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REPORTS OF ORIGINAL INVESTIGATIONS

Off-label drug use in pediatric anesthesia and intensive care according to official and pediatric reference formularies

L'emploi non conforme de médicaments en anesthésie et en soins intensifs pédiatriques selon les formulaires de référence officiels et pédiatriques

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Abstract

Purpose *In pediatric practice, the official drug label often does not accurately reflect the contemporary use of many drugs prescribed to children. Therefore, clinicians frequently use contemporary drug references as a source of prescribing information instead of national formularies. The objective of this study was to compare drug prescriptions between two national formularies and two commnly used contemporary pediatric reference guidelines in the operating room/postanesthetic care unit (OR/PACU), pediatric intensive care unit (PICU), and neonatal intensive care unit (NICU).*

Methods *We performed a retrospective chart review of patients admitted over a one-month period to the NICU and PICU, and for one week during the same month, we reviewed charts of patients in the OR/PACU. The data collected included patients' demographic information, drugs prescribed, and dosage information. We assessed conformity with two national formularies, the Canadian Compendium of Pharmaceuticals and Specialties (CPS) and France's 2009 Dictionnaire Vidal (Vidal), and two contemporary pediatric references, the Hospital for Sick Children Handbook and Formulary and the Lexi-Comp Pediatric Dosage Handbook.*

Results *Across the three clinical units, 59.7% (95% confidence interval [CI] 57.1-62.1%) of prescriptions were identified as being off-label, as defined by the CPS formulary. The odds of having an off-label prescription would have been substantially lower if the contemporary pediatric references (odds ratio [OR] = 0.074; 95% CI 0.065-0.084) or Vidal (OR = 0.70; 95% CI 0.63-0.77) had been used to define the label (both $P < 0.001$ compared with the CPS).*

Conclusion *Drugs are less likely to be off-label if prescribed according to a contemporary pediatric reference rather than according to national formularies. Methodologies used to compile contemporary references might serve as templates to inform a drug's official label.*

Résumé

Objectif *Dans la pratique pédiatrique, les directives officielles de posologie ne reflètent souvent pas véritablement l'utilisation contemporaine de plusieurs médicaments prescrits aux enfants. Pour cette raison, les cliniciens utilisent donc souvent les guides de référence contemporains plutôt que les formulaires nationaux comme source*

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d'informations de prescription. L'objectif de cette étude était de comparer les prescriptions de médicaments réalisées à l'aide de deux formulaires nationaux à deux guides de référence pédiatriques fréquemment utilisés en salle d'opération / en salle de réveil, à l'unité des soins intensifs pédiatriques (USIP) et à l'unité des soins intensifs néonataux (USIN).

Méthode *Nous avons réalisé une analyse rétrospective des dossiers sur une période d'un mois des patients admis à l'USIN et l'USIP et sur une période d'une semaine pour la salle d'opération / salle de réveil. Les données colligées comprenaient les renseignements démographiques du patient, les médicaments prescrits et la posologie. Nous avons évalué la conformité de prescription des médicaments à deux formulaires nationaux (celui de l'Association pharmaceutique canadienne [CPS] et le guide français Vidal) ainsi qu'à deux guides de référence pédiatriques contemporains (Formulaires de l'Hôpital des enfants malades et Lexi-Comp).*

Résultats *Dans les trois unités cliniques, il a été déterminé que 59,7 % (intervalles de confiance [IC] 95 %: 57,1-62,1 %) des prescriptions étaient non conformes selon la définition du formulaire CPS. La probabilité d'une prescription non conforme aurait été considérablement plus basse si les guides de référence pédiatriques contemporains (rapport de cotes [RC] = 0,074, IC = 0,065-0,084) ou le guide Vidal (RC = 0,70, IC = 0,63-0,77) avaient été utilisés afin de définir l'usage conforme (tous deux P < 0,001 par rapport au CPS).*

Conclusion *Lorsqu'ils sont prescrits conformément à un guide de référence pédiatrique contemporain, il est moins probable que les médicaments soient non conformes que si l'on se fonde sur les formulaires nationaux. Les méthodes utilisées pour compiler les guides de référence contemporains pourraient servir de modèle pour éclairer les directives officielles de prescription des médicaments.*

In pediatric medical practice, it has long been the reality that a large proportion of drugs used to treat children are prescribed for indications for which the drugs are not licensed (unlicensed) or are prescribed outside the terms of the product license (off-label).[1-3] While the common practice of using off-label drugs in pediatrics is widely recognized as medically necessary, the lack of pediatric research and knowledge in the area of pediatric evidence-based treatment is of real concern.[4,5] When drugs are studied rigorously in children, it is clear that dosage regimes based on age, weight, and body surface area do not reflect actual pharmacokinetics of the drugs across the various stages of pediatric development.[6] Additionally, while a given drug may be effective in adult models of disease, in children, the optimal dose is often unknown, the efficacy is uncertain, the side effects are not established, and adverse outcomes are not described.

Currently, before a drug is approved for pediatric use, rigorous studies in children (or in a pediatric sub-population, such as neonates) are required in order to devise a product monograph that specifies a clinical indication, a dosing schedule, and a formulation. Once the drug has entered clinical practice, product monographs and national formularies, such as the Canadian *Compendium of Pharmaceuticals and Specialties* (CPS),[7] reflect the approved use of the drug in terms of the dose, the dose interval, and the route of administration. The regulatory body may subsequently alter a drug's license based on clinicians' feedback presented in a problem-based model that reflects safety and toxicity profiles of the drug in clinical practice.

