decisions varied across provinces and was dependent on whether HTA recommendations were positive (ie, listed [L] and listed with restrictions [LwR]) or negative (ie, do not list [DNL]).[18-22] In Ontario, more than 90% of new drugs assessed by CADTH between 2009 and 2015 with positive recommendations were funded, whereas half of the drugs with negative recommendations still received funding.[13,18,19]

Figure 1. Pricing and reimbursement process for new drugs in Canada (except for Quebec). Note. Dotted arrows indicate processes that might occur, but it is either at the discretion of the competent authority or do not necessarily occur on a routine basis.



*The Patented Medicine Prices Review Board monitors prices of in-patent drugs upon entry in the Canadian market and on an ongoing basis. †CADTH assesses new drugs including drugs with a new indication, new combination products, new drug formulations, and subsequent-entry of non-biological complex drugs.[9] Not all drugs approved by Health Canada undergo assessment by CADTH. Assessment is initiated upon request of manufacturers or of drug programs. ‡Not all drugs reviewed by CADTH may undergo negotiations through the pCPA. After the publication of a recommendation by CADTH (either positive or negative),[10] the pCPA can decide whether to initiate a negotiation or not. Since 2015, Quebec is also participating in joint pricing negotiations by the pCPA. §Given that not all drugs will undergo negotiations through the pCPA, and it is at the discretion of the provinces/territories to participate or not in joint negotiations, provinces have the option to negotiate individually rather than jointly, after issue of the HTA recommendation. Before the establishment of the pCPA, in 2010, this was the pathway followed. ‖Provinces are not mandated to follow the outcome of the pCPA negotiation or CADTH's recommendation. Funding remains a provincial competency.[4,5,11] Source: Adapted from the literature.[4,11,13-17] CADTH indicates Canada's Drug and Health Technology Agency; HTA, health technology assessment; pCPA, pan-Canadian Pharmaceutical Alliance.

Nevertheless, in British Columbia, fewer than the half of drugs with negative recommendations received funding.[19]

The Case of Orphan Drugs

Access variations are further highlighted in the case of orphan drugs. These drugs treat rare diseases[11] and usually carry high price tags despite their associated high clinical uncertainty.[23,24] Therefore, in HTA terms, these drugs are generally cost-ineffective.[23,25,26]

Contrary to other healthcare systems,[26] Canadian national authorities do not treat orphan drugs differently than non-orphan drugs: the Canadian drug regulator, Health Canada, does not offer orphan designation at marketing authorization (MA), CADTH does not implement a specialized value assessment framework, and the pCPA does not apply special criteria during pricing negotiations. Nevertheless, specialized funds for drugs of high unmet need and cost are available in the Canadian provinces.

Subgroup analyses on orphan drugs conducted by existing studies[13,18,27] showed larger variability in the agreement between CADTH's recommendations and provincial funding than the variability seen on non-orphan drugs. Other studies[5,11] showed that positive HTA recommendations did not necessarily translate to successful pricing negotiations for non-oncology orphan drugs or guarantee that provinces funded these drugs.

National Strategy for Drugs for Rare Diseases in Canada

The reasons why Canada has so far failed to implement a national orphan drug strategy remain unclear. One contributing factor might be the presence of the Special Access Programme which allows patient access to non-approved drugs through clinical studies.[1,28] In addition, Canada's close proximity to the United States (where there is an orphan drug regulation) might allow Canada to indirectly benefit from the increased research and development stimulus for orphan drugs seen in the United States.[1]

Currently, the Canadian government is trying to establish a national strategy for orphan drugs.[29] The strategy aims to address the following questions: (1) how to improve access to these treatments and make access more consistent, (2) how to ensure that funding decisions are informed by the best available evidence, and (3) how to ensure that spending on orphan drugs does not threaten the sustainability of the healthcare system?[29-31] Although funding for its materialization has been secured,[32] the national strategy remains in a developmental stage and the exact activities have not been outlined yet. Nevertheless, key Canadian stakeholders have suggested some potential options that could be part of the national strategy. For example, they have called for a national framework for coverage decision-making, which will entail a single approach and common principles for deciding which orphan drugs should be publicly covered and under what conditions (ie, identifying patient populations that would be more likely to benefit from them[29]). In addition, stakeholders have suggested the establishment of a coordinating body that would improve communication and collaboration across all key Canadian stakeholders and would provide a better evidence-base for decision-making through both consistent evidence collection (including infrastructure for collection of real-world evidence) and evaluation of a drug's added clinical benefit.[29,30,33] Finally, Canadian stakeholders have called for the explicit involvement of patients and clinicians in the decision-making process.[30,31]

Given the continuous efforts to harmonize access across Canada, to our knowledge, our study is the first to explore whether CADTH's recommendations for orphan drugs translate into coverage decisions in Ontario, the most populous Canadian province. Unlike existing evidence that comes either from subgroup analyses or from studies with small sample sizes or of limited timeframes,[5,13,19] we used a large sample of orphan drugs approved and marketed in Canada between October 2002 and April 2022. Finally, to test what other factors might be associated with funding in Ontario, we performed a logistic regression analysis.

