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- Rivaroxaban for Left Ventricular Thrombus

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Diversion Inattention: Time for Action!

Clarence Chant

Drug diversion, defined as the "unlawful channeling of regulated pharmaceuticals from legal sources to the illicit marketplace", is a problem that is neither new nor rare.[1] Opioids are commonly diverted, but benzodiazepines, anabolic steroids, and other noncontrolled agents such as propofol and erythropoietin are also potential targets. Yet the issue of diversion is not discussed openly in most institutions, and was termed "health care's dirty little secret" in a recent exposé on *W5*,[2] a long-running Canadian documentary television show.

In the era of an ongoing and unabating opioid epidemic, in which diversion of opioids from legal sources such as hospitals is one contributing factor (albeit among many others), it is somewhat counterintuitive that pharmacy team members, recognized as guardians of the medication system, are not paying much attention. In fact, a news report from another broadcaster, which was based on data compiled from access to information requests spanning 2010 to 2017, determined that 5689 reports had been filed with Health Canada for various quantities of opioids missing from hospitals.[3] What is even more disturbing is that for 4375 (77%) of these reports, the reason for the loss was "unknown".[3] These alarming statistics are more than just numbers or scare tactics; they have real clinical, humanistic, and financial consequences. For example, in December 2013, a nurse and a physician were found unconscious in hospital bathrooms at the University of Michigan Health System.[4] Both had overdosed on diverted opioids; although the physician was successfully resuscitated, the nurse died. The ensuing investigations revealed that diversion had been going on for years, with up to 16 000 tablets of oxycodone being diverted within this health system.[4] The University of Michigan eventually agreed to pay US$4.3 million as part of the settlement on this investigation.[5] The degree to which diversion is occurring in Canada, the United States, and internationally is unknown, because of lack of reporting. Although there may be differences in incidence among different jurisdictions, the problem is most likely occurring around the world and requires attention.

The reluctance to openly discuss the topic of drug diversion has many causes, not least the fact that drugs can be diverted by any member of the multiple health disciplines with drug access, approved or otherwise, many of whom have extensive knowledge of the systems and its gaps. Diversion can occur anywhere in the medication system, from procurement to storage to dispensing and administration, and may occur even in facilities with advanced automation and control mechanisms.[6] This was indeed the case at University of Michigan, where more than 100 automated dispensing cabinets (ADCs) were deployed. The diversion was not a failure of the ADCs per se, but represents the reality of a medication system that must balance access control with urgent patient needs, in an environment characterized by complex processes and multiple hand-offs by many staff who know the strengths and, unfortunately, the deficiencies of the system set-up. Common means of diversion range from signing out opioids but not administering (or only partially administering) them to the intended patient or signing out drugs in the operating room for patients whose operations are already completed to the more drastic means of retrieving partially used fentanyl patches from the waste bin and syringing out the remaining contents. The gaps in access control are especially apparent in facilities that use a manual paper system, as is still the case in many Canadian institutions. Furthermore, drug-use symptoms are often subtle, and diversion may involve team members who are personable and seemingly helpful (e.g., offering to administer medications while covering a colleague's break). The lack of systematic tracking and data-gathering further contribute to the cloud of secrecy, and the notion of "snitching" on a colleague may also be unpalatable.

However, all of these considerations must be weighed against the consequences for patients, who may be receiving care from staff who are intoxicated, or who may have suboptimal

pain control because of diversion by staff. Harm can also come to the diverter, who has a medical condition (addiction) and may not be receiving proper treatment by qualified personnel. In addition, the diverter is likely engaged in illegal and unprofessional activities, such as falsifying medical records. On a larger and more serious scale, transmission of infection via syringes used by diverters (which are subsequently refilled with saline and used to inject patients) has significant consequences. In fact, a systematic review of the literature from 2004 to 2014 identified 6 reported outbreaks (2 involving gram-negative bacteremia and 4 involving hepatitis C) that could be attributed to drug diversion, with exposure of more than 30 000 patients, of whom at least 128 became infected![7] These preventable transmissions to innocent patients should be unacceptable to health care workers, whose main goal is to care for patients, not harm them.

To systematically tackle the issue of diversion, each hospital must have an interdisciplinary group, pursuing parallel work streams (education, detection, response/investigation, prevention), with endorsement from the organization's executives. The work should ideally involve not just front-line clinicians and pharmacy team members, but also human resources, informatics, decision support, security, corporate health, and risk/legal staff as needed, with centralized oversight by a corporate steering committee with dedicated resources. As with any large-scale effort, this work cannot be done all at once, especially within health care systems that are constantly dealing with resource allocation dilemmas. But starting small, for example, by promoting awareness and education, can be a reasonable first step. Alternatively, this work could be part of a larger institutional opioid stewardship program. Fortunately, our US colleagues have published a comprehensive guideline on this topic, which should be a "must read" for all pharmacy team members with responsibilities for safeguarding controlled substances.[8] The Canadian Society of Hospital Pharmacists has also developed diversion guidelines,[9] which were published in early 2019, with accompanying educational events and toolkits.

It is time to start examining your own practices related to diversion, as Videau and others[10] have done, describing their experiences elsewhere in this issue. Although the adherence rates reported in that article are not stellar, this work can be framed as a quality improvement exercise that may garner further acceptance by hospitals' C-suites. In fact, which would you prefer: a long, drawn-out investigation by government employees involving subpoenas, staff interviews, and large-scale audits, or a self-directed quality improvement plan that will result in better patient safety and outcomes, and even potentially financial savings?

Let's start paying attention to diversion!

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Détournement et négligence : Il est temps d'agir!

par Clarence Chant

Le détournement de médicaments, défini comme « l'acheminement de médicaments d'ordonnance vers le marché noir » représente un problème qui n'est ni rare ni nouveau[1]. Si les opioïdes sont fréquemment détournés, les benzodiazépines, les stéroïdes anabolisants ainsi que d'autres substances non contrôlées, telles que le propofol et l'érythropoïétine, sont aussi des cibles possibles. Toutefois, le détournement demeure un sujet tabou dans la plupart des établissements et a même été désigné comme « le secret de famille des soins de santé » lors d'un épisode de *W5*, une émission documentaire canadienne qui existe de longue date[2].

Alors que la crise des opioïdes fait rage, phénomène en partie attribuable au détournement de médicaments des hôpitaux, il semble paradoxal que les membres de l'équipe de pharmacie, qui sont les gardiens du système de distribution des médicaments, ne se sentent pas davantage concernés. Le bulletin d'informations d'un autre diffuseur, qui a colligé les résultats obtenus grâce à de multiples demandes d'accès à l'information présentées entre 2010 et 2017, a établi que Santé Canada avait reçu 5689 rapports sur des opioïdes manquants dans des hôpitaux[3]. Plus alarmant encore est le fait que 4375 (77 %) de ces rapports indiquaient que la cause des disparitions était inconnue[3]. Ces statistiques inquiétantes représentent davantage que de simples données visant à faire peur; elles ont des conséquences cliniques, humaines et financières bien réelles. En décembre 2013, par exemple, une infirmière et un médecin ont été retrouvés inconscients dans leurs toilettes respectives d'un hôpital de l'University of Michigan Health System[4]. Tous deux avaient pris une surdose d'opioïdes détournés; le médecin a pu être réanimé, mais l'infirmière est décédée. L'enquête a révélé que le détournement durait depuis des années : plus de 16000 comprimés d'oxycodone ont été détournés dans ce seul établissement hospitalier[4]. L'Université du Michigan a finalement accepté de payer 4,3 millions de dollars américains en dédommagement à la suite de l'enquête[5]. En raison de l'absence de déclarations, il est impossible de déterminer l'ampleur du détournement au Canada, aux États-Unis ou à l'international. Même si les taux varient d'une région à l'autre, ce phénomène est forcément répandu à travers le monde et mérite notre attention.

Les causes de cette réticence à parler ouvertement du détournement de médicaments d'ordonnance sont nombreuses, notamment le fait que n'importe quel professionnel de la santé ayant un accès autorisé ou non aux médicaments et qui connaît le système et ses faiblesses peut détourner ce type de médicaments. Le risque de détournement existe à tous les niveaux du système, de l'approvisionnement à l'entreposage en passant par la distribution et l'administration; même les établissements possédant des systèmes pointus de contrôle automatisé ne sont pas à l'abri[6]. C'est ce qui est arrivé à l'Université du Michigan, où plus de 100 cabinets de distribution automatisés avaient été installés. Le détournement n'était pas attribuable à ces machines, mais il représentait plutôt la réalité d'un système de santé tenu de répondre à la fois aux besoins des patients et de contrôler l'accès aux médicaments dans un environnement où les échanges et les opérations complexes foisonnent et où, malheureusement, le personnel connaît aussi bien les forces que les faiblesses du système. Prescrire des opioïdes et ne pas les administrer (ou partiellement) ou prescrire des médicaments à un patient qui a déjà subi son opération représentent des techniques de détournement répandues. Un moyen plus radical consiste retirer de la poubelle les timbres de fentanyl utilisés pour en extraire le contenu restant avec une seringue. La gestion de l'accès aux médicaments est particulièrement perméable dans les établissements qui emploient encore un système de comptabilisation manuel et papier encore très répandu au Canada. De plus, les symptômes de la consommation de médicaments peuvent être subtils et le détournement peut être réalisé par des membres de l'équipe qui semblent bien intentionnés, en s'offrant pour administrer des médicaments à la place d'un collègue qui prend une pause, par exemple. L'absence de suivi systématique et de récolte de données contribue à obscurcir le secret, et c'est sans compter qu'il est mal vu de dénoncer un collègue.

Toutefois, ces considérations doivent être comparées aux conséquences sur les patients qui reçoivent parfois des traitements de la part d'un membre du personnel sous influence ou qui doivent endurer de la douleur en raison d'un détournement. Le danger guette aussi l'auteur du détournement, qui peut souffrir de dépendance sans recevoir le traitement approprié. De plus, il peut être impliqué dans des activités illégales qui contreviennent

à profession, comme la falsification de dossiers médicaux. Plus sérieusement encore, la transmission d'infection par les seringues qu'utilisent les auteurs de détournements (réutilisées pour injecter des solutions salines aux patients) a des conséquences bien réelles. En effet, un examen systématique des études réalisées entre 2004 et 2014 a révélé six foyers d'infection (deux impliquant des bactéries à Gram négatif et quatre, l'hépatite C) attribuables au détournement de médicaments d'ordonnance, qui auraient pu toucher plus de 30 000 patients, dont 128 au moins ont été infectés[7]. Ces contaminations évitables sont inacceptables pour les professionnels de la santé, dont l'objectif premier est de prendre soin des patients et non de leur causer du tort.

Pour lutter systématiquement contre le phénomène de détournement, chaque hôpital doit mettre sur pied un groupe interdisciplinaire œuvrant dans plusieurs domaines (éducation, détection, enquête, prévention) avec l'assentiment des cadres de l'établissement. Idéalement, le groupe devrait comprendre non seulement les cliniciens de première ligne et les membres de l'équipe de pharmacie, mais aussi les ressources humaines, les informaticiens, les conseillers, l'équipe de la sécurité, les responsables de la santé des employés et le personnel juridique, sans oublier une supervision par le comité de direction centralisé possédant les ressources nécessaires. Comme dans toute entreprise de grande envergure, on ne peut tout faire en même temps, surtout lorsqu'on doit agir au sein d'établissements hospitaliers constamment aux prises avec des dilemmes posés par l'attribution des ressources. Promouvoir la sensibilisation et l'éducation constituerait donc un premier pas raisonnable. Par ailleurs, cette démarche pourrait s'inscrire dans le cadre d'un plus vaste programme de gestion responsable des opioïdes. Heureusement, nos collègues américains ont publié des lignes directrices exhaustives sur le sujet[8], que les membres des équipes de pharmacie responsables de surveiller l'usage des substances règlementées devraient obligatoirement lire. La Société canadienne des pharmaciens d'hôpitaux a aussi publié en 2019 des lignes directrices accompagnées d'outils et d'activités éducatives[9].

Il est temps de se pencher sur nos propres pratiques en matière de détournement et de partager nos expériences, comme le font Videau et collab. dans le présent numéro[10]. Même si les taux d'adhésion rapportés dans cet article ne sont pas phénoménaux, ce travail peut être vu comme un exercice d'amélioration qualitative qui ralliera le comité décisionnel d'autres hôpitaux. Préférez-vous une enquête gouvernementale impliquant des assignations à comparaître, des vérifications à grande échelle et des rencontres avec le personnel ou bien un plan d'amélioration conçu et mis en place à l'interne qui assurera la sécurité des patients et peut-être même, des épargnes à long terme?

Commençons dès maintenant à nous soucier du détournement.

[Traduction par l'éditeur]

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Compliance with Recommended Practices for Management of Controlled Substances in a Health Care Facility and Corrective Actions

Manon Videau, Suzanne Atkinson, Maxime Thibault, Denis Lebel, and Jean-François Bussières

ABSTRACT

Background: Pharmacists are required to maintain a secure inventory of medications and to ensure proper, safe, and diversion-free dispensing practices.

Objectives: The primary objectives of this study were to determine compliance with recommended practices for the management of controlled substances in a mother–child teaching hospital and to identify actions to improve compliance. The secondary objective was to identify steps in the drug pathway for controlled substances and associated failure modes in the study hospital.

Methods: This descriptive cross-sectional study used a framework developed by the California Hospital Association (CHA) to assess compliance with recommended practices for the management of controlled substances in hospitals. For each criterion, a research assistant observed practices within the pharmacy, on patient care units, at outpatient care clinics, and in operating and delivery rooms. The level of compliance was recorded as compliant, partially compliant, or noncompliant. An Ishikawa diagram was developed to illustrate steps in the drug pathway and associated failure modes related to the use of controlled substances in the study hospital.

Results: The pathway for controlled substances at the study hospital was compliant for 56 (49.6%) of the 113 CHA criteria, partially compliant for 27 (23.9%) of the criteria, and noncompliant for 24 (21.2%) of the criteria; the remaining 6 (5.3%) criteria were not applicable. This practice evaluation highlighted 22 corrective actions, 12 (55%) that could be implemented in the short term, 8 (36%) suitable for implementation in the medium term, and 2 (9%) suitable for both the short and medium term. A total of 57 potential failure modes related to the use of controlled substances were identified.

Conclusions: The pathway for controlled substances at the study hospital was compliant with almost half of the CHA criteria, and 22 corrective actions were identified. Pharmacists, physicians, and nurses should be mobilized to optimize the use of controlled substances throughout the drug-use process.

Keywords: controlled substances, practice guidelines, management audit, drug diversion

RÉSUMÉ

Contexte: Les pharmaciens sont responsables de maintenir à jour les réserves de médicaments et doivent faire en sorte que les pratiques de distribution soient adéquates, sûres et exemptes de détournement.

Objectifs : Les objectifs principaux de la présente étude consistaient à déterminer le degré de conformité aux pratiques de gestion des substances contrôlées, recommandées dans un hôpital universitaire mère-enfant, et de trouver des mesures pour améliorer leur degré de conformité. L'objectif secondaire visait à recenser les étapes que suivent les substances contrôlées dans le circuit des médicaments et les modes de défaillance qui y sont associés dans l'hôpital à l'étude.

Méthodes : La présente étude descriptive et transversale s'appuyait sur un cadre mis au point par la California Hospital Association (CHA), qui sert à évaluer le degré de conformité aux recommandations relatives aux pratiques de gestion des substances contrôlées dans les hôpitaux. Pour chaque critère, un assistant de recherche observait les pratiques dans le service de pharmacie, les unités de soins, les cliniques de consultation externe et les salles d'opération ou les salles d'accouchement. Il évaluait le degré de conformité à l'aide d'un des qualificatifs suivants : conforme, partiellement conforme ou non conforme. Un diagramme d'Ishikawa a été conçu pour illustrer les étapes du circuit des médicaments et les modes de défaillance associés à l'utilisation de substances contrôlées dans l'hôpital à l'étude.

Résultats : Le circuit des substances contrôlées à l'hôpital où se déroulait l'étude était conforme à 56 (49,6 %) des 113 critères de la CHA, partiellement conforme à 27 (23,9 %) critères et non conforme à 24 (21,2 %) critères; les 6 (5,3 %) critères restants n'étaient pas applicables. Cette évaluation des pratiques a mis en évidence 22 actions correctives, dont 12 (55 %) pouvaient être mises en place à court terme, 8 (36 %) à moyen terme et 2 (9 %) à court ou à moyen terme. Les investigateurs ont repéré 57 modes de défaillance potentiels liés à l'utilisation de substances contrôlées.

Conclusions : L'analyse du circuit des substances contrôlées à l'hôpital où se déroulait l'étude a révélé que près de la moitié des critères de la CHA étaient conformes, et 22 actions correctives ont été proposées. Les pharmaciens, médecins et infirmières devraient participer à l'optimisation

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de l'utilisation des substances contrôlées dans l'ensemble du processus de distribution des médicaments.