In reality, changes to reflect new pediatric information in a given drug label are relatively uncommon. Once a drug enters the market, its unofficial indications, dosing schedule, and formulation can evolve over time and can become markedly different from the licensed indication. This evolution is shaped by well-designed, unbiased, investigator-initiated research and by clinical experience, historical precedent, and institutional and/or individual custom and practice. Also, the formulation of a given drug may be unsuitable for children, and may therefore require manipulation by a pharmacist. Since this type of information is usually not presented in the official drug monograph or in the CPS, clinicians often have no option but to refer to contemporary reference formularies or published medical literature as resources for clinically relevant prescribing information. Contemporary reference formularies are either institutionally or commercially produced compendiums. The formularies are based on surveillance of government regulations, pharmaceutical manufacturer announcements, published literature findings on new drug availability, new dosage forms, as well as revisions to contraindications, warnings, and other labelling changes.

Although described in other countries,[8-10] the extent of off-label drug prescribing that may be occurring in perioperative and critical care units for children in Canada is largely unreported. The primary objective of this study was to compare drug prescriptions using the CPS with those using the combination of two commonly used contemporary pediatric reference guidelines available in Canada, the Lexi-Comp Pediatric Dosage Handbook (Lexi-Comp), 16th edition (Hudson, OH, USA)[11] and The Hospital for Sick Children (Sick-Kids) Handbook and Formulary 2008/09.[12] We hypothesized that a combination of these specialized guidelines would better reflect actual use of the drug than the regulatory license. Secondary objectives included: 1) to benchmark the prevalence in the use of off-label medications, as defined by Health Canada-approved product monographs in the CPS in a Canadian pediatric hospital;

2) to identify the off-label medications and the reasons for such designation; and 3) to compare the CPS formulary with that of another industrialized country, i.e., France's, 2009 Dictionnaire Vidal (Vidal).[13]

Methods

After institutional research ethics board approval, we performed a retrospective inception cohort study of all prescriptions in three areas of a Canadian pediatric tertiary care hospital, i.e., the operating room/postanesthetic care unit (OR/PACU), the pediatric intensive care unit (PICU), and the neonatal intensive care unit (NICU). The study took place throughout May 2009 and lasted one month for the NICU and PICU and one week for the OR/PACU. May was chosen because it reflects a watershed month in our institution between admission diagnoses typical of the winter and those of the spring and summer. All patients admitted to these study areas during the study period were included. Patients admitted to other units of the hospital were not considered as they have been reported elsewhere.[14]

Data sources included the medical chart, the anesthetic record, the nursing medication administration record, and the pharmacy record. During the study month, a single reviewer recorded each drug prescription along with patient demographics (age, sex, weight, diagnosis or procedure undertaken). The patient's weight and age corresponded with the day and the clinical unit on which the prescription was issued. A second reviewer cleaned the data by evaluating the off-label status assigned by the first reviewer.

All prescriptions were compared with at least three sources: 1) the 2009 Compendium of Pharmaceuticals and Specialties (CPS)[7]; France's Dictionnaire Vidal (Vidal)[13]; and 3) two contemporary pediatric reference guidelines, the Lexi-Comp Pediatric Dosage Handbook (Lexi-Comp)[11] and the 2008/09 Toronto Hospital for Sick Children Drug Handbook and Formulary (Sick-Kids).[12]

To determine if a prescription was within the guidelines of the contemporary pediatric reference guidelines and formularies, reviewers initially checked the prescription in Lexi-Comp.[11] If there was no guideline identified in the initial search, the prescription was then checked against the Sick-Kids handbook and formulary.[12] If the prescription was in agreement with either reference, it was considered *on-label*. If the prescription was not in agreement with either reference, it was considered *off-label* for contemporary pediatric references and formularies. This approach was taken because it reflects actual practice of clinicians and pharmacists in this and other institutions.

A prescription was considered *off-label* if it met at least one of the following criteria:

1. *Dose:* The prescribed dose was in excess of the therapeutic dose referenced.
2. *Age:* The prescribed drug was either contraindicated for the age of the patient or there was no indication in the patient's age.
3. *Route:* The prescribed route of administration was different from the reference.
4. *No information for children:* No pediatric information was available in the reference for the prescribed drug.
5. *Contraindicated:* The prescribed drug was contraindicated for children and / or inadvisable due to a lack of pediatric clinical trials.
6. *Formulation modification:* The prescribed drug formulation did not exist in reference.
7. *Special Access Program*: The prescribed drug was not approved for commercialization and was obtained with the approval of Health Canada under the special access program.
8. *Drug not listed*: The drug was not listed in the reference source.

In order to classify the drugs, we referred to the World Health Organization Collaborating Centre for Drug Statistics Methodology, which classifies drugs according to the Anatomical Therapeutic Chemical Classification System.[15] This classification system divides drugs into different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics.

Statistical analyses were conducted using SPSS 16.0 (SPSS Inc., Chicago IL, USA) and R 2.10.0.[16] A generalized linear mixed model (implemented by using GLMMPQL function in MASS package in R) was used to estimate the prevalence and 95% confidence intervals (CI) of off-label prescriptions and to compare the odds of off-label prescriptions among clinical areas and formularies. Random intercept was included in the model to adjust for the clustering of prescriptions by patients. A two-sided P value of < 0.05 was considered as indicating a statistically significant difference.

Results

During the study period, 51 patients were admitted to the PICU, 38 to the NICU, and 139 to the OR/PACU, resulting in 3,391 drug prescriptions (Table 1). Patient demographic data were available for all patients. Drug information was available for all prescriptions from the CPS, the Lexi-Comp, and the Sick-Kids formularies. The prescribed drug was not listed in the Vidal reference source for 39 (3.7%) of the PICU prescriptions. These prescriptions were therefore considered off-label for this formulary.