Methods

Sample Selection

Given that Canada does not have an orphan designation or an official definition of rare diseases (with the recent exception of Quebec[34]), we recognize that selecting a sample of orphan drugs in Canada comes with inherent limitations. To ensure that an appropriate sample of orphan drugs has been selected insofar possible, we used both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to account for differences in the jurisdictional definitions of rare diseases.[35] Although more commonality between Canada and the United States may have been expected, both Health Canada and the Canadian Organization for Rare Disorders[29,36] unofficially use EMA's definition of rare disease (ie, a disease that affects < 5 in 10 000 people[37]) rather than the FDA definition (ie, a rare disease affects $< 200\,000$ people of the general population[38]).

The sample selection process followed is similar to that of an earlier study[25] with adjustments based on this study's objectives. First, we identified all orphan drugs approved by the US FDA between January 2000 and December 2021 through the FDA Orphan Drug Product designation database, including first indication(s) at MA and extension of indication(s) with an orphan designation.

Second, we checked whether the set of FDA-approved orphan drug indications were granted an orphan designation by the EMA using the full list of the EMA's orphan designations and additional searches on the EMA website. Because Canada unofficially uses the EMA's definition of rare diseases,[29,36] we excluded drug-indication pairs with no orphan designation in Europe. Nevertheless, orphan drug-indication pairs which were not approved by the EMA (but had been granted an orphan designation) were included in our sample to not limit the sample size: evidence has shown that more orphan drugs were granted MA by the FDA than the EMA.[39] Drug-indication pairs with a withdrawn or expired orphan designation in Europe were also included to not limit the sample size.

Third, we checked whether the matched drug-indication pairs were marketed in Canada (ie, were granted MA and were commercially launched according to the Health Canada's Drug Product Database). Drug-indication pairs with no MA by Health Canada, drugs with a different approved indication than that of the FDA and that granted an orphan designation by the EMA, and drug-indication pairs which were not marketed in Canada (or were subsequently withdrawn from the market) were excluded.

Finally, the drug-indication pairs that did not have a reimbursement review by CADTH, or for which there was no manufacturer dossier submission before June 2022 (when the data collection was completed), were excluded.

Data Collection and Study Variables

MA: information on whether the drug-indication pairs had been granted standard MA or conditional MA and/or had undergone priority review at the time of approval was recorded through the Notice of Compliance-Drug Products database of Health Canada. Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.013 provides a detailed description of the 2 specialized pathways for MA.

HTA: information on HTA recommendations, the main reasons for recommendation, the reported incremental cost-effectiveness ratio (ICER), the annual costs per patient, the date of HTA assessment, whether there has been an HTA re-submission, and whether the drug-indication treated patients younger than 18 years old (ie, pediatric patients) was collected through the reimbursement reviews of CADTH for the most recent assessments (in cases of re-submissions).

Recommendations were categorized into the following: "list" [L], "list with restrictions" [LwR], and "do not list" [DNL]. LwR recommendations were divided by clinical and economic restrictions and further subgroups, following the classification used in an earlier study[25] and by CADTH.[9] Recommendations issued by both the Common Drug Review (CDR) and the pan-Canadian Oncology Drug Review (pCODR) have changed over time,[13] while CADTH harmonized all recommendations and procedures in 2020.[9] The main reasons for HTA recommendations were categorized following the classification used in an earlier study.[25] Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.013 provides information on how the recommendations issued by CDR and pCODR have evolved, and illustrates examples of the restrictions and main reasons for recommendation provided by CADTH.

For the logistic regression and the kappa analyses, HTA recommendations were grouped into the following: (1) positive HTA recommendation (including L and LwR) and (2) negative HTA recommendation (DNL). The reported ICERs were grouped following the categorization used in another study.[40]

Pricing negotiations: the outcomes of pricing negotiations were extracted by the Brand Name Drug Negotiations Status database of the pCPA. Pricing negotiations were categorized as follows: (1) "successful negotiations" (ie, resulting in a letter of intent), (2) "unsuccessful negotiations" (ie, when an agreement was not reached or when a negotiation was not pursued), and (3) no information available (ie, when a drug-indication pair was not found in the database [n = 21] or when negotiations were active or under consideration at the time of data collection [n = 13]). The negotiation status was recorded for the most recent negotiation (in cases of re-negotiations). For the logistic regression and the kappa analyses, negotiations with no information were recorded as "unsuccessful" because their outcomes were unknown.