Mots clés : substances contrôlées, guide de pratique, audit opérationnel, détournement de médicaments

INTRODUCTION

Stealing controlled substances is difficult in health care settings. Prescribing, dispensing, and administering such substances rely on a structured process that involves numerous professionals and witnesses, policies and procedures, tools and technologies. Each year, doctors, nurses, and pharmacists who try to divert controlled substances face the dire consequences of their attempts, including fines, disciplinary discharge, or temporary or permanent suspension from work.[1] Although this system is highly effective, clinical staff and administrators must be proactive in preventing diversion, especially as the health care landscape evolves through automation.

Under the Convention on Psychotropic Substances of 1971, which was adopted at the United Nations Conference for the Adoption of a Protocol on Psychotropic Substances, signatory countries undertake to put in place, by means of their own legislation, a system of international controls on psychotropic substances.[2] This convention responds to "the diversification and expansion of the spectrum of drugs of abuse and [introduces] controls over a number of synthetic drugs according to their abuse potential on the one hand and their therapeutic value on the other."[2]

In Canada, the *Controlled Drugs and Substances Act*, passed in 1996, provides a legal framework for the distribution and sale of controlled substances.[3] Several sets of regulations fall under this legislation, including the *Narcotic Control Regulations*,[4] the *Benzodiazepines and Other Targeted Substances Regulations*,[5] and the *Precursor Control Regulations*.[6] For the purposes of this article, we use the term "controlled substances" to describe narcotics, including opioids, controlled drugs, and benzodiazepines dispensed by community and hospital pharmacies. These substances are described in Schedules I to V of the legislation.

Under this legal framework, Canadian pharmacists are required to maintain a secure medication inventory and to ensure proper, safe, and diversion-free dispensing practices. In addition, the legal framework for each province includes provisions requiring that pharmacists maintain adequate control of controlled substances; for example, statement 3.5 of the Standards of Practice of the Ordre des pharmaciens du Québec (the college of pharmacists for the province of Quebec) states that the pharmacist puts in place control mechanisms to prevent diversions.[7]

However, some legally dispensed doses may be diverted, either by health care professionals or by patients, to illegal distribution channels (e.g., the black market).[8] In addition, illegal controlled substances (e.g., heroin, carfentanyl) may enter the Canadian market through various channels, including e-commerce or illegal importation by transport of goods or by humans. The availability of legal and illegal controlled substances contributes to misuse, addiction, and overdose.

Canada and the United States are among the top users of opioids per capita, and consumption in these countries continues to increase, even while pain remains poorly managed for some patients.[9,10] Currently, the main challenge is to effectively combat misuse and diversion while maintaining access to effective pain management. According to the International Narcotics Control Board of the United Nations, the average dose of morphine consumed per capita in 2015 was 117.7 mg in Canada but only 61.0 mg in the United States, 32.2 mg in Australia, 22.8 mg in the United Kingdom, and 27.6 mg in France.[11] These utilization rates are notably influenced by the availability of various commercial forms, but also by the prescription of these substances to patients. As such, physicians and pharmacists contribute to the availability of these substances for patient care.

According to the government of Canada, the country is facing a national opioid crisis: "The growing number of overdoses and deaths caused by opioids, including fentanyl, is a public health emergency. This is a complex health and social issue that needs a response that is comprehensive, collaborative, compassionate and evidence-based."[12] The Canadian Institute for Health Information has provided evidence of the crisis, reporting that a total of "21.3 million prescriptions for opioids were dispensed in 2017, compared with 21.7 million in 2016. This is the first decline in overall prescription numbers between 2012 and 2017."[13] Despite this decrease in prescriptions, O'Connor and others[14] reported that opioid poisonings resulted in an average of 16 hospitalizations a day in 2016/17, a 53% increase over the previous 10 years. The Federal Action on Opioids initiative has reported that "the opioid crisis can be linked to the rapid rise in rates of drug overdoses and death involving both: prescription opioids; and increasingly toxic illegal drugs due to the increased presence of powerful illegal substances, such as fentanyl, a drug 50-100 times more potent than morphine."[15] The Canadian government also reported that there were 3286 apparent opioid-

related deaths in Canada in 2018, of which 93% were accidental (unintentional).[16] In response to this crisis, the government has put into place a national Consultation on the Canadian Drugs and Substances Strategy.[17]

In 2007, Baldisseri reported that 10% to 15% of health care professionals misuse drugs (including opioids [1.1%] and tranquilizers [2.3%]) or alcohol during their lifetime, a rate similar to that observed in the general population.[18] These professionals, who are exposed to controlled substances in the course of their work, are at risk of contributing to the problem of diversion.[19] The extent of substance diversion in the hospital setting is unknown and difficult to quantify. Health care professionals have privileged access to controlled substances, and problems related to overprescribing, misuse, and diversion may contribute to adverse events, omission of doses for patients, and other unintended consequences.[19,20] In response to current legal obligations, the risks of diversion and abuse, and the opioid crisis, the Quebec Ministry of Health and Social Services issued a warning to hospital directors about the risk of theft of narcotics in hospitals (Lafleur P, "Vigilance accrue pour les narcotiques" — letter sent by e-mail to presidents and directors general of public health care and social services establishments, July 9, 2018). Given the enteral and parenteral use of controlled substances in hospitals and the pivotal role played by hospital pharmacists in the proper use of these substances, we were interested in compliance with recommended practices for controlled substances in our health care facility.

The primary objectives of this descriptive cross-sectional study were to determine compliance of the study hospital with recommended practices for the management of controlled substances and to identify potential actions to improve compliance. The secondary objective was to identify the steps of the drug pathway for controlled substances in the hospital setting and associated failure modes within the study hospital.

METHODS

Practice Setting

The study was conducted from January to April 2018 at Centre hospitalier universitaire Sainte-Justine, a 500-bed mother–child academic hospital located in Montréal, Quebec. At this facility, every drug prescription is validated by a pharmacist and is visible to nursing staff within the patient care file or is accessible through a paper or electronic medication administration record (MAR), depending on the hospital department.

Management of Controlled Substances

The controlled substances listed on the hospital's formulary are distributed in patient care units by means of automated dispensing cabinets (ADCs) (n = 40); distribution in ambulatory clinics is recorded in a handwritten controlled substance log. In the operating and delivery rooms, an anesthesia narcotics box holds a standard selection of controlled substances and a controlled substances log, where the anesthesiologist documents the doses administered and destroyed during each working day. The ADCs are interfaced bidirectionally with the pharmacy information system. To obtain a dose from an ADC, the nurse must enter an access code and password or provide biometric identification (fingerprint). The ADCs are replenished by authorized senior pharmacy technicians using barcode readers; the process must be witnessed. Caregivers participate in inventory control through blind counts of doses dispensed by the ADC or witnessed counts (at each shift change) of doses stored in a locked cabinet. Any discrepancy in inventory must be reconciled by the assistant head nurse on the shift. Unresolved discrepancies are subject to joint investigation by the pharmacy department (a senior pharmacy technician and/or pharmacist) and the administrator of the patient care unit.

Controlled substances are generally dispensed in single-dose format. However, a majority of formats usually require additional manipulation by nurses to put the prescribed dose into a syringe or bag. A few products are dispensed in bottles (e.g., morphine and codeine in liquid form for oral administration). The preparation and administration of most controlled substances requires a double check and double signature on the MAR. Some prescriptions of controlled substances are not validated by the pharmacist because they are required on an urgent basis (e.g., in an emergency situation or in an operating or delivery room). Waste and destruction of residual quantities are performed and documented by nursing staff, with all processes being witnessed by another member of the nursing staff.

Compliance Framework

Before we could assess compliance of the hospital's practices for management of controlled substances, it was necessary to identify a suitable tool for this purpose. We used Google and Google Scholar to search the Internet for relevant tools, using the keywords "controlled substances" and "hospital" and "diversion". After review of all tools identified in the search, we selected a framework produced by the California Hospital Association (CHA).[21] No equivalent tool reflecting Canadian regulations was found. This framework, first published in 2013 to support hospital self-assessment for secure management of controlled drugs and prevention of their diversion, incorporates 12 themes, 24 key statements, and 113 compliance criteria according to stages of the drug pathway. [Note: The framework has since been updated, but the updated version was not available at the time of our study.]

For each criterion, a research assistant (M.V.) observed practices within the hospital pharmacy, on the patient care units, in outpatient care clinics, and in the operating and delivery rooms, and recorded the level of compliance as compliant, partially compliant, or noncompliant. Because US and Canadian requirements for the management of controlled substances are different,

practices that were deemed noncompliant with criteria derived from US regulations but compliant with equivalent Canadian regulations were recorded as compliant. Where no equivalence between Canadian and US regulations was found, the criterion was designated as not applicable. The categorization was subsequently validated by the other members of the research team, with disagreements resolved by consensus. Corrective actions were identified for each compliance criterion that was categorized as noncompliant or partially compliant. An action plan and schedule for implementing the corrective actions were also produced.

Ishikawa Diagram

In addition to assessing the compliance of hospital practices for management of controlled substances, we developed an Ishikawa diagram of steps in the drug pathway for use of controlled substances in hospitals, as well as the associated failure modes at the study hospital. The purpose of the diagram was to identify and better understand weaknesses in the drug pathway that could lead to diversion. This diagram was developed iteratively by a research assistant (M.V.), with validation by the rest of the research team (S.A., M.T., D.L., J.-F.B.).

RESULTS

The pathway for controlled substances at the study hospital was compliant with 56 (49.6%) of the 113 CHA criteria, partially compliant with 27 (23.9%) of the criteria, and noncompliant with 24 (21.2%) of the criteria; the remaining 6 criteria (5.3%) were not applicable (Table 1). Under Canadian regulations, any unexplained loss of controlled substances must be traced and reported to Health Canada within 10 days, but there is no obligation to report to a board of pharmacy. Similarly, Canada does not have the equivalent of the US Drug Enforcement Administration form 222 for ordering controlled substances. These criteria were therefore considered not applicable in the Canadian context. The practice evaluation highlighted 22 corrective actions, 12 (55%) that could be implemented in the short term, 8 (36%) suitable for implementation in the medium term, and 2 (9%) suitable for both the short and medium term. These proposed actions included the creation of a subcommittee (under the auspices of the pharmacy and therapeutics committee) to monitor controlled substances, updates of policies and procedures, and development of new audit and training tools.

The Ishikawa diagram (Table 2) highlighted 14 major steps in the management of controlled substances in health care facilities: selection, ordering (procurement), receipt, transport, storage, computerization (e.g., ADCs), prescription, compounding (including validation), dispensing, administration, waste and disposal or destruction (of both unexpired and expired/unusable drugs), equipment, and quality management. Different personnel would be involved at each of these steps. In addition, we identified 57 potential failure modes. Eight of these failure modes related to the prescribing of controlled substances by the physician. Prescribing too many different substances or too many doses at the time of discharge from hospital can lead to a variety of outpatient problems, including overdose, accidental intoxication, and resale. The failure modes related to selection, ordering (procurement), receipt, transport, storage, computerization, pharmaceutical validation, and destruction (of pharmacy stock) would involve primarily pharmacy staff. As such, staff members must ensure that inventory is tracked at all times and that prescribed drugs are appropriate for each patient. Failure modes affecting administration, return, waste, and destruction (e.g., of partial doses not administered) are more likely related to nurses' practice. All of these failure modes can contribute to misuse of controlled substances within the hospital and after patient discharge, including abuse, prolonged use, dependence, overdose, intentional or involuntary intoxication, and diversion.

DISCUSSION

To our knowledge, this is the first study describing compliance with recommended practices for management of controlled substances in a Canadian health care facility. In 2011, McClure and others[22] published the results of a survey of 135 pharmacy departments in acute care facilities in the United States to identify diversion-detection practices for controlled substances. They found that 65% of respondents reported using surveillance cameras directed at the storage areas for controlled substances in the pharmacy, 31% restricted access to these storage areas, 31% prohibited personal items (e.g., purses, backpacks) in the storage areas for controlled substances, and 4% altered drug packaging by deconditioning or marking the label packaging to prevent theft and resale.[22]

We found that practices at the study hospital were fully compliant with about half of the CHA criteria and partially compliant with another quarter of the criteria; however, practices were noncompliant with about 20% of the criteria. The hospital's pharmacy department has fully satisfied the requirements of the national accreditation body (Accreditation Canada) and the Ordre des pharmaciens du Québec; furthermore, it offers state-of-the-art drug management (e.g., single-dose distribution, centralization of preparations, traceability of drug preparation through digitization, narcotic boxes in operating rooms) and technologies (e.g., electronic MARs, ADCs with barcode readers in all care units). Nonetheless, this study has shown that improvements can still be made to optimize the management of controlled substances.

Some of the technologies already being used in the study hospital could contribute to reducing the risk of diversion. ADCs increase the traceability of medication-related activities by allowing confirmation, through user name, password, or biometric features, of anyone involved in replenishing or dispensing drug doses. However, this technology is not flawless, and previous studies have highlighted failure modes associated with this equipment. Dubois and others[23] assessed risks of diversion associated

Table 1 (Part 1 of 2). Profile of Compliance Relating to Management of Controlled Substances in Health Care Institutions and Corrective Actions

Themes and Key Statements*	Level of Compliance (% of Criteria)				Corrective Actions
	C	PC	NC	NA	
Safety teams / organizational structure 1. Organization defines CS diversion-prevention program (*n* = 4 criteria)	0	50	50	0	*Short term* 1. Implement a permanent subcommittee of the pharmacy and therapeutics committee, dedicated to CS *Medium term* 2. Develop a formal CS diversion-prevention program
2. Organizational structure is in place that supports an effective CS diversion-prevention program (*n* = 5 criteria)	0	80	20	0	*Short term* 3. Update relevant policies and procedures (e.g., contracts, purchase orders, inventory records, stock replenishment documents)
3. Organization proactively collaborates with local law enforcement (*n* = 1 criterion)	0	0	100	0	See corrective action 2 (develop formal CS diversion-prevention program)
4. Organization fulfills all reporting requirements for diversion or loss of CS (*n* = 3 criteria)	0	33	0	67	*Short term* 4. Develop a web page to quickly report diversion/loss and its management, including notification to regulatory authority
Access to information, accurate reporting, monitoring, surveillance, detection systems 5. Organization reviews and audits relevant data that could indicate potential CS diversion (*n* = 1 criterion)	100	0	0	0	None required.
6. Organization tracks and reviews measures recommended by medication safety committee or other designated groups reporting directly to a medical staff committee (*n* = 4 criteria)	50	50	0	0	*Short term* 5. Develop structured approach involving at least 3 trained pharmacy technicians and 2 pharmacists to periodically and systematically audit a sample of transactions from the pharmacy information system, ADCs, and MARs 6. Develop a checklist of all key activities of the CS pharmacy technician to maintain a high level of awareness
Facility expectations 7. Organization communicates the expectation that staff "speak up" when they become aware of an issue related to CS diversion (*n* = 2 criteria)	50	50	0	0	*Medium term* 7. Hold an annual event on CS use and misuse to increase awareness of ethical obligations of all stakeholders and establish an anonymous reporting process
8. Organization establishes full disclosure policy (*n* = 1 criterion)	100	0	0	0	None required.
9. Organization's staffing practices support an effective organization-wide CS diversion-prevention program (*n* = 6 criteria)	33	17	50	0	*Short term* 8. Develop a dedicated page on the hospital intranet for all key messages, documents, and tools regarding CS 9. Review the register for paper and electronic signatures of prescribers
10. Organization does not allow sharing of pass codes (*n* = 1 criterion)	100	0	0	0	None required.
Education of staff (and patients) 11. Organization has in place an effective and comprehensive training and education program for all staff on CS diversion prevention (*n* = 7 criteria)	14	43	43	0	*Medium term* 10. Develop an e-learning program for nursing and medical students and residents 11. Develop a CS committee within the regulatory authority and in key pharmacy associations to share good practices and challenges
Storage and security 12. Organization stores CS and other high-risk items securely, in all settings and circumstances (*n* = 1 criterion)	100	0	0	0	None required.
13. Organization has process in place for securing CS (*n* = 13 criteria)	69	8	23	0	*Short term* 12. Include in the revised policies and procedures information about patients' own CS (e.g., cannabis oil)

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Table 1 (Part 2 of 2). Profile of Compliance Relating to Management of Controlled Substances in Health Care Institutions and Corrective Actions

Themes and Key Statements*	Level of Compliance (% of Criteria)				Corrective Actions
	C	PC	NC	NA	
14. Organization uses camera surveillance in high-risk areas as appropriate (*n* = 1 criterion)	100	0	0	0	*Medium term* 13. Add camera surveillance in key areas of patient care wards, operating room, and emergency department
Procurement 15. Organization effectively and safely handles procurement in the hospital pharmacy (*n* = 10 criteria)	60	0	0	40	*Medium term* 14. Provide additional ADCs for ambulatory clinics for CS management
Prescribing 16. Organization's ordering and prescribing practices minimize the risk of CS diversion (*n* = 5 criteria)	60	40	0	0	*Short and medium term* 15. Periodically review preprinted orders to optimize CS prescribing 16. Conduct periodic spot audits in operating and delivery rooms
Preparation and dispensing 17. Organization's preparation and dispensing practices minimize the risk of CS diversion (*n* = 12 criteria)	33	50	17	0	*Short term* 17. Purchase secure transport box for stock replenishment by technical staff
Administration 18. Organization's CS administration practices minimize the risk of CS diversion (*n* = 6 criteria)	83	0	17	0	See corrective action 3 (update relevant policies and procedures [e.g., contracts, purchase orders, inventory records, stock replenishment documents])
Handling of waste 19. Organization's "waste" handling practices maintain chain of custody, to minimize the risk of CS diversion (*n* = 6 criteria)	50	0	50	0	*Short term* 18. Conduct periodic spot audits for waste and returns *Medium term* 19. Purchase a Raman spectrophotometer for CS identification
20. Organization's practices for handling unused CS, empty CS containers, and CS returned to pharmacy minimize the risk of diversion (*n* = 10 criteria)	80	10	10	0	*Short term* 20. Include in the revised policies and procedures information about drug returns
Monitoring of CS and process if diversion is suspected 21. Organization removes access to CS if diversion is suspected (*n* = 2 criteria)	100	0	0	0	None required.
22. Organization regularly monitors CS through inventory, reports, and audits (*n* = 9 criteria)	22	33	45	0	*Medium term* 21. Develop a structured report to support interhospital comparisons (e.g., DDD, oral morphine equivalent dose)
23. Process is in place to resolve CS discrepancies (*n* = 2 criteria)	100	0	0	0	*Short term* 22. Develop a video for nursing staff
24. Organization has a standard process to investigate cases of potential diversion (*n* = 1 criterion)	100	0	0	0	None required.
Overall no. (%) (*n* = 113)	56 (49.6)	27 (23.9)	24 (21.2)	6 (5.3)	

ADC = automated dispensing cabinet, C = compliant, CS = controlled substance, DDD = defined daily dose, MAR = medication administration record, NA = not applicable, NC = noncompliant, PC = partially compliant.
*Based on 2013 framework of the California Hospital Association.[21]

with ADCs and identified 27 failure modes specific to this type of equipment, with a 1.2% inventory discrepancy for movement of controlled substances in 19 cabinets over a 5-month period. Elsewhere, Crowson and Monk-Tutor[24] demonstrated that the number of individuals likely to divert controlled substances from decentralized ADCs was 1.12 per 100 beds. More recently, a medical resident at the Montreal Children's Hospital (in the same city as the setting for the current study) was arrested in possession of several vials of fentanyl that he had diverted from operating room carts.[25] Although most health care facilities in Canada now use ADCs, this single technological measure is insufficient to detect and eliminate diversions. Some authors have described additional tools for comparing prescriptions with doses dispensed and actually administered.[26,27] Without these audit tools, it is possible to bypass the ADCs.