Table 1 Patient demographics (age, sex, and weight) and diagnostic category / procedure by clinical unit

	PICU $n = 51$	NICU $n = 38$	OR/PACU $n = 139$
Male *n* (%)	35 (66.0)	18 (47.4)	84 (60.4)
Age at 1st prescription			
Median (IQR)	5.5 yr (0.9-12.8 yr)	1.5 days (0-13.8 days)	8.3 yr (4.1-14.6 yr)
Weight at 1st prescription (kg)			
Median (IQR)	18.3 (8.7-40.0)	2.8 (1.8-3.4)	25.9 (15.9-55.3)
Diagnostic Category / Type of Operation			
n (%)	Respiratory (ARDS) 14 (29)	Respiratory distress 8 (21)	General Surgery 30 (22)
	Cardiovascular 11 (22)	Short Gestation 8 (21)	Endoscopy 27 (19)
	Trauma 7 (14)	Birth Asphyxia 3 (8)	Dental Surgery 20 (14)
	Neurological 5 (10)	Neonatal Jaundice 2 (5)	Orthopedic Surgery 19 (14)
	Metabolic / endocrine 3 (6)	Interstitial emphysema 2 (5)	ENT Surgery 17 (12)
	Heme-Oncology 1 (2)	Neurological 2 (5)	Ophthalmic Surgery 16 (12)
	Other 6 (12)	Cardiovascular 1 (3)	Neurosurgery 4 (3)
		Metabolic 1 (3)	Cardiac Surgery 3 (2)
		Other 2 (5)	Plastic Surgery 3 (2)

PICU = pediatric intensive care unit; NICU = neonatal intensive care unit; OR/PACU = operating room / postanesthesia care unit; IQR = inter-quartile range; ARDS = acute respiratory distress syndrome; ENT = ear, nose and throat

Off-label exposure

The odds of having an off-label prescription would have been substantially lower compared with the CPS references if the contemporary pediatric references (OR 0.074, 95% CI: 0.065 - 0.084; $P < 0.001$) or the Vidal (OR 0.70, 95% CI: 0.63 - 0.77; $P < 0.001$) had been used to define the label. This observation was also true for each of the three clinical areas, except for PICU where CPS and Vidal references had similar odds ratios (Table 2). Across the whole study population, the frequency of off-label prescriptions was 59.7% (95% CI: 57.1-62.1%) based on CPS, 9.8% (95% CI: 8.7-11.1%) based on contemporary pediatric references, and 50.7% (95% CI: 48.2-53.3%) based on the Vidal. Depending on the clinical unit, 89-99% of patients received at least one off-label prescription (Table 2). The types of drugs prescribed reflected the clinical activity and patient population in each clinical area (Fig. 1).

Principal reasons for identifying drugs as off-label

The main reasons for identifying drugs as off-label were: 1) *no information for children*; 2) *formulation modification*; 3) *age of child*; 4) *prescribed dose*; and 5) *contraindicated in children* (Table 3). Although each clinical area had identified slightly different principal reasons for off-label designations, the contemporary pediatric references would have reduced the chances of this occurring had they been used to define the label (Table 3).

Most frequently used off-label medications

For each clinical area, the individual drugs identified most frequently by the CPS formulary as being off-label are listed in Table 4 and compared with the contemporary pediatric and Vidal formularies. The majority of drugs listed are currently not patent-protected or designated as over-the-counter medications.

Discussion

Similar to studies recently reported, this study demonstrates that off-label prescriptions in a Canadian pediatric surgical and critically ill population remain the norm rather than the exception.[3,9,14] It identifies the principal reasons why the most commonly prescribed off-label drugs were recognized as being off-label. The main objective for this study was to ascertain whether the frequency of off-label prescriptions would have been reduced substantially if an alternative method (e.g., contemporary pediatric references) were used to inform the official drug label.

From 15-26% of the prescriptions were designated as being off-label, as defined by the contemporary pediatric references. This does not imply that these prescriptions were erroneous, as the physician may have sourced the prescribing information from the literature or from another reference not included in the study. However, it is policy in our institution that all prescriptions (with the exception of the operating room) be validated by a pharmacist. For this validation, staff pharmacists refer to the CPS, the

Table 2 Off-label prescriptions in pediatric intensive care unit (PICU) neonatal intensive care unit (NICU), and operating room / postanesthetic care unit (OR/PACU). Comparison of the total, percentages, and mean number of off-label prescriptions, and the odds ratio (OR) of having an off-label prescription in the three clinical care units as defined by the Canadian Compendium of Pharmaceutical Specialties (CPS), Pediatric References (Lexi-Comp Pediatric Dosage Handbook and the Hospital for Sick Children Drug Handbook and Formulary), and France's Dictionnaire Vidal