Coverage: information on funding status in Ontario was extracted from the general formulary database of the Ontario Drug Benefit Formulary/Comparative Drug Index, the drug formulary of the Cancer Care Ontario, the Ontario Drug Benefit Program, the Exceptional Access Program Reimbursement, the List of Disorders, Covered Drugs, and Supplements and Specialty Foods of the Inherited Metabolic Diseases Program. Additional searches were performed on the Ministry of Health of Ontario and the Ontario Public Drug Programs webpages.

Coverage decisions were grouped into (1) "funded" and (2) "not funded". For funded drug-indication pairs, we recorded whether the drug-indication pairs were available through a specialized fund(s). Drug-indication pairs suggested for limited use in the Ontario Drug Benefit Formulary were considered as "funded" (n = 1).

Additional study variables: the second level Anatomical Therapeutic Chemical code was extracted using the Anatomical Therapeutic Chemical code/Defined Daily Dose Index 2020 of the World Health Organization Collaborating Centre to identify cancer and non-cancer indications and availability of therapeutic alternatives within our sample. We recorded whether a recall or safety alert has been issued using the Recalls and Safety Alerts database of Health Canada. To identify drug-indication pairs designed to treat ultra-orphan diseases (prevalence of 1 in 50 000 or 2 in 100 000[41-43]), we used the Prevalence and Incidence of Rare Diseases data from Orphanet.[44] Finally, we recorded first-in-class drug-indication pairs (ie, the first drug approved within a therapeutic class or a drug using new mechanisms of action[45,46]) using the FDA's Novel Drug Approvals reports and a previous study.[46]

Statistical Analysis

Descriptive statistics were used to analyze trends in HTA recommendations, outcomes of pricing negotiations, and coverage decisions in Ontario.

Cohen's kappa scores were used to test the level of agreement between (1) HTA recommendations and coverage decisions in Ontario, (2) HTA recommendations and outcomes of pricing negotiations, and (3) outcomes of pricing negotiations and coverage decisions in Ontario. Results were interpreted following the Landis and Koch[47] benchmark scale.

We performed a binary logistic regression analysis to test the relationship between coverage decisions in Ontario (dependent variable) and various covariates relevant to decision-makers.[40] These included the following: (1) HTA recommendation; (2) whether the drug-indication pairs had a conditional MA or (3) had undergone priority review, given that these drugs are responding to high unmet need and therefore, are likely to be prioritized for coverage; (4) whether the drug-indication pairs were first-in-class, as a proxy for market competition; (5) whether there has been a recall or safety alert given that this might trigger de-listing (nevertheless, evidence from 2015 showed that serious safety alerts did not have an impact on funding status in Ontario[48]); (6) whether the drug-indication pairs had a cancer indication because cancer drugs are assessed by a different committee (pCODR) within CADTH; (7) whether the drug-indication pairs were used to treat paediatric patients; (8) whether they are considered ultra-orphan because decision-makers might show greater flexibility; (9) whether there has been an HTA re-submission, which is usually triggered when additional evidence has been generated to revert previously negative recommendations; (10) whether pricing negotiations by the pCPA were successful or not; and (11) the ICER reported by CADTH because funding of orphan drugs can be sensitive to the drug's cost-effectiveness.[40] To account for other factors that might influence our dependent variable we controlled for the year of the HTA recommendation and the year of MA as changes in the assessment processes or administrative changes might have occurred over time.

Finally, to test the robustness of our results, we performed a sensitivity analysis exploring the impact of therapeutic alternatives within our sample and the annual drug costs per patient on funding in Ontario. A description of how we estimated annual drug costs, when unavailable by CADTH, is presented in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.013.