Several factors may have contributed to the noncompliance observed in our study. Canadian regulations differ from US regulations in various aspects (e.g., in Canada, organizations are prevented by law from having a "for cause" policy for drug testing). The comparison of practices at the study hospital against

Table 2 (Part 1 of 2). Ishikawa Diagram of the 14 Steps in the Drug Pathway for Controlled Substances in Health Care Facilities and Associated Failure Modes

Step of Drug Pathway for CS	Failure Modes for CS
1. Selection on a hospital formulary	1. Suboptimal product selected 2. Suboptimal concentration selected 3. Inappropriate format selected
2. Procurement	4. Unauthorized order sent to a drug manufacturer or wholesaler 5. Wrong product ordered 6. Wrong quantity ordered
3. Receipt	7. Loss of packing slip or bill 8. Wrong product selected for data entry 9. Wrong quantity selected for data entry 10. Wrong storage location used 11. CS product replaced by a faked alternative 12. CS quantity confirmed on drug procurement software, but drug diverted/stolen 13. Data for CS quantity not entered in drug procurement software and drug diverted/stolen
4. Transport	14. Product stolen before arrival at final destination 15. Sharing by authorized staff of access codes for pneumatic tubing
5. Storage in pharmacy department	16. Unauthorized individuals having access to storage area 17. Product stored at wrong location 18. Product replaced by a faked alternative 19. Product stolen
6. Replenishment of automated dispensing cabinets or locked narcotics box	20. Wrong product replenished 21. Wrong quantity entered 22. Product stolen during replenishment process
7. Prescribing	23. Prescribing of a CS product by unauthorized staff 24. Suboptimal product prescribed 25. Suboptimal concentration prescribed 26. Suboptimal format prescribed 27. Suboptimal quantity prescribed 28. Suboptimal dose prescribed 29. Faked order 30. Modified order
8. Compounding, validation, and dispensing (central pharmacy)	31. Wrong product entered, validated, and dispensed 32. Wrong concentration entered, validated, and dispensed 33. Wrong format entered, validated, and dispensed 34. Wrong quantity entered, validated, and dispensed 35. Wrong dose entered, validated, and dispensed
9. Dispensing from ward stock	36. Sharing of ADC keys or passwords by authorized staff 37. Ampoule of CS reported as being broken while it is diverted 38. CS dose dispensed from ADC is not administered to the patient
10. Administration	39. CS dose dispensed from ADC is registered in the MAR but is not administered to the patient 40. A fraction of the dispensed dose of a prescribed CS is not administered to the patient, and the residual amount is diverted 41. Fake patient created in ADC interface to justify illegal dispensing of CS dose
11. Waste and disposal of unexpired or residual amount	42. Content of a dispensed CS is replaced by an alternative product and is returned to the ADC 43. Unused amount of CS not returned properly to ADC 44. Unused amount of CS not returned properly to ADC but registered in the software as being returned 45. Unused amount of CS not destroyed properly (with a witness) 46. Unused amount of CS replaced by an alternative for diversion

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Table 2 (Part 2 of 2). Ishikawa Diagram of the 14 Steps in the Drug Pathway for Controlled Substances in Health Care Facilities and Associated Failure Modes

Step of Drug Pathway for CS	Failure Modes for CS
12. Waste and disposal of expired or unusable amount	47. Expired or unusable CS replaced by an alternative product and replaced in stock for reuse
	48. Expired or unusable CS not destroyed properly and replaced in stock for reuse
	49. Expired or unusable CS stolen from residual amount in patient care areas
	50. Expired or unusable CS stolen after signature of a witness to confirm destruction or with complacent witness
	51. Unsafe waste container used to dispose of residual CS amount
13. Defective equipment (any stage of pathway)	52. Defective pocket in ADC remains unrepaired
	53. CS stocked in open-matrix drawer
14. Quality management and investigation	54. CS discrepancies remain unresolved
	55. Absence or postponement of control audits (e.g., periodic audits omitted)
	56. Diversion signals are not recognized
	57. Suspected diversion is underreported

ADC = automated dispensing cabinet, CS = controlled substance, MAR = medication administration record.

a US framework is therefore imperfect. Although legislation and regulations governing controlled substances exist in Canada, the relevant federal department (Health Canada) has not published an explicit and comprehensive guide to these substances since 1990,[28] with the exception of an information document for hospitals concerning benzodiazepines and targeted substances, which first appeared in 1998.[29] In Quebec, the Ordre des pharmaciens du Québec has published a selection of its standards of practice to clarify certain terms and conditions related to controlled substances.[30-33] Furthermore, pharmacy management teams are subject to dozens of standards and thousands of compliance criteria, which is challenging for practitioners.[34] Thus, it would be desirable for Health Canada to publish an updated guide covering all legal requirements for the management of controlled substances. In addition, because pharmacy practice falls under provincial jurisdiction, each provincial college of pharmacy must play a role in the application of such a guide. External audits can help to improve practices, and Health Canada has recently resumed its program of large-scale inspection of community pharmacies and pharmacy departments of health care facilities.[35] The various organizations responsible for auditing the drug pathway should work together, using the same audit tool, to ensure agreement on standards and criteria and to channel efforts for the proper use of controlled substances.

Our study highlights 22 corrective actions that could be implemented in the short or medium term. The establishment of a subcommittee for the management of controlled substances, under the auspices of the pharmacy and therapeutics committee, would be a cornerstone for mobilizing physicians, nurses, pharmacists, and risk management counsellors to support implementation of these corrective actions. The pharmacy and therapeutics committee must also ensure proper use and monitoring of controlled substances, through an approach similar to antimicrobial stewardship. Such measures are already in place in the United States, where (since January 1, 2018), hospitals must meet new, revised pain assessment and management standards as a requirement for accreditation by the Joint Commission.[36] The evaluation and improvement of prescribing practices by practitioners is essential to reducing misuse.

In Canada, under the Joint Statement of Action to Address the Opioid Crisis, the Canadian Society of Hospital Pharmacists (CSHP) and other organizations have committed "to work within their respective areas of responsibility to improve prevention, treatment, harm reduction and enforcement associated with problematic opioid use through timely, concrete actions that deliver clear results."[37] On August 1, 2018, CSHP released for consultation its guidelines on secure management and prevention of diversion of controlled drugs and substances in hospitals and health care facilities, and the approved guidelines were published in early 2019.[38] These guidelines are meant to replace Health Canada's outdated 1990 guide, and they incorporate all elements appearing in the CHA framework that was used for the current study. Similar guidelines have been published by the American Society of Health-System Pharmacists.[39] It is hoped that CSHP will also develop a self-assessment tool to facilitate the use of its guidelines.

This descriptive study has provided a detailed and practical description of the risks of diversion of controlled substances in one Canadian health care facility. Although it is reasonable to assume that practices at the study hospital, an academic mother–child facility, are representative of those in other institutions, the results cannot be fully generalized to all Canadian health care facilities. Furthermore, the results of this study cannot be used to quantify the rate of diversion of controlled substances. Nonetheless, the study does describe surveillance measures in place and potential corrective actions, albeit according to a US

standard. These results can be used as a starting point for future comparative analyses.

CONCLUSION

In this study, the pathway for controlled substances at the study hospital was compliant with nearly half of the criteria in a pre-existing framework, and 22 corrective actions were identified to further improve compliance. Pharmacists, physicians, and nurses should be mobilized to optimize the use of controlled substances throughout the drug-use process.

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Health Authority Pharmacists' Perceptions of Independent Pharmacist Prescribing

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ABSTRACT

Background: In many jurisdictions, the pharmacist's role continues to evolve from drug distribution–based service delivery to expanded scopes of practice, including independent prescribing of medications.

Objectives: To assess health authority–based pharmacists' attitudes, beliefs, and perceptions about independent prescribing, to determine how independent prescribing may affect their behaviour, and to identify perceived barriers and enablers to incorporating it into their practice.

Methods: An anonymous, cross-sectional online survey of 677 health authority–based pharmacists employed by Lower Mainland Pharmacy Services in British Columbia collected information in the following domains: demographic characteristics; attitudes, beliefs, and perceptions regarding pharmacist prescribing; anticipated effect of pharmacist prescribing on behaviour; likelihood of applying for this authority, if granted; and barriers and enablers to applying for prescribing authority and incorporating prescribing into their practice. A multivariate regression analysis was performed.

Results: A total of 266 pharmacists (39.3%) responded to the survey. Most respondents agreed that prescribing is important to the profession and relevant to their practice, and that it might enhance job satisfaction. Additionally, respondents agreed that they had the expertise to prescribe. Respondents perceived prescribing as having the potential to positively affect behaviour, including deprescribing, prescribing at time of discharge or transfer, and renewing medications. Enablers to applying for pharmacist prescribing authority included perceived positive impact on patient care and the profession, level of support from management and coworkers, and personal ability. No barriers were identified. About two-thirds of pharmacists indicated they would likely apply for prescribing authority if it were granted through legislation. Pharmacists with a clinical practice or research role were significantly more likely to apply to be a prescriber, whereas those with more than 10 years of experience were less likely to apply.

Conclusions: In this study, health authority–based pharmacists held positive attitudes and beliefs about the value and impact of independent prescribing of medications on their practice and the profession. There were no perceived barriers to applying for prescribing authority or to incorporating prescribing into practice.

Keywords: pharmacists, pharmacy, drug prescriptions, health services, pharmacy research

RÉSUMÉ

Contexte : Dans bien des provinces, le rôle du pharmacien ne cesse d'évoluer, depuis la prestation de services fondée sur la distribution de médicaments à des champs de pratique élargis, comprenant le droit de prescription autonome des médicaments.

Objectifs : Évaluer les attitudes, les croyances et les opinions des pharmaciens rattachés à des régies de santé concernant le droit de prescription autonome, déterminer l'influence de ce droit sur leurs habitudes et recenser les éléments qui, selon eux, entravent ou facilitent l'intégration de ce droit dans leur pratique.

Méthodes : Une enquête transversale anonyme en ligne s'adressant à 677 pharmaciens rattachés à une régie de santé et employés par les services de pharmacie des basses-terres continentales en Colombie-Britannique a permis de recueillir de l'information sur les domaines suivants : caractéristiques démographiques; attitudes, croyances et opinions concernant le droit de prescrire des pharmaciens; effets envisagés sur les habitudes du droit de prescrire accordé aux pharmaciens; probabilité de demander ce droit, s'il existe; et les éléments entravant ou facilitant la demande du droit de prescrire et l'intégration de ce droit dans leur pratique. Une analyse de régression multivariée a été réalisée.

Résultats : Au total, 266 pharmaciens (39,3 %) ont répondu au sondage. La plupart d'entre eux ont affirmé que le droit de prescrire est important pour la profession et pertinent dans le cadre de leur pratique et que cet acte pourrait accroître leur satisfaction au travail. De plus, les répondants affirmaient qu'ils possédaient l'expertise requise pour prescrire. Selon eux, le droit de prescrire pouvait influencer positivement leurs habitudes, notamment en ce qui concerne l'interruption de la prescription, la prescription au moment du congé ou d'un transfert et le renouvellement de médicaments. Parmi les éléments incitant les pharmaciens à solliciter le droit de prescrire, on comptait les effets positifs présumés sur les soins offerts aux patients et sur la profession, le soutien de la part de la direction et des collègues et les capacités personnelles. Aucun obstacle n'a été recensé. Environ deux tiers des pharmaciens ont indiqué qu'ils solliciteraient probablement le droit de prescrire s'il était accordé par la loi. Les pharmaciens en pratique clinique et ceux en recherche étaient beaucoup plus enclins à faire la demande pour devenir prescripteurs alors que ceux comptabilisant plus de dix ans d'expérience étaient moins enclins à faire la demande.

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Conclusions : Dans la présente étude, les pharmaciens rattachés à une régie de santé affichaient une attitude et des croyances positives à propos de la valeur du droit de prescription autonome des médicaments et des effets qu'il aurait sur leur pratique et la profession. On n'a recensé aucun élément perçu comme un obstacle à la formulation d'une demande du droit de prescrire ou à l'inclusion de ce rôle dans la pratique.

Mots clés : pharmaciens, pharmacie, prescriptions de médicaments, services de santé, recherche en pharmacie

INTRODUCTION

Health care delivery models around the world are continuously evolving to better meet patients' needs. One example is the expansion of medication prescribing authority to nonphysician care providers, including pharmacists, nurses, and naturopathic physicians.[1-16] In many jurisdictions, the role of the pharmacist continues to evolve from drug distribution–based service delivery to expanded scopes of practice, including independent prescribing of medications.[1-16] In the United Kingdom, independent prescribing by pharmacists was introduced in 2006.[14] In 2013, prescribing rights were granted to New Zealand pharmacists who had completed a postgraduate pharmacist prescribing course.[15] Prescribing authority for Canadian pharmacists varies across the country, according to provincial legislation. For example, pharmacists in the province of Alberta may apply for and be granted "additional prescribing authorization", which allows them to independently initiate, continue, or adjust any prescription medication, with the exception of narcotics and controlled substances.[16] Studies have shown that patients cared for by Alberta pharmacists with additional prescribing authorization, as compared with control patients receiving usual care, experienced improved outcomes in terms of hypertension, dyslipidemia, overall cardiovascular risk, and diabetes mellitus.[17-20] A recent issue of the *American Journal of Health-System Pharmacy* focused on pharmacist prescribing across the United States and Canada.[1-13] This issue highlighted a variety of models for pharmacist prescribing, primarily through collaborative drug therapy agreements in both inpatient hospital and ambulatory clinic (e.g., stroke, cancer pain) settings, which have led to improvements in medication utilization, as well as clinical and cost outcomes.[2,5-10] Additionally, Gray and Mysak[10] described the implementation of a framework aimed at supporting Alberta health authority–based pharmacists with additional prescribing authorization who practise in collaborative settings, and the intention to make this authorization a standard expectation.

Although initiatives are under way to implement independent prescribing of medications by pharmacists in many jurisdictions in Canada, to date there have been no published assessments of health authority–based pharmacists' perceptions of independent prescribing in British Columbia. Health authority–based pharmacists primarily provide care to patients who have been admitted to hospital or are under the care of a specialty ambulatory clinic affiliated with a hospital. The objective of this study was to evaluate health authority–based pharmacists' attitudes, beliefs, and perceptions of how independent prescribing could affect their practice, to identify anticipated enablers of and barriers to incorporating independent prescribing into their practice, and to identify their intentions to apply for such authority, if granted.