PICU	*CPS*	*Pediatric References*	*Vidal*	*OR (Pediatric references vs CPS) 95% CI*	*OR (Vidal vs CPS) 95% CI*
Prescriptions: off-label / total (%) Odds ratio *vs* CPS (95% CI)	679 / 1,042 (65%)	73 / 1,044 (7%) 0.018* (0.014-0.023)	683 / 1,041 (66%) 1.03 (0.87-1.22)	0.018 * (0.014, 0.023)	1.03 (0.87, 1.22)
Patients: ≥ 1 off-label drug / total (%)	49 / 51 (96%)	24 / 51 (47%)	50 / 51 (98%)		
Off-label prescriptions per patient mean (range)	13.6 (0-49)	3.1 (0-13)	13.7 (0-62)		
Prescriptions per patient mean (range)	20.5 (1-75)	20.5 (1-75)	20.5 (1-75)		
NICU	*CPS*	*Pediatric References*	*Vidal*	*OR (Pediatric references vs CPS) 95% CI*	*OR (Vidal vs CPS) 95% CI*
Off-label prescriptions / total prescriptions, (%) off-label	177 / 268 (66%)	33 / 272 (12%)	119 / 237 (50%)	0.033 * (0.022, 0.051)	0.41* (0.29, 0.58)
Patients with ≥ 1 off-label drug / total number of patients, (%) off-label	33 / 37 (89)	20 / 38 (53)	27 / 37 (73)		
Average off-label prescriptions per patient (min – max)	5.2 (0-28)	0.9 (0-6)	4.4 (0-20)		
Average number of prescriptions per patient (min – max)	7.2 (1-40)	7.2 (1-38)	6.4 (1-30)		
OR/PACU	*CPS*	*Pediatric References*	*Vidal*	*OR (Pediatric references vs CPS) 95% CI*	*OR (Vidal vs CPS) 95% CI*
Off-label prescriptions / total prescriptions, (%) off-label	716 / 1,302 (55%)	210 / 1,277 (16%)	546 / 1,300 (42%)	0.16 * (0.13, 0.18)	0.58 * (0.50, 0.67)
Patients with ≥ 1 off-label drug / total number of patients, (%) off-label	138 / 139 (99%)	108 / 140 (77%)	133 / 139 (96%)		
Average off-label prescriptions per patient (min – max)	5.2 (0-15)	2.7 (0-8)	4.1 (0-11)		
Average number of prescriptions per patient (min – max)	9.4 (1-26)	9.2 (1-26)	9.4 (1-26)		