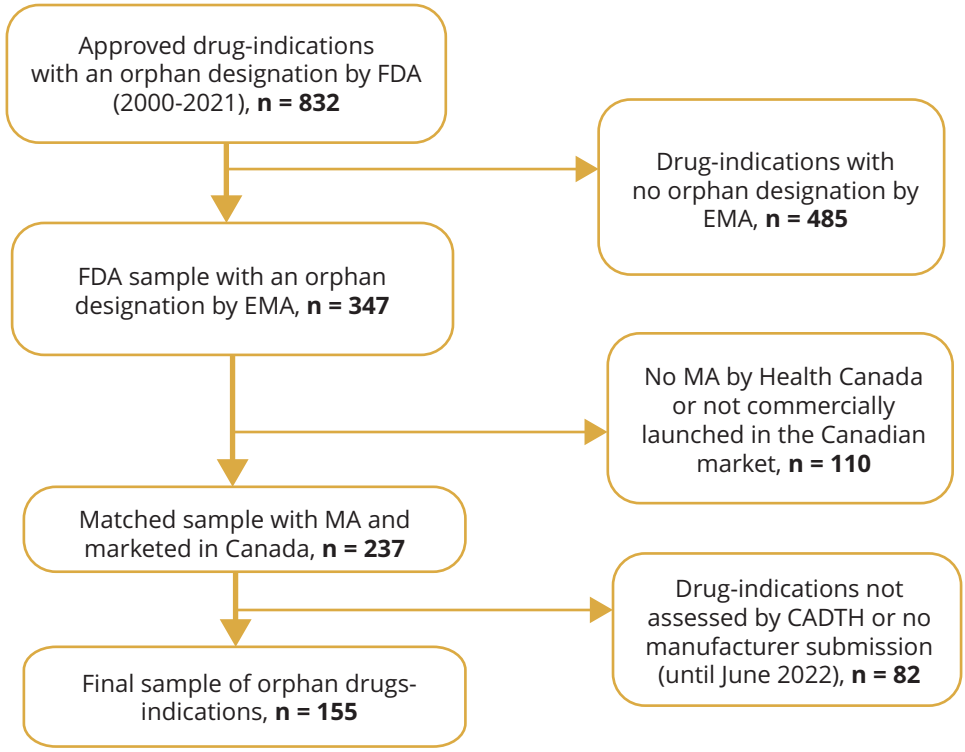
Chi-square and Fisher's exact tests were used to test statistical significance with a P value of $\leq .05$ indicating statistical significance. All data analysis was performed using STATA SE version 17 (StataCorp LLC).

Results

A total of 155 drug-indication pairs were included in our sample. Figure 2 outlines the results of the sample selection process.

Table 1 summarizes the sample characteristics and the results of HTA recommendations, outcomes of pricing negotiations, and coverage decisions in Ontario across our sample. Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2

Figure 2. Flow chart of sample selection.



CADTH indicates Canada's Drug and Health Technology Agency; EMA, European Medicines Agency; FDA, US Food and Drug Administration; MA, marketing authorization.

023.02.013 provides information on these results for different subgroups, including drug-indication pairs treating cancer, ultra-rare diseases, and first-in-class drugs.

HTA Recommendations Issued by CADTH

HTA recommendations are summarized in Table 1 and the main reasons for recommendations per HTA outcome are presented in Figure 3.

Pricing Negotiations Conducted by the pCPA

The outcomes of the pricing negotiations by the pCPA are summarized in Table 1.

HTA and pricing negotiations

From the drug-indication pairs with a positive HTA recommendation (both L and LwR) (n = 122), 78% (n = 95) resulted in successful pricing negotiations, whereas only 3% (n = 4) resulted in unsuccessful negotiations.

From the drug-indication pairs with a negative HTA recommendation (n = 33), 46% (n = 15) resulted in an unsuccessful pricing negotiation. Nevertheless, 21% (n = 7) still resulted in successful pricing negotiations (*P* and Fisher's exact ≤ .01).

Coverage Decisions in Ontario

Coverage decisions in Ontario are summarized in Table 1. Appendix 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.013 provides information on the orphan drug-indication pairs funded in Ontario and the specialized funds these drugs are available through.

HTA and coverage in Ontario

Ninety-five drug-indication pairs (78%) with a positive recommendation by CADTH (including L and LWC) and 17 drug-indication pairs (52%) with a negative recommendation were funded in Ontario (*P* and Fisher's exact ≤ .01).

Twenty-seven drug-indication pairs with a LwR HTA recommendation (23%) and 16 with DNL HTA recommendation (49%) did not receive funding in Ontario (*P* and Fisher's exact ≤ .01).

DNL HTA recommendations with coverage in Ontario (n = 17)

In 15 cases out of the 17 drug-indication pairs with DNL recommendations but funded in Ontario, CADTH could not deem them as either clinically or cost-effective. Fourteen drug-indication pairs had undergone assessment before April 2016 when Ontario stopped routine assessments for drugs assessed by CADTH. Nevertheless, we were able to identify only 3 value assessment reports from the Ontario Ministry of Health, which included both the CED's recommendations and the decision of the Executive Officer. One drug-indication pair had initially an unfavorable recommendation from the CED, because it was not considered good value for money. Nevertheless, the Executive Officer decided to reimburse the drug-indication pair in question as it underwent review through the Ontario's Drugs for Rare Diseases evaluation framework.[49,50] The other 2 drug-indication pairs both had a favorable funding recommendation by the CED and a favorable funding decision by the Executive Officer. Examples of the language used in these reports are presented in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.013.