METHODS

Study Design and Context

A cross-sectional observational study was conducted utilizing an anonymous survey of health authority pharmacists employed by Lower Mainland Pharmacy Services (LMPS) in British Columbia, Canada. This organization provides pharmacy services to 31 sites, including 24 acute care hospitals, in and around Greater Vancouver and the Fraser Valley. At the time of the study, independent pharmacist prescribing was not permitted through legislation in the study jurisdiction. However, health authority pharmacists in this jurisdiction had the authority to modify, continue, or substitute medications in specific situations—for example, adjusting a medication dose on the basis of laboratory values (e.g., renal function, international normalized ratio) or serum drug concentrations, continuing certain medications that a patient was taking before admission, or substituting a drug within the same therapeutic class. The study was approved by the Behavioural Research Ethics Board at the University of British Columbia and the Research Ethics Board at Fraser Health.

Survey Instrument

The anonymous online questionnaire was developed utilizing published studies of pharmacist prescribing surveys[16,21] and the investigators' expertise. The questionnaire was piloted for clarity, comprehensiveness, and data interpretability through testing with a non-probability sample of 12 health authority–based and community-based pharmacists, none of whom participated in the final survey. Minor feedback received from these individuals was incorporated to improve the clarity of the survey. Prescribing was

defined as the independent writing and signing of a prescription or medication order with or without involvement of another health care professional in reaching the decision to prescribe (excluding cases of cosigning or verbal orders), based on the definition used by Heck and colleagues.[16]

The questionnaire collected information in the following domains: demographic characteristics, attitudes and beliefs regarding independent pharmacist prescribing, anticipated effect of independent pharmacist prescribing on respondents' behaviour, respondents' likelihood of applying for independent pharmacist prescribing authority if granted, and barriers and enablers to applying for independent pharmacist prescribing and incorporating it into practice. The survey tool was administered by FluidSurveys and hosted by the University of British Columbia. The survey was open for a 4-week period in February and March 2017. A copy of the survey instrument is included as Appendix 1 (available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/190/showToc).

Study Population

All 680 pharmacists employed by LMPS were eligible to complete the study. Potential participants were identified from e-mail distribution lists for LMPS employee pharmacists. The study involved complete sampling and was not hypothesis-driven, so no sample size calculation was performed. Consent was implied by survey participation, and all responses were kept confidential. No incentives to participate were offered to study participants. The invitation to participate in the study was distributed by personal e-mail, with weekly reminders sent to invitees who had not yet completed the survey.

Data Synthesis

Different scales were used to capture respondents' perceptions of independent pharmacist prescribing. Attitudes and beliefs were assessed by means of 12 statements with responses on a 5-point agreement scale (1 = not at all, 2 = slightly, 3 = somewhat, 4 = moderately, and 5 = strongly). Because the data analysis was based not on the level of agreement (e.g., slightly versus strongly), but rather on whether or not there was agreement with each statement, a post hoc decision was made to classify the response "not at all" as "disagree", and all other responses as "agree", as a means of facilitating data analysis.

Barriers and enablers to incorporating independent pharmacist prescribing into practice were rated on a 9-point scale (from 1 = significant barrier to 9 = significant enabler). Factors with ratings less than 5 were considered "barriers", those with ratings greater than 5 were considered "enablers", and those with a rating of exactly 5 were considered to be neither barriers nor enablers. To facilitate data analysis, perceptions of the potential effects on prescribing behaviour in the context of selected activities were grouped and recoded into categories of "affecting" and "not affecting" behaviour. Pharmacists' intention to apply for independent prescribing authority was assessed on a 4-point scale (1 = not at all, 2 = slightly likely, 3 = moderately likely, and 4 = very likely); to facilitate data analysis, the "not at all" responses were classified as "not likely", and all other responses were classified as "likely".

Data Analysis

Descriptive statistics were used to report frequencies, measures of central tendency, and dispersion of results. Forward multiple logistic regression was used to identify respondents' characteristics that were predictive of their attitudes and beliefs toward independent pharmacist prescribing, their intention to apply for independent pharmacist prescribing, and their perception of the effect of independent pharmacist prescribing on their behaviour. The responses to questions in each of these 3 sections were dichotomized as described in the section "Data Synthesis". An independent regression analysis was performed for each question. In each regression analysis, the dichotomized answers to the question represented the dependent variable, and participant characteristics were independent variables. A bivariate analysis was conducted for respondent characteristics (sex, years of experience, level of education, primary practice area, hospital type) and participants' dichotomized responses to the questions to identify relationships between them. The groupings for primary area of practice were based on the investigators' clinical experience and knowledge of these positions in the health authority environment where the study was conducted.

Variables significant at $p < 0.05$ were considered covariates in the multivariate regression models. An adjusted odds ratio (OR), 95% confidence interval (CI), and corresponding p value were computed with binomial distribution and logit link functions. Whenever a variable had more than 1 option or level (e.g., the 5 levels for the variable primary practice site: tertiary care hospital, community hospital, tertiary and community hospitals, other, and would rather not say), each level was treated independently. For example, the OR reported for tertiary care hospital represents the odds that practising in a tertiary care hospital affected the dependent variable relative to not practising in a tertiary care hospital. However, in the case of education, a bachelor's degree in pharmacy was chosen as the reference category, and the odds for other education levels were compared with the odds for a bachelor's degree. Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington) and IBM SPSS Statistics version 22 (IBM, Armonk, New York) were used for the analyses.

RESULTS

Of the 680 potentially eligible pharmacists, 3 were excluded because of their involvement in the study as investigators; therefore 677 pharmacists were invited to complete the survey. Of

these, 266 responded (response rate 39.3%). The characteristics of respondents are shown in Table 1.

Attitudes and Beliefs about Independent Prescribing

Respondents' attitudes toward and beliefs about independent pharmacist prescribing are presented in Table 2. Most respondents (> 90%) agreed that independent prescribing is important to the profession and relevant to their practice, and that they had the clinical expertise to prescribe. Multiple logistic regression identified participant characteristics that contributed to pharmacists' attitudes toward and beliefs about independent prescribing (Table 2).

Anticipated Effect of Independent Prescribing on Behaviour

Table 3 summarizes data concerning respondents' perceptions of how their behaviour in various scenarios would be affected if they had independent prescribing authority. The behaviours most likely to be affected were deprescribing (77.8%), prescribing on discharge (72.2%), prescribing on patient transfer (67.7%), and renewing medications (66.9%). Multiple logistic regression identified various pharmacist characteristics that contributed to perceptions about how independent prescribing would affect behaviour (Table 3).

Barriers and Enablers

Pharmacists indicated the degree to which they perceived 7 factors as potential barriers to or enablers of their decision to apply for independent prescribing authority and incorporate it into their practice (Figure 1). None of the factors were perceived as barriers. The strongest enablers were perceived impact on the profession (median 8, interquartile range 6–9) and impact on patient care (median 8, interquartile range 6–9).

Intention to Apply for Independent Prescribing Authority

Most pharmacists indicated that they would be moderately likely (28.4% [66/232]) or very likely (37.5% [87/232]) to apply for independent prescribing authority if it were to be granted. Pharmacists with a clinical practice or research role were significantly more likely to apply for independent prescribing authority (OR 3.53 [95% CI 1.57–7.94] and OR 2.58 [95% CI 1.20–5.55], respectively) if it were to be granted. Pharmacists with more than 10 years of experience (relative to those with up to 10 years of experience) were significantly less likely to apply for independent prescribing authority (OR 0.50 [95% CI 0.27–0.95]).

Table 1. Characteristics of Survey Respondents

Characteristic	No. (%) of Respondents*	
Sex, female (*n* = 266)	179	(67.3)
Age group (years) (*n* = 263)		
20–29	65	(24.7)
30–39	85	(32.3)
40–49	59	(22.4)
>50	54	(20.5)
Professional experience ≤ 10 years (*n* = 266)	146	(54.9)
Highest level of education (*n* = 263)		
Accredited Canadian Pharmacy Residency	113	(43.0)
Bachelor of Science in Pharmacy	69	(26.2)
Postgraduate Doctor of Pharmacy	64	(24.3)
Entry-Level Doctor of Pharmacy	6	(2.3)
Master of Science in Pharmacy	6	(2.3)
Other	4	(1.5)
Would rather not say	1	(0.4)
Involved in providing direct patient care* (*n* = 266)	232	(87.2)
Role† (*n* = 263)		
Clinical practice	216	(82.1)
Teaching	144	(54.8)
Dispensary/drug distribution	143	(54.4)
Research	72	(27.4)
Support‡	41	(15.6)
Clinical leadership/management	37	(14.1)
Administrative leadership/management	32	(12.2)
Primary practice site (*n* = 263)		
Tertiary care hospital	141	(53.6)
Community hospital	62	(23.6)
Tertiary care and community hospital	24	(9.1)
Other	21	(8.0)
Would rather not say	15	(5.7)
Primary areas of practice† (*n* = 263)		
General§	141	(53.6)
Specialty**	97	(36.9)
Support‡	73	(27.8)
Critical care or emergency medicine	38	(14.4)
Pediatrics, neonatal medicine, or maternal fetal medicine	25	(9.5)
Psychiatry or mental health/addiction	11	(4.2)

*Defined as working directly with patients to prevent, identify, and resolve drug-related issues.
†Respondents were allowed to select multiple options, if applicable, so the sum of percentages is greater than 100.
‡Defined as antimicrobial stewardship, drug distribution, home parenteral therapy, medication management, medication reconciliation, medication safety, medication use evaluation, or pharmacokinetics.
§Defined as ambulatory outpatient clinic, general medicine, geriatric medicine, medication management, medication reconciliation, rural medicine, surgery, or women's health.
**Defined as anticoagulation management, cystic fibrosis/respirology, cardiology, infectious diseases, leukemia/bone marrow transplant, maternal/fetal medicine, mental health/addiction, nephrology, neurology, oncology, palliative care, psychiatry, rehabilitation, solid organ transplant, or toxicology.

DISCUSSION

This was the first survey to characterize British Columbia health authority–based pharmacists' perceptions of independent pharmacist prescribing and how it might relate to pharmacy practice.

Overall, pharmacists felt that independent prescribing was relevant to their practice and important to the profession.

Table 2. Survey Respondents' Attitudes and Beliefs about Independent Pharmacist Prescribing

Question	Median Response* (IQR)	Agreement† (%)	Covariate	OR‡ (95% CI)	*p* Value
Do you feel it is important for the profession of pharmacy to have independent pharmacist prescribing?	5 (4–5)	96.4	Role: clinical leadership/ management	0.20 (0.05–0.78)	0.021
Do you feel that independent prescribing authority is relevant to your practice?	5 (4–5)	90.4	Role: clinical practice	4.22 (1.66–10.74)	0.002
Do you feel that you require additional training to take on a prescribing role?	3 (2–4)	62.5	Education: ACPR	0.36 (0.15–0.88)	0.025
			Education: postgraduate PharmD	0.05 (0.02–0.14)	<0.001
			Primary area of practice: support	2.38 (1.19–4.78)	0.014
			Role: clinical practice	0.22 (0.08–0.62)	0.004
Do you feel that you have the clinical expertise to be an independent pharmacist prescriber?	4 (3–5)	91.2	Involved in providing direct patient care	6.34 (2.20–18.24)	0.001
			Role: teaching	9.58 (2.08–43.99)	0.004
Do you have the time to incorporate prescribing activities into your practice?	4 (3–5)	85.3	Role: clinical practice	11.80 (4.67–29.79)	<0.001
			Education: other	0.06 (0.01–0.51)	0.011
			Education: entry-level PharmD	0.11 (0.02–0.81)	0.030
Do you feel that having independent prescribing authority would decrease efficiency in your practice?	1 (1–2)	12.4	Role: administrative leadership/management	0.11 (0.01–0.90)	0.040
			Role: clinical practice	0.19 (0.07–0.49)	0.001
Do you feel that having independent prescribing authority would increase efficiency in your practice?	3 (3–5)	85.7	Experience: > 10 years	0.35 (0.16–0.78)	0.010
Do you feel that independent pharmacist prescribing will enhance job satisfaction?	4 (3–5)	88.8	No significant covariates		
Are you concerned about the increased responsibility associated with prescribing?	3 (2–4)	59.8	Primary area of practice: support	1.99 (1.07–3.69)	0.030
			Role: clinical leadership/ management	0.43 (0.21–0.91)	0.027
Are you concerned about increased liability associated with prescribing?	3 (2–4)	68.5	Role: clinical leadership/ management	0.21 (0.10–0.45)	<0.001
Do you feel having prescribing authority would reduce the amount of time spent contacting physicians and leaving suggestions?	4 (3–5)	86.9	Primary area of practice: specialty	3.03 (1.16–7.87)	0.027
			Primary area of practice: critical care	0.35 (0.14–0.86)	0.015
Do you feel your communication with physicians would be more frequent if you had independent pharmacist prescribing?	2 (1–3)	45.0	No significant covariates		
Do you feel communication with physicians would be improved/more effective if you had independent pharmacist prescribing?	3 (2–4)	63.7	No significant covariates		

ACPR = Accredited Canadian Pharmacy Residency, CI = confidence interval, IQR = interquartile range, OR = odds ratio, PharmD = Doctor of Pharmacy.
*Possible responses: 1 = not at all, 2 = slightly, 3 = somewhat, 4 = moderately, 5 = strongly.
†The response "not at all" was classified as "disagree"; all other responses were classified as "agree".
‡An OR > 1 indicates that the presence of the covariate was associated with a higher likelihood of agreement with the statement. An OR < 1 indicates that the presence of the covariate was associated with a lower likelihood of agreement with the statement.

Independent pharmacist prescribing was also perceived to have the potential to increase efficiency in practice and enhance job satisfaction. Pharmacists with a clinical practice role were significantly more likely to consider independent prescribing to be relevant to their practice, whereas those with a clinical leadership or management role were less likely to consider it important to the profession. It is difficult to understand why pharmacists with a clinical leadership or management role would be less likely to consider independent prescribing important to the profession. One possibility is that, unlike the pharmacists reporting to them, these organizational leaders believe that pharmacists are maximally effective without the authority to prescribe. Those with residency or postgraduate Doctor of Pharmacy training, as well as those with a clinical practice role, were less likely to believe that they required additional training for independent prescribing. These results are likely reflective of their increased confidence as practitioners. Pharmacists without these credentials were more likely to believe that they required additional training.

Table 3 (Part 1 of 2). Respondents' Perceptions of the Effect of Independent Pharmacist Prescribing on Their Own Behaviour

Activity*	Response; % of Respondents			Covariate†	OR (95% CI)‡	*p* Value
	Would not affect behaviour (already have this authority)	Would not not affect behaviour (other reasons)	Would affect behaviour (would be helpful and enable me to more easily accomplish this for my patients)			
Prescribe medications the patient was taking before hospital admission during medication reconciliation	21.7	16.1	62.1	Education: ACPR	0.37 (0.17–0.81)	0.012
				Education: postgraduate PharmD	0.23 (0.10–0.53)	0.001
Prescribe medications as part of medication reconciliation during patient transfer	14.9	17.3	67.7	Primary area of practice: specialty	0.52 (0.29–0.95)	0.033
				Role: dispensary/ drug distribution	2.37 (1.31–4.32)	0.005
Prescribe discharge medications	4.0	23.7	72.2	Role: administrative leadership/ management	4.00 (1.16–13.81)	0.028
				Role: clinical practice	3.64 (1.51–8.79)	0.004
				Role: dispensary/ drug distribution	3.78 (1.96–7.28)	<0.001
Prescribe an adjusted dose of medication based on laboratory values and clinical assessment	27.7	8.4	64.1	Involved in providing direct patient care	4.52 (1.62–12.59)	0.004
				Role: research	0.46 (0.25–0.86)	0.015
				Role: administrative leadership/ management	5.14 (1.44–18.40)	0.012
Prescribe an adjusted dose of medication based only on laboratory values	45.4	8.8	46.0	Education: entry-level PharmD	0.08 (0.01–0.78)	0.030
				Education: residency	0.27 (0.13–0.55)	<0.001
				Education: postgraduate PharmD	0.44 (0.20–0.94)	0.035
				Primary area of practice: pediatrics	5.19 (1.76–15.29)	0.003
Prescribe new medications for an inpatient	2.4	34.9	62.7	Primary area of practice: general	1.82 (1.03–3.21)	0.038
				Role: clinical practice	2.37 (1.14–4.96)	0.021
Prescribe new medications for an outpatient	1.2	53.8	45.2	Primary area of practice: specialty	3.44 (1.95–6.07)	<0.001
				Primary area of practice: support	0.48 (0.26–0.89)	0.020
Renew medications	12.9	20.1	66.9	Role: administrative leadership/ management	3.89 (1.13–13.45)	0.032
Perform deprescribing	5.2	16.9	77.8	Experience: > 10 years	0.40 (0.19–0.84)	0.015
				Primary area of practice: critical care	0.41 (0.18–0.97)	0.043
				Role: administrative leadership/ management	8.23 (1.62–41.82)	0.011
				Role: clinical practice	3.92 (1.57–9.79)	0.003
				Role: dispensary/ drug distribution	0.40 (0.19–0.84)	0.016

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Table 3 (Part 2 of 2). Respondents' Perceptions of the Effect of Independent Pharmacist Prescribing on Their Own Behaviour

Activity*	Response; % of Respondents			Covariate†	OR (95% CI)‡	*p* Value
	Would not affect behaviour (already have this authority)	Would not not affect behaviour (other reasons)	Would affect behaviour (would be helpful and enable me to more easily accomplish this for my patients)			
Prescribe over-the-counter medications	45.0	12.0	43.0	Primary are of practice: pediatrics	4.51 (1.69–12.03)	0.003
				Role: teaching	0.58 (0.33–0.998)	0.049
Prescribe a medication without prior discussion with a physician or team	3.2	49.2	47.6	Role: administrative leadership/ management	3.03 (1.05–8.76)	0.041
				Role: clinical practice	4.61 (1.82–11.68)	0.001
Prescribe a medication with prior discussion with a physician or team	27.8	8.1	64.1	Education: entry-level PharmD	0.14 (0.02–0.97)	0.046
				Education: postgraduate PharmD	0.32 (0.14–0.76)	0.009
				Primary area of practice: pediatrics	5.04 (1.40–18.14)	0.013
				Site: non–tertiary care hospital	5.18 (1.31–20.43)	0.019

ACPR = Accredited Canadian Pharmacy Residency, CI = confidence interval, OR = odds ratio, PharmD = Doctor of Pharmacy.
*Activities in relation to the following question: If you were a pharmacist with independent prescribing authority, how would that affect your prescribing behaviour in each of the following activities?
†The analysis was performed by dichotomizing the responses into "affecting" versus "not affecting" behaviour.
‡An OR > 1 indicates that the presence of the covariate was associated with a higher likelihood of perceiving independent pharmacist prescribing as helpful for the behaviour. An OR < 1 indicates that the presence of the covariate was associated with a lower likelihood of perceiving independent pharmacist prescribing as helpful for the behaviour.