* $P < 0.001$. CI = confidence intervals

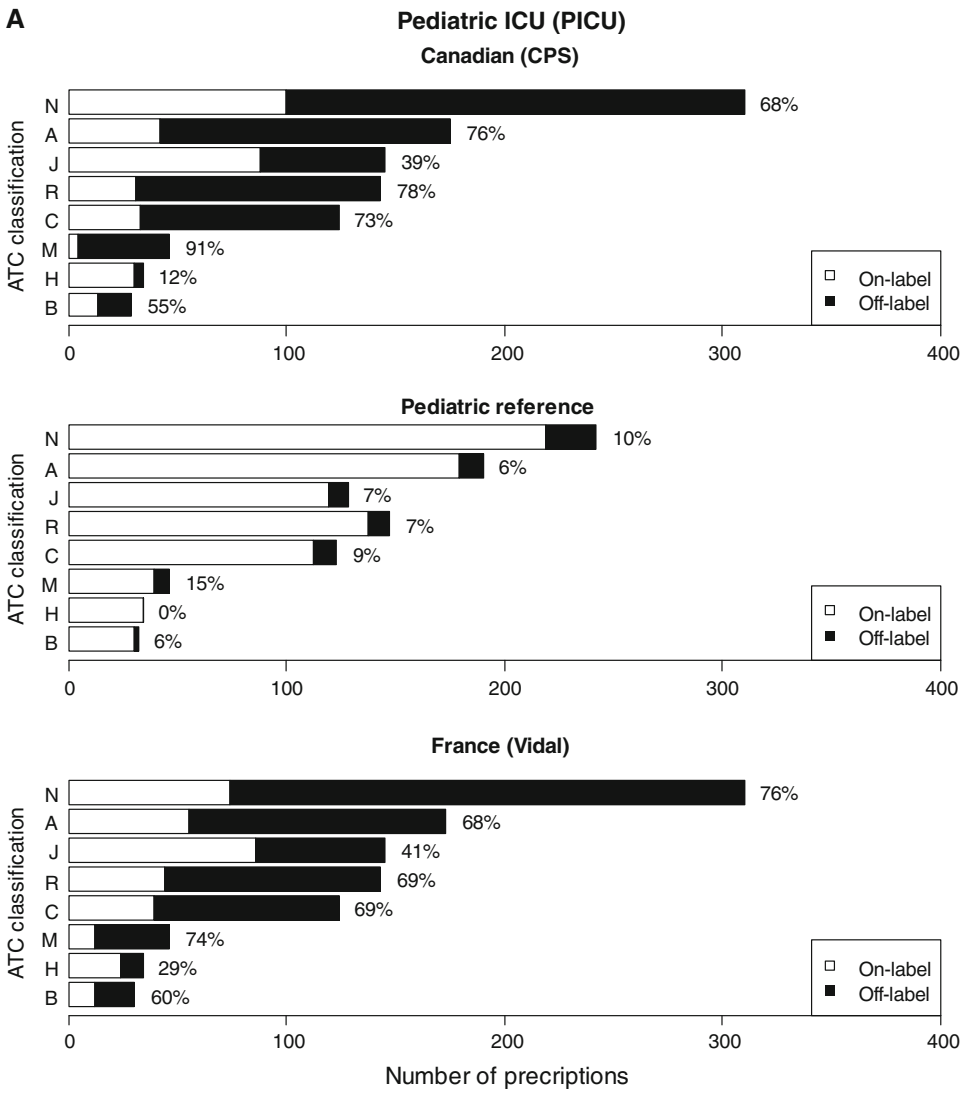


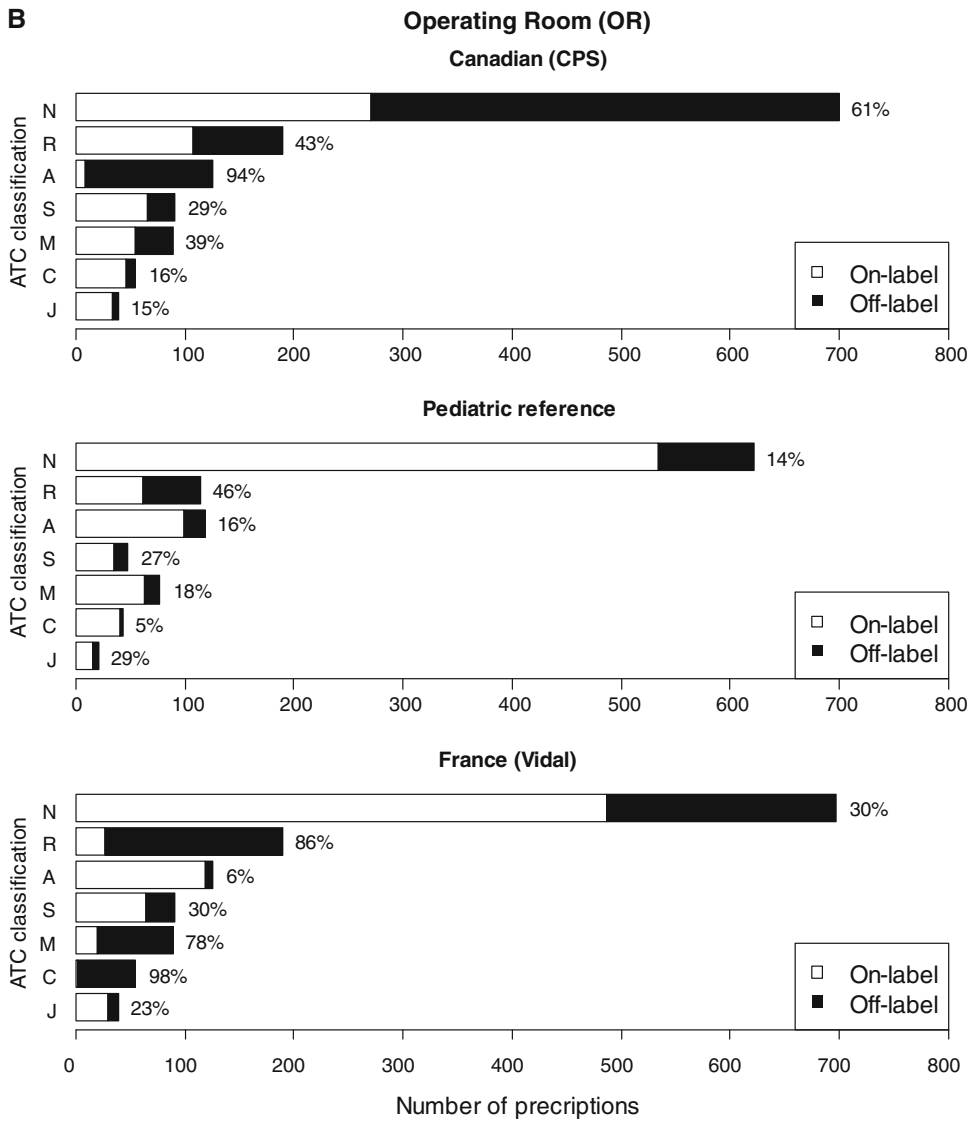
Figure 1 Represents the percentage of drugs identified (in black) as being off-label as a function of total number of drugs prescribed in the A) pediatric intensive care unit (PICU), B) the operating room postanesthetic care unit (OR/PACU), and (C) the neonatal intensive care unit (NICU). The Anatomical Therapeutic Chemical classification system classifies drugs into different groups according to the primary target organ or system on which they act and/or their therapeutic and chemical characteristics. Each drug class is given a five-level code. The first level (presented here) of the code indicates the main anatomical group and consists of one letter. **a**: Drugs acting on the alimentary system, **b**: Drugs acting on blood and blood forming organs, **c**: Drugs acting on the cardiovascular system, **j**: Drugs acting on infections or infestations, **m**: Anti-cancer agents, **n**: Drugs acting on the brain and nervous system, **r**: Drugs acting on the respiratory system, **s**: Drugs acting on sensory organs (e.g., ophthalmological drugs)

contemporary pediatric guidelines, and also primary references (i.e., published articles or other reference books). If a prescription falls outside of published clinical guidelines, the pharmacist usually seeks clarification from the prescribing physician.

We chose to study this issue in the OR/PACU, PICU, and NICU, as these clinical areas have not been well described in a Canadian setting. The Children's Hospital of Eastern Ontario is a tertiary care stand-alone teaching facility serving a population of one and a quarter million people of Eastern Ontario, Western Quebec, and Baffin Island, Nunavut. It has Royal College of Physicians and Surgeons of Canada accredited programs in Anesthesiology, Pediatric Critical Care Medicine, and Neonatology, and is staffed by fellowship-trained specialist physicians. We believe the established methods at this facility reflect current standards of practice in North America. The month of May was chosen *a priori* as it represents a watershed period in our PICU and OR between the admission diagnoses typical of the winter months (e.g., respiratory) and those typical of the summer (e.g., trauma). We determined that the sample size of one month in the PICU and NICU in our institution and one week in the OR would be sufficiently powered to yield statistically significant results based on similar studies reported elsewhere.[9,10] A retrospective design was chosen because we wanted to report actual practice and avoid any potential observer bias (i.e., if clinicians knew they were being observed they might prescribe differently).