Table 1. Sample characteristics and descriptive statistics results.

Sample characteristics	n	%
Cancer indication	71	45.81
Treating paediatric patients	40	25.81
Ultra-orphan	64	41.29
First-in-class	61	39.35
Specialized marketing authorization*	92	59.35
Conditional marketing authorization	25	16.13
Priority review at marketing authorization	70	45.16
HTA re-submission	18	11.61
HTA recommendations		
Positive HTA recommendation (L and LwR)	122	78.71
Negative HTA recommendation	33	21.29
L	3	1.94
LwR	119	76.77
DNL	33	21.29
HTA recommendations (for kappa and regression analyses)		
Positive HTA recommendation (L and LwR)	122	78.71
Negative HTA recommendation	33	21.29
Type of restrictions for LwR recommendations		
Clinical only	11	9.24
Economic only	4	3.36
Both clinical and economic	104	87.39
Type of clinical restrictions for LwR recommendations		
Population	15	13.04
Administration	1	0.87
Specialist prescription/care	10	8.7
Treatment initiation/ continuation/discontinuation	5	4.35
Multiple clinical restrictions	84	73.04
Type of economic restrictions for LwR recommendations		
Price reduction to improve cost-effectiveness	99	91.67
Similar funding with therapeutic equivalents	8	7.41
Reimbursement only in some provinces	1	0.93
ICER		
< CAD50 000/QALY	7	4.52
CAD50 000-CAD175 000/QALY	39	25.16
CAD175 000-CAD500 000/QALY	38	24.52
> CAD500 000/QALY	45	29.03
Not reported	26	16.77
Outcomes of pricing negotiations		
Successful	102	65.81
Unsuccessful	19	12.26
No information†	34	21.94
Outcomes of pricing negotiations (for kappa and regression analyses)		
Successful	102	65.81
Unsuccessful	53	34.19
Coverage decisions in Ontario		
Funded	112	72.26
Not funded	43	27.74

HTA indicates health technology assessment; L, listed; LwR, listed with restrictions; DNL, do not list; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
*Three drug-indication pairs had both conditional marketing authorization and had undergone priority review.
†It is important to highlight that the drug-indication pairs not found in the pCPA database had been assessed by CADTH between 2004 to 2022. Therefore, the lack of data in the pCPA database cannot necessarily be attributed to pCPA's establishment in August 2010. In addition, pricing negotiations (either successful or not) have been recorded in our sample for drugs assessed before August 2010.

Four (out of 17) had an unsuccessful pricing negotiation by the pCPA and 5 had a successful negotiation. For the remaining 8, information was not found in the pCPA database.

Seven of the 17 DNL drug-indication pairs treated ultra-rare diseases, 5 treated paediatric patients, and 12 were first-in-class. Most of these drug-indication pairs (n = 13 out of 17) were available through the Exceptional Access Program.

Positive HTA recommendations with no coverage in Ontario (n = 27)

From the 27 drug-indication pairs with LwR HTA recommendations not funded in Ontario, CADTH deemed that all of them had a significant clinical benefit but were not cost-effective. In 26 cases, both clinical and economic restrictions were suggested by CADTH. Ten had successful pricing negotiations, 4 had unsuccessful negotiations, and 11 had an active negotiation status. Ten of the pairs treated ultra-rare diseases, 7 targeted paediatric patients, and 9 were first-in-class.

Figure 4 showcases coverage in Ontario across different HTA recommendations.

Pricing negotiations and coverage in Ontario

From 102 drug-indication pairs with successful pricing negotiations, 88% (n = 90) received funding in Ontario whereas 12% (n = 12) did not (P and Fisher's exact $\leq$ .01). From the 19 drug-indication pairs with unsuccessful pricing negotiations, 21% (n = 4) were funded in Ontario and 79% (n = 15) were not. From the 34 drug-indication pairs for which the outcome of the pCPA negotiation was not found or negotiations were still active, 18 were funded in Ontario (53%) and 16 were not (47%). The two drug-indication pairs (from the 34) that had an active negotiation status by the pCPA were already funded in Ontario.