Respondents identified many activities in which independent pharmacist prescribing might positively affect their behaviour, including deprescribing, performing medication reconciliation (prescribing on discharge, admission, or transfer), and renewing medications. These results demonstrate that pharmacists may be recognizing an unmet need not addressed by the current system. About half of respondents stated that independent pharmacist prescribing would not change their behaviour with respect to prescribing without prior discussion with a physician or the health care team. This result indicates that pharmacists may prefer to prescribe in a collaborative health care team environment, which is consistent with data from Alberta, where pharmacists were 3 times more likely to use their prescribing authority after an interdisciplinary health care team discussion than to prescribe without prior team discussion.[16]

The strongest enablers for incorporating independent pharmacist prescribing into practice were perceived positive impacts on the profession and on patient care. Other factors, such as support from management and coworkers, competence, and self-confidence, were all perceived to be enablers rather than barriers. These results agree with a recent study of pharmacists in Nova Scotia, in which knowledge, reinforcement, and intentions were positively associated with self-reported prescribing activity.[22] In one previous study, dynamics within the interdisciplinary health care team, self-confidence, competence, level of management support, and perceived impact on work environment were identified as barriers to pharmacist prescribing,[16] but the current study did not confirm these findings. Rather, none of the factors listed in the survey were identified as perceived barriers to incorporating independent prescribing into practice.

These results should be interpreted in light of the study limitations. Given the topic area for this survey study, the 39.3% response rate introduces potential for unknown biases in the results, particularly positivity bias. Also, the study involved pharmacists from a single health authority in a mostly urban area, which may limit the generalizability of the results to rural or other jurisdictions. Also, independent pharmacist prescribing is not yet legislated in the study jurisdiction, and the attitudes, beliefs, perceptions, and intentions of the respondents could change over time, depending on the structure of the authority, if it is eventually granted. This study did not assess all of the possible barriers and enablers to applying for and incorporating independent pharmacist prescribing into practice. Instead, 12 potential barriers and enablers to incorporating pharmacist prescribing into practice

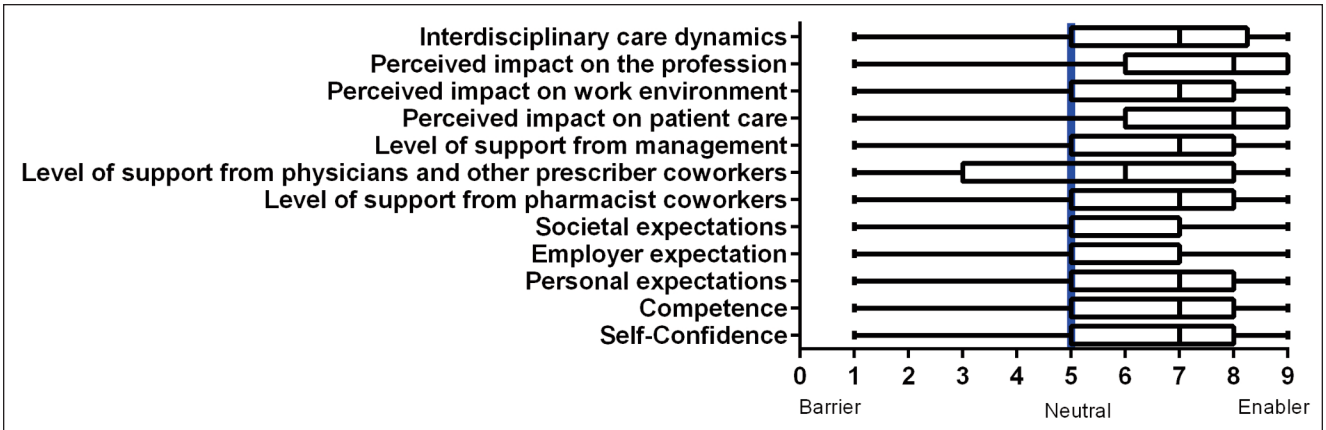

Figure 1. Perceived barriers to and enablers of incorporating independent pharmacist prescribing into practice. Factors were rated on a scale from 1 to 9, where 1 = significant barrier to 9 = significant enabler, and the single horizontal lines indicate the potential range of response for each factor. Data are presented as medians with interquartile ranges; for both societal expectations and employer expectations, the median value was 5.

were included, as were 7 potential barriers and enablers to applying for prescribing authority, based on previously published research in this area.[16,21] Lastly, potential additional training requirements or costs associated with attaining independent prescribing authority were not investigated, so the results may overestimate the likelihood of pharmacists pursuing this authorization.

CONCLUSION

Health authority–based pharmacists who participated in this study held positive attitudes and beliefs about the value and impact of independent prescribing on their practice and the profession. Medication reconciliation, deprescribing, medication renewal, and collaborative prescribing were anticipated to be particularly enhanced by independent pharmacist prescribing. Respondents did not perceive any of the factors listed in the survey as barriers to applying for independent prescribing or incorporating it into their practice. Most respondents were moderately or very likely to apply for independent prescribing authority if it were to become available, particularly those with direct patient care or research roles, as well as those newer to practice (≤ 10 years of experience).

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ORIGINAL RESEARCH

Documentation in the Patient's Medical Record by Clinical Pharmacists in a Canadian University Teaching Hospital

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ABSTRACT

Background: In many studies on documentation, the data are self-reported, which makes it difficult to know the actual level of documentation by pharmacists in patients' medical records. The literature assessing documentation by clinical pharmacists in health care centres is limited.

Objective: To assess the level of documentation in patients' medical records by clinical pharmacists at one large urban hospital.

Methods: This retrospective observational study included all patients who were followed by a clinical pharmacist during their stay in the Centre hospitalier de l'Université de Montreal between July 1 and October 31, 2016. The primary outcome, the level of documentation in patients' medical records, was categorized as minimal, sufficient, or extensive. The quality of notes and the impact of pharmacy students and residents on documentation were evaluated as secondary outcomes.

Results: A total of 779 patient charts from 4 inpatient units were included in the analysis. Of these, 563 (72.3%) were considered to have minimal documentation (at least 1 intervention described in writing), 432 (55.5%) had sufficient documentation (at least 1 note written during the patient's hospitalization), and 81 (10.4%) had extensive documentation (appropriate number of notes in relation to duration of hospitalization). Medication reconciliation performed by pharmacists at the time of admission was documented in 696 (89.3%) of patients' records. The presence of students or residents on a clinical unit was associated with a significant increase in the percentage of charts with at least 1 follow-up note (23.6% [120/508] with students/residents versus 12.5% [34/271] without students/residents; $p < 0.001$) and the mean number of follow-up notes (0.59 versus 0.23, respectively; $p < 0.001$) but had no effect on other variables. Of a total of 777 notes written by a pharmacist, the overall conformity with pre-established criteria was 56.8% (441/777), and conformity was 43.4% (139/320), 75.1% (272/362), and 31.6% (30/95) for admission, follow-up, and discharge notes, respectively.

Conclusions: Documentation by clinical pharmacists in patients' medical records could be improved to achieve the stated goal of the American Society of Health-System Pharmacists and the Canadian Society of Hospital Pharmacists, that all significant clinical recommendations or interventions should be documented.

RÉSUMÉ

Contexte : Les données de bon nombre d'études portant sur la tenue des dossiers médicaux sont autodéclarées, ce qui fait qu'il est difficile de savoir exactement dans quelle mesure les pharmaciens consignent les informations dans les dossiers médicaux des patients. Il n'existe que peu d'études évaluant la tenue des dossiers par les pharmaciens cliniques dans les centres de soins de santé.

Objectif : Évaluer dans quelle mesure les pharmaciens cliniciens d'un important hôpital urbain consignent l'information dans les dossiers médicaux des patients.

Méthodes : La présente étude d'observation rétrospective englobait tous les patients ayant été suivis par un pharmacien clinicien pendant leur séjour au Centre hospitalier de l'Université de Montréal entre le 1er juillet et le 31 octobre 2016. Le principal paramètre d'évaluation, soit le degré de rigueur des inscriptions dans les dossiers médicaux des patients, entrait dans l'une des trois catégories suivantes : minimal, suffisant ou exhaustif. La qualité des notes et l'effet de la participation d'étudiants et de résidents en pharmacie à la tenue des dossiers ont servi de paramètres d'évaluation secondaires.

Résultats : L'analyse a porté sur 779 dossiers médicaux de patients provenant de quatre services hospitaliers. Les investigateurs ont considéré que 563 d'entre eux (72,3 %) appartenaient à la catégorie « minimal » (au moins une intervention consignée par écrit), 432 (55,5 %) se situaient dans la catégorie « suffisant » (au moins une note rédigée au cours de l'hospitalisation du patient) et 81 (10,4 %) se rangeaient dans la catégorie « exhaustif » (nombre adéquat de notes en fonction à la durée de l'hospitalisation). Les bilans comparatifs des médicaments établis par des pharmaciens au moment de l'admission ont été consignés dans 696 (89,3 %) dossiers médicaux de patients. On a associé la présence d'étudiants ou de résidents dans une unité clinique à une hausse significative du pourcentage de dossiers médicaux affichant au moins une note de suivi (23,6 % [120/508] avec des étudiants / résidents contre 12,5 % [34/271] sans étudiants / résidents; $p < 0,001$) et du nombre moyen de notes de suivi (respectivement 0,59 contre 0,23; $p < 0,001$), mais leur présence n'a été associée à aucun autre effet sur les autres variables. Le taux de conformité globale aux critères préétablis des

Keywords: documentation, pharmaceutical interventions, clinical pharmacist, patient chart

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777 notes rédigées par un pharmacien était de 56,8 % (441/777) et le taux de conformité des notes d'admission, de suivi et de congé était respectivement de 43,4 % (139/320), 75,1 % (272/362) et 31,6 % (30/95).

Conclusions : La tenue des dossiers médicaux de patients par les pharmaciens cliniciens devrait s'améliorer pour qu'elle atteigne l'objectif établi par l'American Society of Health-System Pharmacists et la Société canadienne des pharmaciens d'hôpitaux, qui veut que toutes les recommandations et interventions cliniques d'importance soient consignées.

Mots clés : tenue des dossiers, interventions pharmaceutiques, pharmacien clinicien, dossiers médicaux de patients

INTRODUCTION

Over the past several decades, the practice of pharmacy has gradually shifted from drug dispensing to application of the concepts of clinical pharmacy and pharmaceutical care.[1-3] By assuming patient care duties, pharmacists become responsible for documenting in the medical record their activities related to medication reconciliation, clinical problem-solving, therapeutic interventions, and patient education.[3] The practice of documentation has been endorsed by many hospital pharmacist societies and pharmacy organizations worldwide and is included in their standards of practice, helping pharmacists to fulfill their professional obligations to ensure continuity of care and to be fully recognized as part of a multidisciplinary team.[4-6] Over time, clinical pharmacists have used various documentation systems (such as SOAP [subjective, objective, assessment, plan], TITRS [title, introduction, text, recommendation, signature], and FARM [findings, assessment, recommendations/resolutions, management]) to determine what information should be included and how it should be communicated in the patient's medical record.[7]

However, some studies have shown that pharmacists on inpatient units do not routinely complete documentation in patients' medical records and that documentation varies among countries, hospitals, and clinical departments. Between 2005 and 2012, the American Society of Health-System Pharmacists (ASHP) conducted 3 surveys, in which 59.0% to 65.0% of respondents reported that their hospitals required pharmacists to document drug therapy recommendations and progress notes in the patient's permanent medical record.[8-10] In a questionnaire sent to pharmacists in a 900-bed teaching hospital in London, Ontario, 74% (29/39) of respondents reported that they did not write in the patient's medical record.[11] In a subsequent focus group, these pharmacists reported that they recognized the importance of documenting relevant issues but preferred to use oral communication or temporary adhesive notes instead.[11] Similarly, in a cross-sectional descriptive study carried out at the Centre hospitalier universitaire Sainte-Justine in Montréal, Quebec, in 2014 and 2015, only 20% of the interventions performed by pharmacists were recorded in patients' medical records.[12] In the province of Quebec, the Ordre des pharmaciens du Québec evaluated the practice of health facility pharmacists since 2011 in relation to its standards of practice.[13] This round of inspection showed a gap in the documentation of information, with only 50% of pharmacists documenting sufficiently in patients' medical records.[14] Like the clinical guidelines of the Canadian Society of Hospital Pharmacists (CSHP)[4] and the ASHP,[5] Quebec's provincial standards of practice[13] state that all significant clinical recommendations and interventions should be documented in the patient's medical record, according to the pharmacist's clinical judgment. Many published studies have detailed the clinical activities of hospital pharmacists, but they have provided little information about the level of documentation in the patient's medical record.[15,16] In addition, most studies present self-reported data on documentation, which makes it difficult to know the actual level of documentation by the pharmacists, who may be following several patients on a clinical unit.

Taken together, these results highlight the problem of lack of documentation by clinical pharmacists following patients on inpatient units in the hospital setting. Therefore, the objective of this study was to assess the quality and quantity of documentation about clinical interventions by pharmacists in patients' medical records on 4 inpatient units at the Centre hospitalier de l'Université de Montréal (CHUM).

METHODS

Setting

The CHUM is a tertiary academic centre in Montréal, which moved to a new building, with 772 beds, in November 2017. At the time of this study, the CHUM was composed of 3 hospitals (Notre-Dame, Saint-Luc, and Hôtel Dieu), which together had more than 1500 beds. Pharmacy services are provided 24 h/day, with decentralization between the hours of 0800 and 2200. Between 3000 and 3500 medical prescriptions are validated each day. A total of 73 pharmacists (representing 68 full-time equivalents) contribute actively to teaching during the weekdays. On the

inpatient units, there is no clinical position dedicated to a single pharmacist; rather each position rotates among 3 or 4 designated pharmacists. Each year, the department of pharmacy hosts 35 to 40 students and 7 pharmacy residents. These learners contribute to patient care and are present on the inpatient units for prespecified periods.

Various methods are used for communication among health care providers, including written notes in the paper medical records during the patient's hospitalization and electronic charts for previous hospitalizations, which are easily accessible to the medical team. Also, pharmacists may use a parallel electronic documentation system within the pharmacy software, which is accessible only to pharmacy staff. Written information may be composed of SOAP notes in the medical section of a patient's record and recommendations or verbal orders from doctors in the prescription section. At the time of the study, the hospital did not have a computerized physician order entry system.

Study Design

This multicentre retrospective study aimed to evaluate the documentation of interventions in patients' medical records by clinical pharmacists between July 1 and October 31, 2016, in 4 inpatient units: hematology–oncology, solid organ transplantation, cardiology, and hepatology. Patients who had been followed by a clinical pharmacist during hospitalization were identified with the pharmacy department's computer software, BDM Pharmacy (BDM IT Solutions Inc, Saskatoon, Saskatchewan). Patients whose electronic medical records were not available and those who were not followed by a clinical pharmacist were excluded from this study. Four pharmacy students (C.T., C.P.-W., M.-L.D., P.L.) collected the data from patients' medical records held in the electronic clinical information system Oacis (Telus Health, Montréal, Quebec). The students were divided into pairs, with 10% of all data collected by each pair being double-checked by the other pair. The local independent ethics committee and independent institutional review board approved retrieval of data from patients' medical records for the purposes of this study.

Outcomes

The primary outcome was the level of documentation in patients' medical records by clinical pharmacists. A literature search of Google Scholar, PubMed, and Embase databases (with the keywords "documentation", "pharmacist", "impact", "practice standards", "notes", and "hospital") and a systematic review of the clinical guidelines published by various pharmacy professional and scientific societies (including ASHP, CSHP, and the American College of Clinical Pharmacy [ACCP]) yielded no defined criteria for adequate documentation and how to quantify it.