In this study, we did not record whether the drug was prescribed for its licensed indication, as we could not infer the prescribing physician's intent from the medical record. It is likely that some of these medications were off-license as well as off-label. The assumption that each prescription

Figure 1 continued

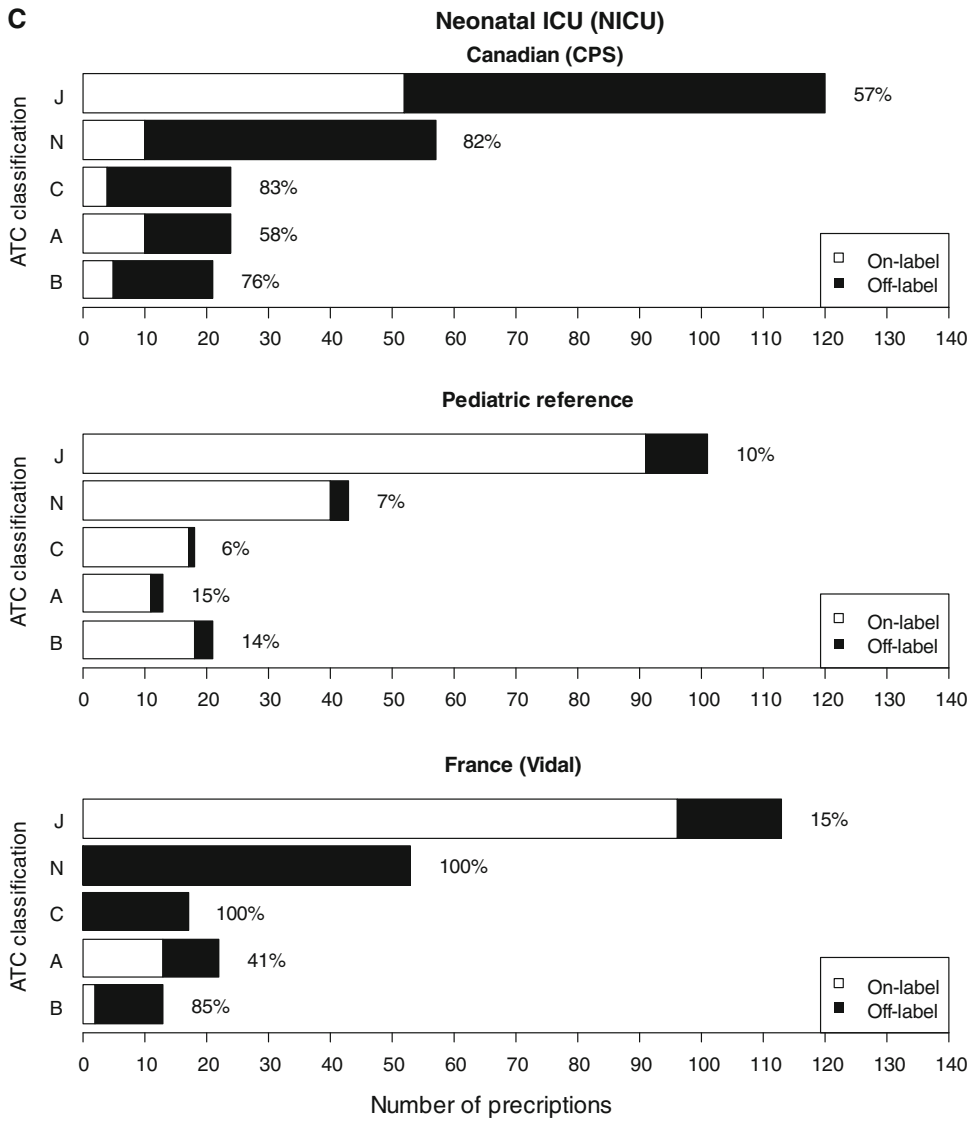


written by the physician was correct is also a potential flaw of this study. This flaw may have led to an overestimation of the number of off-label prescriptions.

Despite there being subtle differences in terms of the types of medications that are identified as being off-label and the reasons for their use, the reality is that the official drug monograph and formularies do not serve pediatric acute medicine as it is currently practiced. Off-label prescribing continues for many reasons. To bring drugs to market, pharmaceutical companies must undertake extensive research at their own expense to provide data to the regulatory about a new product. Traditionally, pharmaceutical companies have not viewed pediatric medicine as lucrative markets to recoup the cost of drug development and testing or to develop pediatric-specific formulations. Undertaking pediatric clinical trials poses substantial challenges for investigators, as it is a heterogeneous population in terms of developmental physiology and pharmacokinetics.[17] Also, obtaining a sufficient sample size to reflect the population of interest is challenging, as the prevalence of many pediatric diseases is low, thus necessitating multi-centre/multi-national studies with the often encountered individual nuances of institutional research ethic boards and national regulatory requirements to be satisfied before patient enrollment begins. Finally, obtaining consent from parents, guardians, and patients is far more complex than in the adult population for the obvious emotional and ethical reasons.[18,19]

Internationally, governments have called for new research and have attempted to improve the impetus for industry to study drugs in children.[20] In the United States, drug companies once had the option of extending the patent of a given drug for six months if they undertook studies in children. It is now required that new drugs be studied in the

Figure 1 continued



pediatric population if children are likely to benefit from the availability of the new drug.[A] These changes have resulted in alterations in the labelling of over 100 medications, because the research identified heterogeneous pharmacokinetics and pharmacodynamics across the stages of child development when these drugs were specifically studied.[6] Similar strategies exist in the European Union where pharmaceutical companies that undertake pediatric research in orphan drugs are given an additional two years on marketing exclusivity.[B] However, in our study, all off-label drugs, except two, were non-proprietary. Therefore, our study population would not benefit from the current strategies of regulatory agencies to entice pharmaceutical companies to undertake pediatric drug research.