Level of Agreement

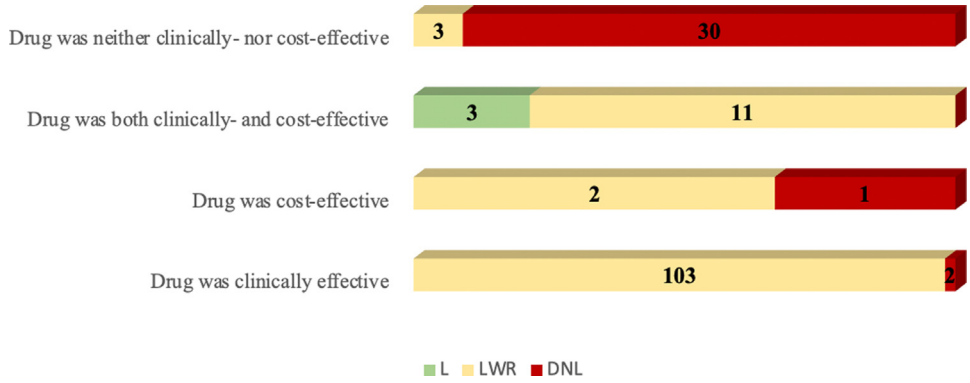
HTA and pricing negotiations

There was moderate agreement between HTA recommendations and the outcomes of pCPA negotiations (kappa = 0.464), whereas the degree of concordance (ie, the proportion of the same HTA recommendations and outcomes of pricing negotiations) was 78% ($P \leq .01$).

HTA and coverage in Ontario

There was fair agreement between HTA recommendations and coverage decisions in Ontario (kappa = 0.237), and the degree of concordance was 72% ($P \leq .01$).

Figure 3. Main reason for recommendation across HTA outcomes by CADTH. Note: data labels show the number of drug-indication pairs.



CADTH indicates Canada's Drug and Health Technology Agency; DNL, do not list; L, listed; LwR, listed with restrictions.

Pricing negotiations and coverage in Ontario

There was moderate agreement between the outcomes of pCPA negotiations and coverage decisions in Ontario (kappa = 0.4894). The degree of concordance was 78% ($P \leq .01$).

Association Between Coverage Decisions in Ontario and Covariates

Table 2 summarizes the results of the logistic regression analysis. Receiving funding in Ontario was increasingly likely, and statistically significant, to occur when there was a successful pricing negotiation by the pCPA (odds ratio 17.23 [95% confidence interval 3.77-78.73], $P \leq .0001$) and when a positive HTA recommendation had been issued by CADTH (odds ratio 7.25 [95% confidence interval 1.11-47.33], $P = .04$).

Funding in Ontario was also likely when a drug-indication pair had received conditional MA, underwent priority review, and had a cancer indication. Contrary, first-in-class and ultra-orphan drug-indication pairs were less likely to receive funding in Ontario. Nevertheless, all these results were not statistically significant.

Sensitivity analysis

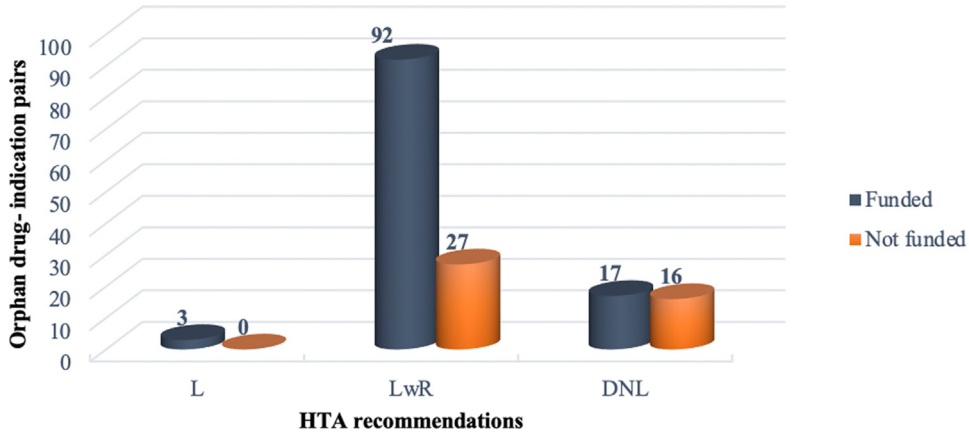
Our results did not change significantly in the sensitivity analysis. Nevertheless, the likelihood of receiving funding in Ontario for drug-indication pairs with a conditional MA or those who had undergone priority review was statistically significant. Results of the sensitivity analysis are presented in Appendix 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.013.

A full list of the drug-indication pairs sample is provided in Appendix 7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.013.

Discussion

We found that positive HTA recommendations were a good predictor of funding in Ontario for orphan drugs. Nevertheless, we observed only fair agreement between CADTH recommendations and coverage decisions in Ontario. Our results broadly align with older studies in Canada on non-orphan drugs.[13,18-20,22] However, they are not aligned with the results of a more recent study,[51] which showed a substantial agreement between recommendations by CADTH's CDR and listing decisions in Ontario for non-orphan drugs. In comparison with older studies,[13,18-20,22] our percentage agreement was higher, signalling that efforts to improve alignment between HTA recommendations and funding decisions in Canada might have been successful to some extent.