The authors of the present article (4 pharmacy students and 3 clinical pharmacists with 4, 6, and 10 years of experience, respectively) formed a committee to establish detailed criteria defining whether documentation in the patient's medical record was minimal, sufficient, or extensive in relation to clinical practice standards. "Minimal" documentation was defined as at least 1 written intervention in the patient's medical record, such as a note in the medical section or a suggestion or verbal order in the prescription section. This composite end point was intended to represent any visible indication of the pharmacist's activity in the patient record. "Sufficient" documentation was defined as the presence of at least 1 note in the medical section of the patient's medical record, regardless of the patient's length of stay in hospital. "Extensive" documentation was defined as the presence of at least 1 admission, follow-up, or discharge note for hospital stays of up to 2 days; an admission note and a discharge note for hospital stays between 3 and 6 days; or an admission note, a follow-up note, and a discharge note for hospital stays of 7 days or longer. No discharge note was expected for any patient who died during the hospital stay, was transferred to another care unit or health facility, or was discharged on a weekend. These criteria were based on several studies that have demonstrated the benefits of a pharmacist's medication management during transitions of care, in particular at hospital admission and discharge, on clinical outcomes such as medication discrepancies, adverse drug event–related hospital revisits, emergency department visits, and/or hospital readmissions.[17,18]

The secondary outcomes included the conformity of notes with pre-established criteria, the effect of the presence of pharmacy students and residents on the documentation of interventions, and the percentage of suggestions for modification of drug therapy in the prescription section of the patient's medical record that were explained and detailed in the medical notes. Medication reconciliation electronically entered by the pharmacist into the pharmacy software was also collected.

The criteria for evaluating conformity of documentation were inspired by the CSHP guidelines.[4] For all types of notes, the heading "pharmacy", the date and time of the note, and the pharmacist's signature were required. For admission notes, the pharmacist had to state the reason for consultation and had to mention medication reconciliation, the patient's allergies and/or intolerances, the pharmacist's analysis of pharmacotherapy, and an intervention plan. For follow-up notes, an analysis and a plan were required. For discharge notes, patient counselling and discharge medication reconciliation had to be described. To be considered in conformity, a note had to meet all of the criteria for the particular note type. The number of interventions by pharmacists documented in the prescription section, consisting of suggestions made by the pharmacist or the pharmacist's transcription of verbal instructions from the medical team, was collected to understand the involvement of pharmacists in documentation in patients' medical records, independent of written admission, follow-up, and discharge notes (as described above).

Statistical Analysis

Continuous variables are presented as means (with standard deviations) or medians (with interquartile ranges [IQRs]), whereas categorical variables are described as frequencies. The χ^2 test (for proportions) and the Mann-Whitney *U* test (for differences between means) were used to analyze the distribution of categorical and continuous variables, respectively, with a significance level of 0.05. Statistical analysis was carried out with SPSS 24.0 software (IBM, Armonk, New York).

RESULTS

A total of 779 patients followed by a clinical pharmacist at the CHUM between July 1 and October 31, 2016, were selected for this study. One additional patient was excluded because the electronic record was not available. The duration of hospitalization was up to 2 days for 112 (14.4%) of the patients, between 3 and 6 days for 263 (33.8%), and 7 days or more for 404 (51.9%), with a median of 7 days. The numbers of patients' medical records with minimal, sufficient, and extensive documentation were 563 (72.3%), 432 (55.5%) and 81 (10.4%), respectively (Table 1). These results are detailed according to clinical unit in Figure 1. Medication reconciliation done by pharmacists at the time of admission was documented in 696 (89.3%) of patients' medical records.

Among the total of 777 notes written by pharmacists in the patients' medical records, the overall conformity in relation to pre-established criteria was 56.8% (441/777), with conformity being higher for follow-up notes (75.1% [272/362]) than for admission notes (43.4% [139/320]) and discharge notes (31.6% [30/95]) (Table 2). The main effect on documentation of having pharmacy students or residents on the clinical unit was an increase in the number of patient records with at least 1 follow-up note (23.6% [120/508] with students/residents versus 12.5% [34/271] without students/residents; $p < 0.001$) and the mean number of

Table 1. Level of Documentation and Interventions Included in Patients' Medical Records

Characteristic	No. (%) of Records* (*n* = 779)	
Level of documentation†		
Extensive	81	(10.4)
Sufficient	432	(55.5)
Minimal	563	(72.3)
Intervention documented in the prescription section		
Verbal orders		
Records with ≥ 1 verbal order	142	(18.2)
No. of verbal orders per record (median and IQR)	1	(1–2)
Suggestions		
Records with ≥ 1 suggestion	369	(47.4)
No. of suggestions per record (median and IQR)	1	(1–2)
Verbal orders and/or suggestions		
Records with ≥ 1 verbal order or suggestion (or both)	426	(54.7)

IQR = interquartile range.
*Except where indicated otherwise.
†Extensive documentation was defined as presence of ≥ 1 admission, follow-up, or discharge note for hospital stays ≤ 2 days; an admission note and a discharge note for hospital stays of 3–6 days; or an admission note, a follow-up note, and a discharge note for hospital stays ≥ 7 days. Sufficient documentation was defined as presence of ≥ 1 note in medical section of patient's medical record, regardless of the patient's length of stay in hospital. Minimal documentation was defined as ≥ 1 written intervention in patient's medical record, such as a note in the medical section or a suggestion or verbal order in the prescription section.

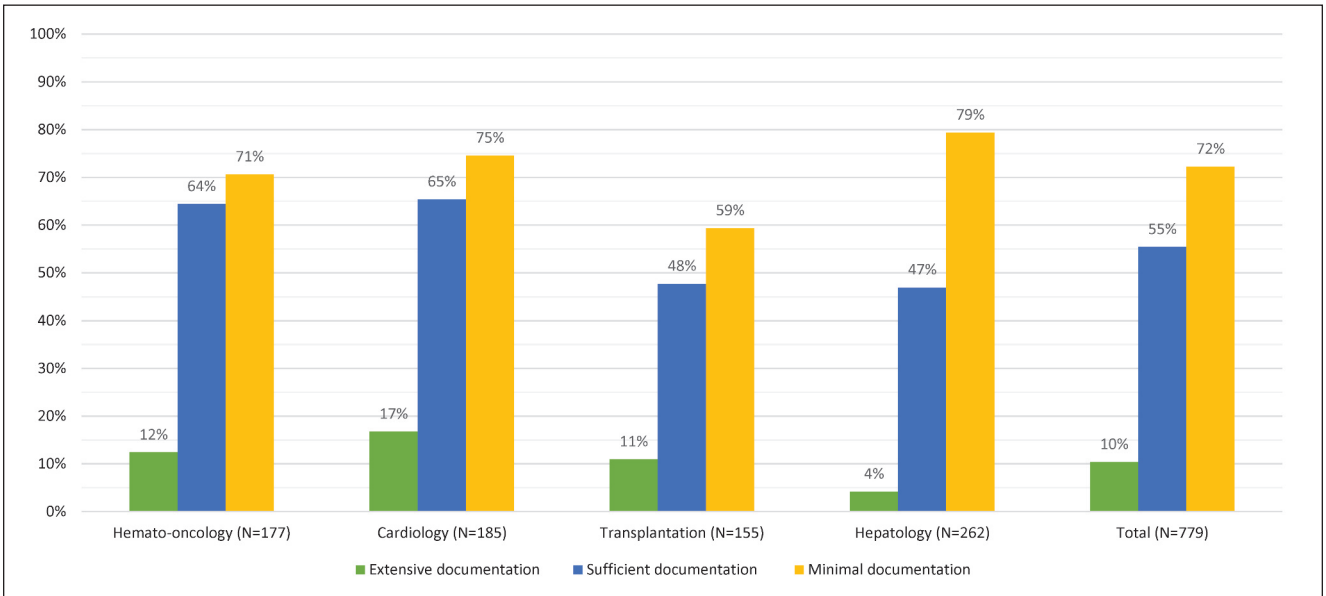

Figure 1. Level of documentation in patients' medical records, by clinical unit.

Table 2. Conformity of Admission, Follow-up, and Discharge Notes*

Characteristic	No. (%) of Records
Admission notes	*n* = 320
Title heading "Pharmacy"	318 (99.4)
Date and time	236 (73.8)
Pharmacist's signature	319 (99.7)
Reason for consultation	305 (95.3)
Mention of medication reconciliation	316 (98.8)
Patient's allergies and/or intolerances	242 (75.6)
Analysis of pharmacotherapy	295 (92.2)
Plan of intervention	258 (80.6)
Overall conformity	139 (43.4)
Follow-up notes†	*n* = 362
Title heading "Pharmacy"	361 (99.7)
Date and time	309 (85.4)
Pharmacist's signature	360 (99.4)
Analysis of pharmacotherapy	358 (98.9)
Plan of intervention	315 (87.0)
Overall conformity	272 (75.1)
Discharge notes	*n* = 95
Title heading "Pharmacy"	95 (100)
Date and time	68 (71.6)
Pharmacist's signature	94 (98.9)
Discharge medication reconciliation	70 (73.7)
Mention of patient counselling	80 (84.2)
Overall conformity	30 (31.6)

*Conformity was assessed in relation to guidelines of the Canadian Society of Hospital Pharmacists.[4]
†A patient's medical record could have more than 1 follow-up note. The *n* value of 362 refers to the total number of follow-up notes assessed.

follow-up notes (0.59 versus 0.23, respectively; $p < 0.001$) (Table 3). Although the presence of pharmacy students or residents was associated with a trend toward increased rate of sufficient documentation (57.7% [293/508] versus 51.3% [139/271]; $p = 0.09$), it did not affect the rates of extensive or minimal documentation. The principal topic of intervention in the follow-up notes was related to safety (44.5% [161/362]), efficacy (20.4% [74/362]), dose adjustment (13.8% [50/362]), compliance (5.5% [20/362]), drug interactions (3.6% [13/362]), access to medication (1.4% [5/362]), and other (10.8% [39/362]). When we analyzed the suggestions and verbal orders that clinical pharmacists wrote in the prescription section, we found that suggestions were combined with a note in the medical section (64.8% [239/369]) more often than were verbal orders (24.6% [35/142]).

DISCUSSION

To our knowledge, this is the first multicentre study to evaluate the level of documentation in patients' medical records by clinical pharmacists using a method that did not involve self-reporting. With regard to the primary outcome, the level of documentation was minimal, sufficient, and extensive in 72.3%, 55.5%, and 10.4% of patients' medical records, respectively. These results are similar to those in a study by Ballandras and others,[12] who reported that 58.4% of patients' medical records had at least 1 written note from a pharmacist resulting from a pharmaceutical intervention. The wide disparity between the proportions of records with extensive and sufficient documentation may be explained by several factors. For most of the records that did not meet the criteria for extensive documentation, the reason was lack of a discharge note (affecting 85.9% of eligible records [578/673]). Given the lack of a definition for "optimal" documentation in pharmacy organizations' standards of practice, the interpretation varies among individual pharmacists, especially in our context, where 3 or 4 designated clinical pharmacists rotate through the same clinical area. For this reason, a committee (consisting of all the authors) developed the criteria for 3 levels of documentation by consensus. These criteria were based on previous studies that have demonstrated the benefits of pharmacists' medication management during transitions of care and are compatible with clinical pharmacy practice in North America.[17,18]

The criteria for extensive documentation were based on the assumption that for a longer hospital length of stay, the pharmacist would have more time to see the patient and more occasions to document interventions in the patient's medical records. We believe that efforts should be made to improve these results to achieve the standards of practice established by various pharmacy groups (e.g., ASHP, CSHP, ACCP).

The overall conformity of admission, follow-up, and discharge notes with pre-established criteria (based on CSHP guidelines[4]) was 43.4%, 75.1%, and 31.6%, respectively. In general, most of the records met most of the criteria, but often a single required element was missing, which meant that the note did not fulfill the criteria for conformity (Table 2). The study also aimed to evaluate the impact of pharmacy students and residents on the documentation of interventions in patients' medical records. The involvement of these learners had a significant effect on the number of records with at least 1 follow-up note (23.6% versus 12.5%, $p < 0.001$) and the mean number of follow-up notes (0.59 versus 0.23, $p < 0.001$), which had a positive effect on the mean number notes per record (1.13 versus 0.73, $p < 0.007$). These results aligned with those reported in other studies, which have demonstrated that the educational activities of students and residents in health care establishments have a positive influence on patient care.[19-21] The presence of pharmacy students and residents did not significantly affect the other variables. However, this study was not powered to assess a difference between the presence and absence of residents and students on the inpatient units. The calculation of a sample size was not possible because of the absence of data on documentation by pharmacy learners. Taken together, these results suggest that clinical pharmacists cannot actively follow more patients on the clinical unit, despite the presence of a student, probably because time must be spent in direct teaching activities.

Table 3. Effect of Students and Residents on Documentation

Outcome	Category; No. (%) of Records*		*p* Value
	Student or Resident Present (*n* = 508)	No Students or Residents Present (*n* = 271)	
Quality of documentation			
Extensive	50 (9.8)	31 (11.4)	0.49
Sufficient	293 (57.7)	139 (51.3)	0.09
Minimal	370 (72.8)	193 (71.2)	0.63
Note type			
Admission note	215 (42.3)	105 (38.7)	0.36
≥ 1 follow-up note	120 (23.6)	34 (12.5)	< 0.001
Mean no. of follow-up notes/PMR	0.59	0.23	< 0.001
Mean no. of admission, follow-up, and discharge notes/PMR	1.13	0.73	0.007
Discharge note†	61/436 (14.0)	34/237 (14.3)	0.91

NS = not significant, PMR = patient's medical record.
*Except where indicated otherwise.
†In this row, the denominators (total number of patients' medical records for which a discharge note was expected) are less than the total number in each category because a discharge note was not expected if the patient died, was transferred to another care unit or health establishment, or was discharged on a weekend.

As part of minimal documentation, nearly two-thirds of the suggestions and one-quarter of verbal orders in the prescription section were detailed or explained elsewhere in the patient's medical records. These results were expected, because the existence of a verbal order implies that the pharmacist verbally explained the intervention to the medical team, and such orders reflect the important place of oral communication with the medical team.[11] To promote a multidisciplinary approach and to help comprehension of their role and interventions, pharmacists should write a summary of any verbal discussion in the medical section of the patient's record.[11] In this study, the records of almost 30% of the patients contained no formal documentation by a pharmacist. This result was surprising, because the clinical pharmacists completed medication reconciliation at admission for 89.4% of patients across the 4 inpatient units. It is possible that some interventions were discussed verbally with the medical team, without documentation; in addition, the pharmacists may have chosen to not see some patients because they prioritized other patients.[22]

The overall documentation by pharmacists in patients' medical records could be increased. In our centre, all medication reconciliations are done by pharmacists. With appropriate supervision, pharmacy technician–centred medication reconciliation programs have led to effective medication history-taking, documentation and communication of data, and enhanced pharmacotherapy safety.[23,24] The clinical tasks of pharmacists in Canada and the United States have been expanding, which has made it more difficult for pharmacists to follow the same number of patients as in the past.[25-27] Because the workload may be too great in inpatient units with rapid turnover of patients, such as hepatology, pharmacists may not have the time to write multiple notes in patients' medical records. Clinical pharmacists could prioritize their patients, because high-risk patients should benefit the most from their interventions.[22,28] To our knowledge, there is little information available on methods to classify high-risk patients on a clinical unit with already highly demanding medication needs, such as oncology or solid organ transplantation. As described above, pharmacists often document their interventions in the pharmacy software, without recording the information in patients' medical records. To increase productivity and enhance documentation, pharmacists could print electronic documentation from the pharmacy software and include it in the patient's medical record.[29,30] Another way to increase efficiency and achieve better conformity of documentation would be to use preprinted forms.[31] Also, improving communication among doctors, pharmacists, and unit coordinators could help pharmacists to know when a patient will be discharged. Doing so could help to increase the number of discharge notes, thereby increasing the proportion of records with extensive documentation. Finally, as pharmacy practice is continuously changing and improving, it will be important to develop educational presentations and documents to raise pharmacists' and students' awareness regarding practice standards for documentation.[32]

This study had both strengths and limitations. Collection of the data by 2 pairs of students may have introduced observation bias. To limit such bias, 10% of all records were double-checked and corrected, if appropriate, by the other team of students. The patients' medical records were handwritten and although the observers were vigilant, some data may have been missed (e.g., if pharmacists did not identify themselves adequately in the record

or if the quality of the handwriting was poor). However, the large number of records analyzed (with exclusion of only 1 record) may have compensated for these limitations. Another limitation was the absence of testing for interindividual variability between clinical pharmacists. However, the goal of the study was not to identify differences among pharmacists, but rather to determine tendencies and trends, in order to ameliorate the practice of a group of pharmacists.

This study examined an issue that is very poorly investigated and reported in the literature. Comparing the results of this study with results of similar analyses in other health care centres would be of interest. We believe that the results of this study can be generalized to other North American centres. A strength of the study was its focus on the actual number of patients being followed by pharmacists on weekdays, rather than total admissions to an inpatient unit, whether or not the patients were being followed by a pharmacist. A retrospective study was an appropriate design for this study, because it limited the observation bias that might have been introduced with a prospective study.