In this study, the two contemporary pediatric reference formularies performed better than the CPS. We contacted the pharmacy departments of 16 university teaching hospitals across Canada*, to ascertain which reference formularies they used. All reported using Lexi-Comp, and ten of 16 reported using the Hospital for Sick Children Drug Handbook and Formulary. These formularies are based on data that comes from a variety of sources, including investigator-initiated research. In the case of the Hospital for Sick Children Drug Handbook and Formulary, a multidisciplinary review process is undertaken prior to the inclusion of new information. This review team consists of physicians, pharmacists, and experts in medical

[A] United States Congress. Best Pharmaceuticals for Children Act Pediatric Research Act 2007 Reauthorization. Improvements to Existing Law. Public Law (H.R. 3580):110-85.

[B] European Union Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal product for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) no 726/2004.

Table 3 Three main reasons for prescriptions being designated *off-label* in each clinical unit: pediatric intensive care unit (PICU), neonatal intensive care unit (NICU), and operating room / postanesthetic care unit (OR/PACU); Comparison of the Canadian Compendium of Pharmaceutical Specialties (CPS), Pediatric Reference (Lexi-Comp Pediatric Dosage Handbook and the Hospital for Sick Children Handbook and Formulary), and France's Dictionnaire Vidal

Unit	Reason for Off-Label Designation	CPS *n* of off-label / *n* of total prescription (%)	Pediatric References *n* of off-label / *n* of total prescription (%)	Vidal *n* of off-label / *n* of total prescription (%)
PICU	No information for children	235 / 1,042 (22.6%)	5 / 1,044 (0.5%)	120 / 1,041 (11.5%)
	Formulation modification	213 / 1,042 (20.4%)	9 / 1,044 (0.9%)	269 / 1,041 (25.8%)
	Dose	203 / 1,042 (19.5%)	6 / 1,044 (0.6%)	230 / 1,041 (22.1%)
NICU	Dose	78 / 268 (29.1%)	1 / 272 (0.4%)	29 / 237 (12.2%)
	Formulation modification	65 / 268 (24.3%)	0 / 272 (0%)	11 / 37 (4.6%)
	Age	42 / 268 (15.7%)	0 / 272 (0.0%)	27 / 237 (11.4%)
	No information for children	42 / 268 (15.7%)	0 / 272 (0%)	52 / 237 (21.9%)
OR / PACU	No information for children	294 / 1,302 (22.6%)	0 / 1,277 (0%)	81 / 1,300 (6.2%)
	Dose	182 / 1,302 (14.0%)	32 / 1,277 (2.5%)	152 / 1,300 (11.7%)
	Contraindication	171 / 1,302 (13.1%)	0 / 1,277 (0%)	15 / 1,300 (1.2%)

Table 4 The top 20 most frequently prescribed drugs and the percentages for which they were prescribed off-label in the A) pediatric intensive care unit (PICU), B) neonatal intensive care unit (NICU), and C) the operating room / postanesthetic care unit (OR/PACU)

Drug name	CPS *n* of off-label / *n* of total prescriptions (%)	Pediatric References *n* of off-label / *n* of total prescriptions (%)	Vidal *n* of off-label / *n* of total prescriptions (%)
A. Top 20 Most frequently identified off-label prescriptions in the PICU			
acetaminophen	108 / 130 (83%)	11 / 130 (8%)	106 / 129 (82%)
ranitidine	50 / 50 (100%)	0 / 50 (0%)	50 / 50 (100%)
dimenhydrinate	41 / 48 (85%)	2 / 54 (4%)	34 / 48 (71%)
furosemide	40 / 71 (56%)	0 / 71 (0%)	35 / 71 (49%)
lorazepam	36 / 36 (100%)	0 / 36 (0%)	36 / 36 (100%)
diphenhydramine	34 / 36 (94%)	1 / 36 (3%)	29 / 36 (81%)
clonidine	27 / 27 (100%)	0 / 27 (0%)	27 / 27 (100%)
ibuprofen	22 / 23 (96%)	1 / 23 (4%)	11 / 23 (48%)
spironolactone	16 / 16 (100%)	0 / 16 (0%)	16 / 16 (100%)
salbutamol	15 / 20 (75%)	0 / 20 (0%)	15 / 20 (75%)
ondansetron	14 / 23 (61%)	1 / 26 (4%)	4 / 22 (18%)
Morphine SO4	12 / 44 (27%)	0 / 44 (0%)	19 / 44 (43%)
codeine	11 / 11 (100%)	0 / 11 (0%)	11 / 11 (100%)
diazepam	11 / 13 (85%)	11 / 13 (85%)	13 / 13 (100%)
lansoprazole	11 / 12 (92%)	9 / 12 (75%)	12 / 12 (100%)
midazolam	11 / 11 (100%)	0 / 11 (0%)	0 / 11 (0%)
vancomycin	11 / 15 (73%)	0 / 15 (0%)	3 / 15 (20%)
cefotaxime	10 / 11 (91%)	0 / 11 (0%)	0 / 11 (0%)
ketorolac	9 / 9 (100%)	0 / 9 (0%)	9 / 9 (100%)
chlorhexidine	8 / 8 (100%)	2 / 8 (25%)	6 / 8 (75%)
B. Top 20 most frequently identified off-label prescriptions in the NICU			
gentamicin	32 / 46 (70%)	0 / 46 (0%)	3 / 43 (7%)
fentanyl	17 / 17 (100%)	1 / 17 (6%)	17 / 17 (100%)
acetaminophen	16 / 18 (89%)	3 / 18 (17%)	18 / 18 (100%)
vancomycin	8 / 8 (100%)	0 / 8 (0%)	0 / 8 (0%)