Figure 4. Coverage decisions in Ontario and HTA recommendations by CADTH ($P = .01$). Note: data labels show the number of drug-indication pairs.



DNL indicates do not list; HTA, health technology assessment; L, listed; LwR, listed with restrictions.

Table 2. Results of the logistic regression model of predictors of funding in Ontario.

Variables	*P* value	Odds ratio	95% confidence interval
Successful pCPA pricing negotiation	≤ .001*	17.23	3.77-78.73
Positive HTA recommendation	.04†	7.25	1.11-47.33
Conditional MA	.14	4.70	0.60-36.82
Priority review MA	.09	2.46	0.87-6.97
Cancer indication	.08	3.42	0.88-13.33
Paediatric indication (patients < 18 years old)	.40	1.71	0.49-5.95
Ultra-rare indication	.67	0.79	0.27-2.32
First-in-class	.36	0.54	0.14-2.02
Safety recall and alerts	.54	2.15	0.19-23.75
Cost-effectiveness ratio			
< CAD50 000/QALY	Reference		
CAD50 000 to CAD175 000/QALY	.05*	0.13	0.02-0.96
CAD175 000 to CAD500 000/QALY	.05*	0.12	0.01-1.02
≥ CAD500 000/QALY	.12	0.24	0.04-1.41
Not reported‡	.12	0.12	0.01-1.70
With an HTA resubmission	.23	0.25	0.03-2.41
MA year	.93	0.98	0.54-1.75
HTA year	.09	0.61	0.34-1.07

Note. Pseudo R^2 = 0.4550.
HTA indicates health technology assessment; MA, marketing authorization; pCPA, pan-Canadian Pharmaceutical Alliance; QALY, quality-adjusted life-year.
*$P \leq .0001$.
†$P \leq .05$.
‡CADTH did not report the cost-effectiveness ratio for 27 drug-indication pairs in our sample.

Similar to other studies in non-orphan drugs, more than half (52%) of the drug-indication pairs with a negative HTA recommendation were available in Ontario, predominately through specialized funds. Although these drugs received DNL recommendations, pan-Canadian pricing negotiations were held, and these drugs received funding in Ontario. Interestingly, most of these drug-indication pairs were deemed as neither clinically nor cost-effective by CADTH and some of them also had unsuccessful pricing negotiations by the pCPA. Therefore, a question arises as to how drugs that have not shown a significant therapeutic benefit and have not gone through successful pricing negotiations are still being offered to patients in Ontario.

This might be because of the ability of each province to decide whether to fund a drug considering their budget, health priorities and needs, and the possibility to further negotiate prices and conditions of use. In addition, Ontario, similar to some other Canadian provinces (ie, Alberta and Quebec), implements its own value assessment framework to evaluate orphan drugs in alignment with its strategic priorities.[52,53] Drugs eligible for review, through the Ontario framework, include those that (1) treat a disease with an incidence rate of < 1 in 150 000 live births or new diagnoses annually and (2) demonstrate no availability or feasibility of adequately powered randomized controlled trials.[54,55] Available clinical evidence is then assessed to establish the added clinical benefit while identifying patients that are likely to benefit the most from the treatment. Therefore, conditions of drug use are more limited and efficient for the local context.[27,49,50] Nevertheless, cost-effectiveness is not used as a criterion during these assessments.[54] Therefore, recommendations through this framework are expected to differ from those issued by CADTH. In addition, the Ontario value assessment framework differs from frameworks implemented in other provinces, such as in Alberta.[27]

Positive HTA recommendations did not always translate to successful pricing negotiations by the pCPA or funding in Ontario. This finding was only broadly in line with previous findings for non-oncology orphan drugs in Canada.[5] Nevertheless, in our sample, the percentage of positive HTA recommendations with unsuccessful pricing negotiations was still very low (3.28%). This was further highlighted in both the kappa and regression analyses: the pCPA pricing negotiations with both HTA recommendations and coverage in Ontario showed moderate agreement. Successful pan-Canadian pricing negotiations were the strongest predictor of coverage in Ontario. Nevertheless, we still observed drugs with unsuccessful or absent/incomplete pricing negotiations that received funding in Ontario. This is in line with previous studies highlighting that Ontario, as the most populous province, has the greatest negotiation power and a larger proportion of drugs funded through the use of product listing agreements when compared with other provinces.[13,21,27]

There is an international debate on whether specialized processes for orphan drugs should exist.[11,23,24,26,56-64] Based on our findings, we can only conclude that a national strategy for orphan drugs in Canada is needed to alleviate "postal-code lottery" and make access to orphan drugs a national priority. Bearing in mind that these very costly treatments can add tremendous financial pressures to provincial budgets and threaten the sustainability of the healthcare system, better uptake of HTA recommendations should be ensured and further contingency steps should be adopted.