CONCLUSION

This study assessed the level of documentation of clinical interventions in patients' medical records by pharmacists on 4 inpatient units at the CHUM. Despite the increased availability and use of advanced technology, objective data supporting clinical functions can be difficult to quantify. This study highlights variability in the level of documentation. The guidelines of the ASHP and the CSHP state that all significant clinical recommendations and interventions should be documented; however, these guidelines do not indicate the minimal documentation rates recommended or how often documentation should be done during a patient's hospitalization. With the constant evolution of pharmacy practice, further studies are needed to evaluate documentation by pharmacists in health care establishments. Such studies could help in establishing comprehensive guidelines to ensure that pharmacists document information and interventions in patients' medical records.

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ORIGINAL RESEARCH

Impact of a Layered Learning Practice Model on Delivery of Clinical Pharmacy Key Performance Indicators under a Tertiary Care Centre Oncology Service

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ABSTRACT

Background: The layered learning practice model (LLPM), within which a pharmacist supervises both a pharmacy resident and a student, mitigates the growing demand for clinical rotations that has accompanied national expansion of Doctor of Pharmacy programs. A Canadian collaborative of hospital pharmacists established consensus on 8 clinical pharmacy key performance indicators (cpKPIs), activities associated with improved patient outcomes. Increased implementation of the LLPM alongside cpKPI measurement offers opportunities to compare the LLPM with standard practice in terms of pharmaceutical care delivery.

Objective: To quantify clinical productivity, as measured by proportions of eligible patients receiving cpKPIs and absolute numbers of completed cpKPIs, across scenarios involving pharmacists working with and without pharmacy learners.

Methods: In this retrospective observational study, pharmacy students, pharmacy residents, and pharmacists recorded completion of 7 cpKPIs for oncology inpatients over a total of 6 months in 2017 and 2018. Clinical productivity was described across the following 3 scenarios: presence of one or more pharmacists with one resident and one or more students (P-R-S); presence of one or more pharmacists with one or more students (P-S); and presence of one or more pharmacists only (P; standard practice).

Results: During the study, there were 685 recorded admissions to the inpatient oncology service. Generally, the proportions of patients who received cpKPIs were similar for scenarios with and without pharmacy learners present. Standardized to 20 pharmacist workdays, the total number of cpKPIs 1, 2, 3, 5, 6, and 7 (255 with P-R-S scenario, 281 with P-S scenario, and 258 with P scenario) and the total number of drug therapy problems resolved (i.e., cpKPI 3; 153 with P-R-S scenario, 180 with P-S scenario, and 149 with P scenario) were similar across the scenarios. Scenario P had fewer admitted patients per pharmacist workday (3.2) than scenarios P-S and P-R-S (3.4 and 3.7, respectively), which may have contributed to a trend toward greater proportions of patients receiving cpKPIs under scenario P.

Conclusions: Compared with standard practice, integration of pharmacy learners within an oncology unit did not appear to impair clinical

RÉSUMÉ

Contexte : Le modèle de pratique avec apprentissage à plusieurs niveaux (traduction libre de : *Layered Learning Practice Model*, [LLPM]), où un pharmacien supervise un résident et un étudiant en pharmacie, permet de réduire la demande croissante de stages cliniques qui a suivi le développement national des programmes de doctorat en pharmacie. Un regroupement canadien composé de pharmaciens d'hôpitaux a établi un consensus sur huit indicateurs clés de rendement relatifs à la pharmacie clinique (ICRpc), activités associées à l'amélioration des résultats thérapeutiques. L'accélération de la mise en œuvre du LLPM, parallèlement à l'évaluation des ICRpc, offre des occasions de comparer le LLPM aux pratiques courantes en ce qui a trait à la prestation de soins pharmaceutiques.

Objectif : Quantifier la productivité clinique, en fonction des proportions de patients admissibles, profitant des ICRpc et des nombres absolus d'ICRpc évalués, dans des scénarios où les pharmaciens travaillent ou non avec des étudiants ou des résidents.

Méthodes : Dans la présente étude d'observation rétrospective, des étudiants et des résidents en pharmacie ainsi que des pharmaciens ont enregistré l'évaluation complète de sept ICRpc pour des patients hospitalisés en oncologie sur une durée totale de six mois en 2017 et 2018. La productivité clinique a été décrite à l'intérieur des trois scénarios suivants : participation d'au moins un pharmacien accompagné d'au moins un résident et un étudiant (P-R-É); participation d'au moins un pharmacien accompagné d'au moins un étudiant (P-É); et participation d'au moins un pharmacien, sans étudiant ou résident (P : pratique courante).

Résultats : Au cours de l'étude, on a enregistré 685 admissions au service d'hospitalisation en oncologie. Généralement, les proportions de patients profitant des ICRpc étaient semblables dans les trois scénarios. Basé sur une unité de mesure de 20 jours de travail de pharmacien, le nombre total d'ICRpc 1, 2, 3, 5, 6 et 7 (255 pour le scénario P-R-É, 281 pour le scénario P-É et 258 pour le scénario P) et le nombre total de problèmes pharmacothérapeutiques réglés (c'est-à-dire ICRpc 3; 153 pour le scénario P-R-É, 180 pour le scénario P-É et 149 pour le scénario P) étaient semblables dans les différents scénarios. Le scénario P présentait moins de patients admis par jours de travail de pharmacien (3,2) que les scénarios

productivity, as demonstrated by the comparable proportions of patients receiving cpKPIs and the total number of completed cpKPIs.

Keywords: clinical pharmacy key performance indicators, layered learning practice model, hospital pharmacy, pharmacy learner, clinical productivity

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P-É et P-R-É (respectivement 3,4 et 3,7), ce qui peut avoir contribué à créer une tendance montrant une plus grande proportion de patients profitant des ICRpc dans le scénario P.

Conclusions : Comparée à la pratique courante, l'intégration d'étudiants ou de résidents en pharmacie dans un service d'oncologie ne semblait pas réduire la productivité clinique, comme l'illustrent les proportions comparables de patients profitant d'ICRpc et le nombre total d'ICRpc évalués.

Mots clés : indicateurs clés de rendement relatifs à la pharmacie clinique, *layered learning practice model*, pharmacie hospitalière, étudiant en pharmacie, productivité clinique

INTRODUCTION

Health care–related key performance indicators (KPIs) are quantifiable measures of quality that may be used to track an organization's performance in specific critical processes and outcomes.[1] KPIs have been shown to be associated with positive patient outcomes.[2] The measurement of KPIs contrasts with workload metrics—the frequencies at which various activities are performed—which are not necessarily correlated with patient outcomes.[2] By extension, a clinical pharmacy KPI (cpKPI) is a standardized quantitative measure of progress for a specific clinical activity performed by a pharmacist.[1] As such, cpKPIs serve as objective indicators by which to measure the efficiency of delivery of evidence-based patient care processes.[3]

In 2013, a Canadian collaborative of clinical pharmacists and hospital pharmacy leaders established consensus on 8 national cpKPIs representing essential patient care processes.[4] These 8 cpKPIs (Table 1) relate to aspects of an admitted patient's hospital course and are associated with evidence-informed improvements in meaningful patient outcomes.[4] For instance, it has been shown that inpatient team–based pharmacists who perform proactive patient care activities, such as conducting admission medication reconciliation and resolving drug therapy problems (DTPs), significantly reduce the number of hospital readmissions and patient mortality.[1,5,6] By reporting the value of clinical pharmacy services through quantification of cpKPIs, hospital administrators have standardized metrics that may support the maintenance or expansion of clinical pharmacy services to provide evidence-based care.[2]

With the expansion of entry-to-practice Doctor of Pharmacy (PharmD) and PharmD Bridging programs across Canada, there has been an increase in the demand for clinical experiential rotations that pharmacy learners must complete.[7] To accommodate a larger number of learners and to meet the increasing demands of the health care system, practice sites have implemented the layered learning practice model (LLPM).[8-10]

Table 1. Canadian Consensus Clinical Pharmacy Key Performance Indicators (cpKPIs)*

cpKPI	Description
1. Admission medication reconciliation	Proportion of patients who received documented admission medication reconciliation (and had resolution of identified discrepancies), performed by a pharmacist
2. Pharmaceutical care plan	Proportion of patients for whom a pharmacist developed and initiated a pharmaceutical care plan
3. Drug therapy problems (DTPs)	Number of DTPs resolved by a pharmacist during an admission
4. Interprofessional patient care rounds	Proportion of patients for whom a pharmacist engaged in interprofessional patient care rounds to enhance medication management
5. Patient education during hospital stay	Proportion of patients for whom a pharmacist provided education about their disease(s) and medication(s) during their admission.
6. Patient education at discharge	Proportion of patients for whom a pharmacist provided medication education at discharge
7. Discharge medication reconciliation	Proportion of patients who received documented discharge medication reconciliation (and had resolution of identified discrepancies), performed by a pharmacist
8. Bundled patient care interventions	Proportion of patients for whom a pharmacist provided comprehensive direct patient care by working in collaboration with the health care team. The consensus bundle cpKPI includes 5 interlinked activities in patient care: • admission medication reconciliation • pharmaceutical care and/or resolution of DTPs • participation during interprofessional patient care rounds • patient education (during hospitalization and/or at discharge) • discharge medication reconciliation.

*Adapted, with permission of the Canadian cpKPI Collaborative, from *Canadian Consensus on Clinical Pharmacy Key Performance Indicators: Knowledge Mobilization Guide*.[4]

Within the LLPM framework, pharmacy learners at different levels of training (i.e., pharmacy students, pharmacy residents) provide patient care under the guidance of a pharmacist preceptor.[8,9,11] Delgado and others[11] found that this model enabled pharmacy students to effectively act as "pharmacist extenders", providing comprehensive pharmacy services to patients who would otherwise not be reached. This model also facilitates near-peer teaching among learners, whereby senior peers provide learning support to junior students, drawing on their comparable knowledge base.[7] It offers students access to more learning opportunities without unduly increasing the pharmacist's workload, and enables residents to hone their skills as preceptors through mentoring of pharmacy students within a supervised structure.[7,12] In a qualitative study, Bates and others[13] assessed the delivery of experiential education to Advanced Pharmacy Practice Experience students and pharmacy residents in an oncology LLPM environment. They found that the LLPM framework was well perceived by learners and did not compromise the achievement of knowledge-based learning objectives.

Chow and others[14] evaluated whether there was a difference in the number of patients who received admission medication reconciliation (one of the Canadian consensus cpKPIs) between learner–pharmacist pairs and pharmacists alone. The authors of this 6-month study concluded that the number of admission medication reconciliations completed per 5-week rotation increased by a median of 5 when a pharmacy learner was present.[14] In another study, Bates and others[9] described the frequency at which patients in malignant hematology and medical oncology services received discharge medication reconciliation and counselling in an LLPM. They observed that with this model, 51% of all patients received personalized education upon discharge from the pharmacy team, compared with 0% of patients before the study.[9] Accordingly, the authors reported that the integration of pharmacy learners into an LLPM expanded the provision of pharmacist services.[9]

There is a lack of literature describing and quantifying clinical productivity in the LLPM, and an even greater paucity of literature quantifying the contributions of pharmacy learners to patient care. More specifically, no published studies have evaluated the delivery of all 8 cpKPIs in the presence of pharmacy learners. In this pilot study, we aimed to bridge these gaps in the literature by capturing data for all of the cpKPIs recommended by the Canadian cpKPI Collaborative and by quantifying the delivery of patient care services by different combinations of pharmacy professionals across a spectrum of the LLPM. We evaluated clinical productivity, as measured by the completion of cpKPIs by pharmacists working in the presence or absence of pharmacy learners (students with or without residents).

This study involved the following 3 scenarios under an inpatient medical oncology service of a tertiary care centre at different times during the study timeframe: presence of one or more pharmacists with one resident and one or more students (P-R-S); presence of one or more pharmacists with one or more students (P-S); and presence of one or more pharmacists only (P; standard practice).

The primary objectives were to describe the proportions of patients who received cpKPIs 1 through 7 across the aforementioned scenarios under an inpatient medical oncology service; to determine the contributions of each respective pharmacy professional for each cpKPI across the aforementioned scenarios under the same inpatient service; and to describe the number of cpKPIs performed per pharmacy professional, standardized to 20 pharmacist workdays, across the aforementioned scenarios under the same inpatient service. The secondary objectives were to compare the number of DTPs resolved by each pharmacy professional, standardized to 20 pharmacist workdays, across the aforementioned scenarios under the medical oncology service, and to determine the proportion of eligible patients who received bundled patient care interventions (i.e., cpKPI 8) across the aforementioned scenarios under the same inpatient service.

METHODS

We conducted a retrospective observational pilot study under the inpatient medical oncology service at a single tertiary care teaching centre. The inpatient medical oncology service is an interdisciplinary team that provides care to patients with acute, often complex health care needs. Patients admitted to the inpatient medical oncology service include those with acute infections, thromboembolism, cancer- or chemotherapy-related complications, or symptoms of the underlying malignancy, and those needing disposition planning and palliation. The service is staffed with 2 full-time equivalent pharmacists who generally work 7.5-h workdays from Monday to Friday, with occasional weekends. About 65% of each pharmacist's time is dedicated to the provision of direct patient care services, which includes clinical activities defined by the cpKPIs. About 25% of each pharmacist's time is devoted to centralized pharmacy distribution tasks, including verification of chemotherapy orders and screening of medication orders for hospitalized inpatients. The remaining (estimated) 10% of time is directed toward administrative, educational, research, or quality improvement-based initiatives. Preceptorship of pharmacy learners within this practice framework is generally performed within the time allotted for provision of clinical services, although departmental efforts are made to help alleviate some distribution service requirements for pharmacists when they are working as preceptors with assigned students.

A 6-month convenience period was established and served as a feasible timeframe during which multiple pharmacy learners (residents and students) had planned direct patient care oncology rotations. During the study, 4 medical oncology pharmacists (total of 2 full-time equivalent positions), 2 pharmacy residents, and 5 PharmD students (4 fourth-year pharmacy students and 1 post-bachelor PharmD Bridging student) were involved in providing care on the medical oncology service. Appendix 1 (available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/

190/showToc) provides the specific dates and durations of the respective rotations and a description of scheduling overlap.

All pharmacy professionals (pharmacists, pharmacy residents, and pharmacy students) received both standardized instruction and a copy of the project manual (Appendix 2, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/190/showToc). The project manual classified each cpKPI and provided examples of the various DTPs, categorized from A to G (as listed in Addendum B of Appendix 2). Each participant was also given a package of customized printed stickers, denoting each of the 7 standardized cpKPIs. Pharmacists were given white stickers, pharmacy residents were given pink stickers, and pharmacy students received yellow stickers. Upon performing a particular cpKPI, the individual was instructed to affix the appropriate sticker onto his or her own daily patient care roster (Addendum C of Appendix 2). Certain of the cpKPIs required additional documentation (Table 2). For example, participants were instructed to track the number and types of DTPs identified and resolved by documenting a letter (A to G) on the labels, which were assigned to specific DTPs. No patient-specific data were collected.

Before the study began, there was a 2-week lead-in period (March 27 to April 7, 2017), during which participants recorded completion of cpKPIs, to become familiar with the cpKPI documentation procedures. The aim of the lead-in period was to equip pharmacist preceptors with the knowledge and skills to ensure appropriate recording of cpKPIs for themselves and their pharmacy learners. The lead-in period was applied only for the first group of participants; subsequent pharmacy professionals who contributed to data collection received standardized instruction and the project manual (described above). Data recorded during the lead-in period were not included in data analyses.

Completed cpKPIs were recorded for all patients admitted under the medical oncology service at the hospital during the periods April 10 to September 15, 2017, and January 8 to February 9, 2018 (for a total study timeframe of 6 months). Patients who did not receive any pharmacy services that would warrant recording of a cpKPI were included, to ensure accurate estimation of proportions of patients receiving the respective cpKPIs. Patients who died during their admission were not eligible to receive cpKPI 6 (education at discharge), cpKPI 7 (discharge medication reconciliation), or the bundled patient care intervention, and were excluded from these assessments. Whenever a pharmacy learner was present under the oncology service, debriefing sessions occurred daily. During these meetings, the oncology pharmacist(s) and the pharmacy learner(s) reviewed respective patient care plans and discussed the clinical activities that had been performed during the day. This process encouraged standardized documentation and facilitated appropriate assignment of cpKPIs among participants who may have provided pharmaceutical care to the same patients.

During the study, patient care rosters with the affixed stickers were collected weekly and stored in a secure area within the pharmacy. A de-identified, password-protected quality assurance database was created to electronically record the number and timing of completed cpKPIs. The recorded data from patient rosters were entered into the electronic database by a PharmD student and were validated by the primary investigator (J.W.). Approval for this study was granted by the institutional Research Ethics Board.