Table 4 continued

Drug name	CPS *n* of off-label / *n* of total prescriptions (%)	Pediatric References *n* of off-label / *n* of total prescriptions (%)	Vidal *n* of off-label / *n* of total prescriptions (%)
enoxaparin	7 / 7 (100%)	0 / 7 (0 %)	6 / 6 (100%)
cefotaxime	6 / 6 (100%)	4 / 6 (67%)	5 /6 (83%)
hydrocortisone	6 / 7 (86%)	0 / 7 (0%)	2 / 7 (29%)
ranitidine	6 / 6 (100%)	0 / 6 (0%)	6 / 6 (100%)
calcium gluconate	6 / 7 (86%)	0 / 0 (0%)	5 / 7 (71%)
ampicillin	5 / 31 (16%)	6 / 31 (19%)	0 / 31 (0%)
clonidine	5 / 5 (100%)	2 / 5 (40%)	5 / 5 (100%)
dopamine	5 / 5 (100%)	0 / 5 (0%)	0 / 0 (0%)
morphine HCl	5 / 5 (100%)	0 / 5 (0%)	5 / 5 (100%)
fluconazole	4 / 4 (100 %)	0 / 4 (0%)	1 / 1 (100%)
acyclovir	3 / 3 (100 %)	2 / 3 (67%)	2 / 3 (67%)
cholestyramine	3 / 3 (100 %)	3 / 3 (100%)	3 / 3 (100%)
cloxacillin	3 / 3 (100%)	0 / 3 (0%)	3 / 3 (100%)
dexamethasone	3 / 4 (75%)	0 / 4 (0%)	0 / 0 (0%)
furosemide	3 / 6 (50%)	0 / 6 (0%)	6 / 6 (100%)
glycerine	3 / 3 (100%)	0 / 3 (0%)	2 / 3 (67%)
C. Top 20 most frequently identified off-label drugs in the OR/PACU			
fentanyl	177 / 177 (100%)	0 / 176 (0%)	20 / 177 (11%)
ondansetron	113 / 113 (100%)	0 / 113 (0%)	1 / 113 (0.9%)
acetaminophen	83 / 136 (61%)	58 / 137 (42%)	70 / 137 (51%)
propofol	48 / 123 (39%)	26 / 124 (21%)	37 / 123 (30%)
midazolam	47 / 47 (100%)	1 / 46 (2%)	45 / 46 (98%)
dimenhydrinate	44 / 147 (30%)	11 / 149 (7%)	124 / 149 (83%)
codeine	29 / 29 (100%)	4 / 29 (14%)	29 / 29 (100%)
remifentanyl	20 / 20 (100%)	0 / 2 (0%)	3 / 20 (15%)
ketorolac	16 / 53 (30%)	2 / 54 (4%)	54 / 54 (100%)
acetaminophen - caffeine - codeine	14 / 14 (100%)	0 / 14 (0%)	9 / 14 (64%)
rocuronium	12 / 27 (44%)	10 / 27(37%)	12 / 27 (44%)
diphenhydramine	8 / 8 (100%)	0 / 8 (0%)	8 / 8 (100%)
bupivacaine - epinephrine	7 / 33 (21%)	1 / 34 (3%)	6 / 34 (18%)
tetracaine	7 / 54 (13%)	53 / 53 (100%)	53 / 53 (100%)
morphine	6 / 67 (9%)	2 / 69 (3%)	3 / 69 (4%)
polymyxin - bacitracin	5 / 10 (50%)	1 / 10 (10%)	10 / 10 (100%)
methylprednisolone	4 / 4 (100%)	0 / 4 (0%)	1 / 4 (25%)
bupivacaine	4 / 12 (33%)	0 / 12 (0%)	0 / 12 (0%)
lidocaine	4 / 29 (14%)	6 / 29 (21%)	0 / 29 (0%)
succinylcholine	4 / 4 (100%)	1 / 4 (25%)	0 / 4 (0%)

CPS = Canadian Compendium of Pharmaceutical Specialties; Pediatric References = Lexi-Comp Pediatric Dosage Handbook and the Hospital for Sick Children Handbook and Formulary; Vidal = France's Dictionnaire Vidal

NICU = neonatal intensive care unit; CPS = Canadian Compendium of Pharmaceutical Specialties; Pediatric References = Lexi-Comp Pediatric Dosage Handbook and the Hospital for Sick Children Handbook and Formulary; Vidal = France's Dictionnaire Vidal

OR/PACU = the operating room / postanesthetic care unit; CPS = Canadian Compendium of Pharmaceutical Specialties; Pediatric References = Lexi-Comp Pediatric Dosage Handbook and the Hospital for Sick Children Handbook and Formulary; Vidal = France's Dictionnaire Vidal

informatics who review and weigh available information before making a recommendation whether to include a new drug or to change a guideline. This process could serve as a template where a national level could grandfather the current use of established drugs into the license on the basis of high quality research. The process could then go forward

to inform a progressive licensing process that reflects the actual life cycle of the drug in clinical practice. This process could also identify where knowledge gaps exist and could potentially guide investigators to address identified knowledge gaps. Before this transformation can happen, the stakeholders in pediatric health in Canada, both in government and in healthcare delivery, need to reach a consensus on the way to tackle this problem in partnership. The strategy should include determining priorities, forming networks of collaboration, and establishing areas of expertise so that the criteria for the official label to safely reflect the life-cycle of the drug can be stipulated.

In conclusion, off-label prescribing continues to be an integral part of the care of children in Canada. In all likelihood, the pharmaceutical company bringing the drug to market would study newer drugs more comprehensively in children than it would study the older drugs. A fresh approach by regulatory agencies is required to address this important problem. The approach taken by contemporary reference formularies offers a framework on the means to address this issue at a national level.

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