First, Canada could benefit from a single definition of rare diseases. Currently, different orphan drugs are subject to assessment through provincial specialized frameworks, which could immediately result in access variations. Second, in line with the suggestions of Canadian stakeholders,[33] a national and systematic

approach for the value assessment of orphan drugs (post-approval) could be a part of a national framework for more consistent coverage decision-making across Canada. Taking into account that orphan drugs are inherently different from drugs treating more common diseases, value assessment could further consider that the balance between their potential benefits and funding risks will be different from that of drugs for more common diseases.[29] A national approach to collecting and assessing real-world evidence could also be paramount to complement limited clinical evidence and assist in assessments on whether the added therapeutic benefit of orphan drugs, when used in a real-world setting, could outweigh the associated costs and risks. Clinical evidence could be further supplemented through the explicit and consistent involvement of patients and clinicians during value assessments and coverage decision-making. Nevertheless, it is important to highlight that involved patient groups should have no potential conflicts of interest. By having a national approach for the assessment of orphan drugs, increasing reliance on real-world evidence, and involving patients and clinicians more explicitly, issues around clinical uncertainty could be effectively addressed and clinical conditions regarding the use of these drugs could be homogenized across provinces. Previous evidence suggested that provincial criteria for the use of orphan drugs are not always consistent with the clinical restrictions suggested by CADTH,[12] contributing further to access variations. Third, it would be beneficial for all provinces/territories to actively participate in the national strategy for orphan drugs to contribute to cooperative work and knowledge sharing, potentially through the establishment of a coordination body as suggested by key Canadian stakeholders.[29] Similarly, active participation of all jurisdictions/territories during joint pricing negotiations could further increase their negotiating power and lead to higher price reductions (currently, only 1 or 2 jurisdictions or the pCPA, as a representative of participating jurisdictions, may take the lead during price negotiations[4,65]). Fourth, better alignment in the efforts of all the involved authorities (ie, Health Canada, CADTH, pCPA, and the provincial Ministries of Health) could be encouraged through joint initiatives to increase consistency, information exchange, and timely access and ensure that efforts to optimize access are successful across the access pathway (from MA to coverage decisions). Examples of such initiatives are the parallel review process (which allows HTA to commence before MA approval), as already seen in Canada, or the new HTA interim acceptance decision in Scotland for drugs granted a conditional MA.[25] Finally, having consistent and clear pre-specified criteria for funding decision-making of orphan drugs across all provinces could alleviate access discrepancies and increase transparency in decision-making. For instance, stakeholders would have a better understanding of how HTA recommendations are being used and to what extent they inform pricing negotiations and coverage decisions. Nevertheless, we remain partly skeptical on having common funding decisions for orphan drugs across Canada: first, because of the decentralized nature of the Canadian healthcare system and differences in the available local resources and second, because of potential inter-jurisdictional variations in the needs of patients,[27] which might result in undue pressures on certain provinces to fund therapies, which might not be required simply because of epidemiological reasons.

Limitations

First, our sample might not be as accurate and inclusive as possible, given that Canada has no orphan designation nor an official definition of what is considered a rare disease.[35] Nevertheless, by using both the FDA and the EMA definitions of rare diseases, we tried to control for jurisdictional differences in the definitions used and any potential limitations that might have arisen by only comparing Canada with either Europe or the United States. Second, drug-indication pairs with an active pCPA negotiation at the time of data collection were categorized as unsuccessful for the kappa and regression analyses because we were unaware of their outcomes. Third, our study focused on coverage using public resources; therefore, coverage of these drugs through private health insurance was not captured. Fourth, to establish associations between HTA recommendations and coverage decisions, we controlled for covariates that were relevant to decision-makers and, in our opinion, were more likely to have an impact on funding. Nevertheless, other system- and macro- factors might have an impact on coverage outcomes. Finally, our sample is limited to orphan drugs and 1 Canadian province. A lack of a control group of non-orphan drugs and other provincial coverage decisions did not allow us to explore whether the orphan status of drugs and/or the province in question might have had an impact on the associations seen in our results.

Conclusion

There was only fair agreement between CADTH's recommendations and coverage in Ontario. Although positive HTA recommendations were strongly associated with coverage in Ontario, a negative HTA recommendation did not necessarily result in no pan-Canadian pricing negotiations and no funding in Ontario. Because available budgets and health priorities may vary across provinces, the introduction of a national strategy for orphan drugs could harmonize, at least to some extent, access to these treatments across Canada.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2023.02.013.

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