Statistical Analysis

Given the exploratory nature of this study, descriptive statistics were used to report the study outcomes. As recommended by the Canadian cpKPI Collaborative,[4] data for cpKPIs 1, 2, 4, 5, 6, and 7 are reported as proportions of patients receiving the cpKPIs, and data for cpKPI 3 are reported as total number of

Table 2. Additional Sticker Documentation Requirements for Tracking Clinical Pharmacy Key Performance Indicators (cpKPIs) on Patient Care Rosters

cpKPI Label	Additional Documentation
Admission medication reconciliation (AMR)	• Reviewed the AMR • Identified and resolved discrepancies
Pharmaceutical care plan	No additional documentation required
Drug therapy problems (DTPs)	• Reported the type of DTP resolved by documenting an assigned letter on the label: (A) Unnecessary drug therapy (B) Requires additional drug therapy (C) Inappropriate drug therapy (D) Dose too low (E) Dose too high (F) Adverse drug reaction (G) Inappropriate adherence
Interprofessional patient care rounds	• Attended bullet rounds • Attended other rounds
Patient education during hospital stay	No additional documentation required
Patient education at discharge	No additional documentation required
Discharge medication reconciliation (DMR)	• Reviewed the DMR • Identified and resolved discrepancies

DTPs resolved. As an additional aspect of cpKPI 3, the proportion of patients with DTPs resolved is also reported. The number of 7.5-h pharmacist workdays was determined by summing the total number of pharmacist working days during the respective intervention periods, which serves to account for differences in staffing or vacation that occurred between periods. The number of cpKPIs performed within each scenario was then adjusted to 20 pharmacist workdays to demonstrate the volume of respective cpKPIs completed per pharmacist over a period approximating 1 month of clinical service. In addition, we report on each pharmacy professional's contributions to the total proportions of patients receiving the various cpKPIs and the number of cpKPIs standardized to 20 pharmacist workdays. Because this was a descriptive study, no formal statistical analyses were performed.

RESULTS

In total, 685 recorded admissions to the hospital's medical oncology service occurred over the 6 months of the study (April 10 to September 15, 2017, and January 8 to February 9, 2018). The number of admitted patients per pharmacist workday, a surrogate marker of pharmacists' workload, was lower for the pharmacist-only scenario (3.2) than for the P-S and P-R-S scenarios (3.4 and 3.7, respectively) (Table 3).

Figure 1 depicts the total proportions of eligible patients who received the various cpKPIs, as well as contributions to patient care from each pharmacy professional within each of the scenarios. Despite a consistent trend for pharmacists to contribute less to overall patient care when learners were present, more so when both a pharmacy resident and one or more students were present, the total proportions of patients receiving cpKPIs appeared generally similar across all scenarios. Furthermore, there may have been a trend toward higher proportions of patients receiving cpKPIs in the pharmacist-only scenario, compared with scenarios in which pharmacy learners were present. Scenario P was also noted to have a greater proportion of eligible patients who received bundled patient care interventions, relative to scenarios P-S and P-R-S (Figure 2). These findings may be attributable to the fact that the pharmacist-only scenario had full staffing, with no vacation, and also had the smallest relative workload, as represented by the number of admitted patients per pharmacist workday, compared with scenarios in which pharmacy learners were present (Table 3).

The largest identified discrepancy in care delivery occurred for cpKPI 7, discharge medication reconciliation. Within the LLPM model investigated here, daily pharmacist and learner debriefings occurred in the afternoon, the time of day when many patients are discharged; this could explain, in part, the difference in completion of cpKPI 7 among different scenarios.

At least one member of the clinical pharmacy team contributed to patient care through attending and participating in the daily interdisciplinary discharge rounds (cpKPI 4). Because of this consistent attendance at rounds, all patients within the study were deemed to have received cpKPI 4 throughout their respective admissions, and there were no differences among the scenarios.

The total number of cpKPIs 1, 2, 3, 5, 6, and 7, standardized to 20 pharmacist workdays, was similar across scenarios (255 with the P-R-S scenario, 281 with the P-S scenario, and 258 with the P scenario) (Figures 3 and 4). We also observed a potential trend toward resolution of more DTPs with pharmacy learners present (153 with the P-R-S scenario, 180 with the P-S scenario, and 149 with the P scenario) (Figure 4). The most common DTP resolved across all scenarios was initiation of medications for patients (reported as "additional drug" in Figure 4), which included chemotherapy and associated supportive care medications, such as antiemetics. The second most commonly resolved DTP across all scenarios was discontinuation of a medication because a clinical indication was lacking. The absolute increase in DTPs identified when learners were present may be attributable to the comprehensiveness of learners' respective care plans and their thorough review of medications.

DISCUSSION

In this study—which to our knowledge is the most comprehensive of its type to date—the pharmacist-only scenario had a lower number of admitted patients per pharmacist workday than the scenarios with pharmacy learners present. This difference in workload may have affected the results displayed in Figure 1, which appears to show a slightly greater proportion of patients receiving the various cpKPIs under scenario P than under scenarios P-S and P-R-S. In practical terms, clinical productivity did not appear to be impaired with the integration of pharmacy learners on the medical oncology team. Despite the progressive reductions in pharmacists' contributions to completed cpKPIs in

Table 3. Baseline Characteristics across the 3 Scenarios

Characteristic	Scenario		
	Pharmacist	Pharmacist–Student	Pharmacist–Resident–Student
No. of admitted patients	210	354	222
No. of pharmacist workdays	66	103	60
No. of admitted patients/pharmacist workday	3.2	3.4	3.7

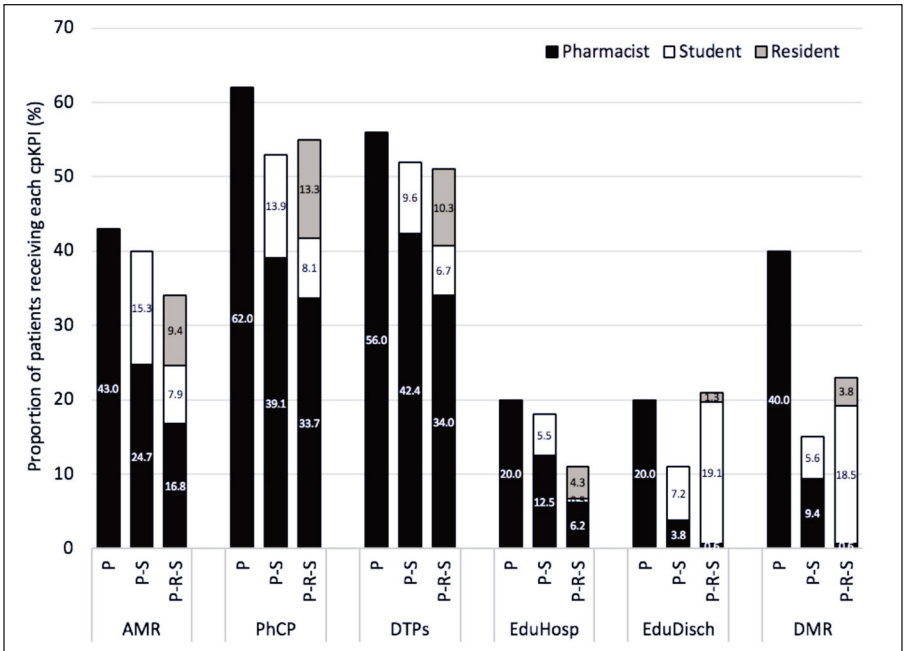

Figure 1. Proportions of eligible patients who received clinical pharmacy key performance indicators (cpKPIs) within each scenario. All patients (100%) received interprofessional patient care rounds in all 3 scenarios (where P = pharmacist present; P-S = pharmacist and student present; and P-R-S = pharmacist, resident, and student present). Abbreviations for cpKPIs: AMR = admission medication reconciliation, PhCP = pharmaceutical care plan, DTPs = drug therapy problems, EduHosp = education during hospitalization, EduDisch = education during discharge, DMR = discharge medication reconciliation.

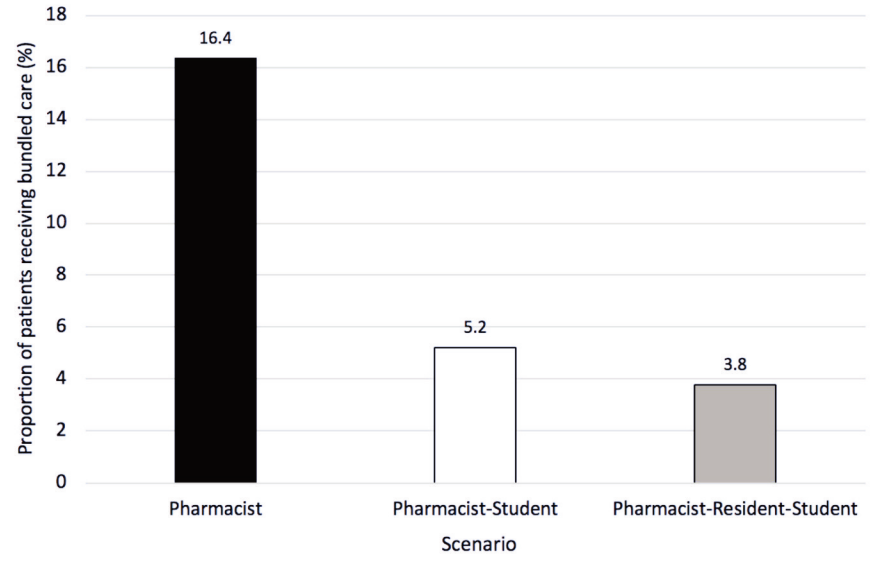

Figure 2. Proportions of eligible patients who received bundled patient care interventions within each scenario.

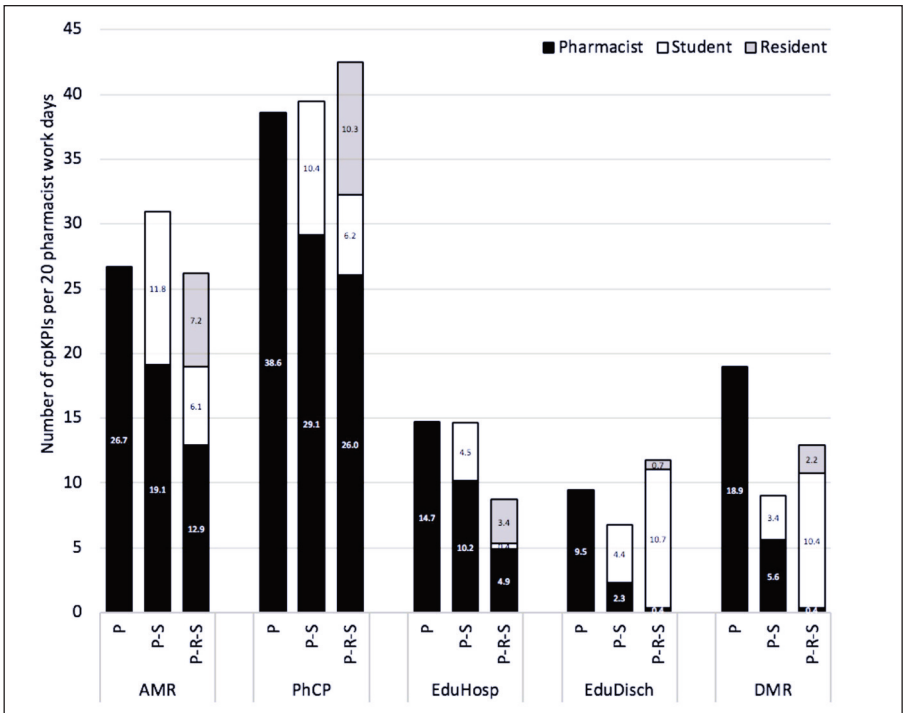

Figure 3. Number of clinical pharmacy key performance indicators (i.e., cpKPIs 1, 2, 5, 6, and 7) performed, with standardization to 20 pharmacist workdays. Scenario abbreviations: P = pharmacist present; P-S = pharmacist and student present; P-R-S = pharmacist, resident, and student present. Abbreviations for cpKPIs: AMR = admission medication reconciliation, PhCP = pharmaceutical care plan, EduHosp = education during hospitalization, EduDisch = education during discharge, DMR = discharge medication reconciliation.

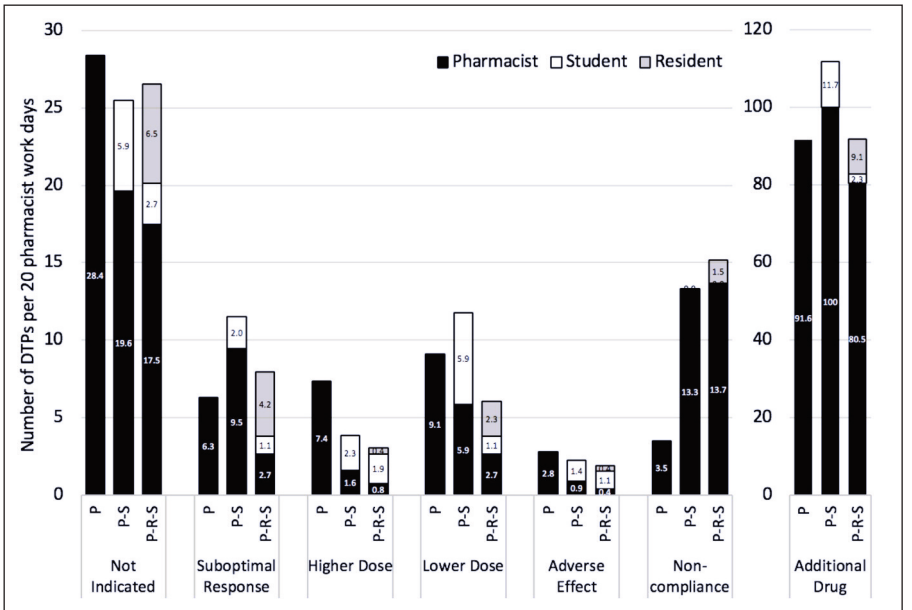

Figure 4. Number of drug therapy problems (DTPs) resolved, standardized to 20 pharmacist workdays. Scenario abbreviations: P = pharmacist present; P-S = pharmacist and student present; P-R-S = pharmacist, resident, and student present.

the presence of pharmacy students and a pharmacy resident, the proportions of patients receiving cpKPIs were largely comparable across all scenarios. This result is emphasized by the fact that the absolute total numbers of completed cpKPIs were largely consistent across the 3 scenarios. For this study, describing completed cpKPIs in an absolute fashion is important to demonstrate the maintenance and consistency of clinical productivity with learners present. This approach contrasts with reporting completed cpKPI proportions alone, which may be influenced by overall pharmacist staffing and patient volume across the respective scenarios.

Providing orientation, instruction, teaching, and mentorship to learners requires time that might otherwise be directed to clinical activities, which might in turn raise concerns about potential detriments to patient care. However, this study has shown that clinical work does not have to be neglected when learners are present. Rather, pharmacy activities can be appropriately delegated to, and completed by, pharmacy learners, thereby maintaining clinical productivity within an LLPM. A next logical avenue of research would be to explore rotational structures and strategies to improve clinical productivity within an LLPM. The provision of standardized, reproducible training and orientation, consistent definition of the roles of pharmacy professionals, and delegation of specified clinical tasks are all areas of potential optimization that may help to increase clinical productivity during pharmacy learner rotations.

The mean patient length of stay is another possible confounding factor that might have influenced the proportions of patients receiving cpKPIs across the scenarios. Although length of stay was not reported or examined in this study, scenarios with patients admitted for a longer duration would be more likely to have a greater proportion of patients receiving cpKPIs and, by extension, bundled patient care interventions. This study also did not specifically address the timing of hospital discharge. Patients whose discharges occurred outside of standard clinical or rotation hours, including evenings, weekends, or holidays, likely did not receive cpKPI 6 (discharge medication education) or cpKPI 7 (discharge medication reconciliation).

Another limitation of this study was the reliance on consistent and standardized documentation of completed cpKPIs by participants. During their medical oncology rotation, pharmacy learners were expected to develop pharmaceutical care plans for new patients and to perform follow-up for previously assigned patients, among other patient care activities and responsibilities. However, at the time of this study, the study institution did not have a systematic method of electronically tracking completion of patient-specific cpKPIs or resolution of specific DTPs by pharmacy team members. The multiple competing interests of pharmacy learners and clinical pharmacists might have precluded reliable documentation of all cpKPIs performed, a duty that was secondary to the provision of patient care. By extension, another limitation of this pilot study was the lack of evaluation of interindividual variations in cpKPI reporting among clinical pharmacists and pharmacy learners. Furthermore, workload and clinical productivity were not compared between pharmacy professionals at the same level of training. Further research is encouraged to confirm and extend the findings of this pragmatic study.

Notably, our study results corroborate those of Chow and others,[14] who derived data from an electronic health record that tracked completion of cpKPIs. Those authors investigated whether the presence of pharmacy learners partnering with pharmacists affected the delivery of admission medication reconciliation, relative to standard practice.[14] When standardized to a 5-week period, the investigators noted that the presence of a pharmacy learner significantly increased the number of admission medication reconciliations performed, with a median increase of 5 (29 versus 24).[14] In our study, if the number of admission medication reconciliations were to be standardized to 25 pharmacist workdays (equivalent to a 5-week work period), there would be a similar increase of 5.3 with the presence of one or more pharmacy students (38.6 versus 33.3).

Although there is an established body of pharmacy practice research showing the impact of pharmacist interventions on patient outcomes,[5,15,16] it is unknown whether pharmacy learner–specific interventions also lead to positive clinical outcomes. Literature comparing the quality of pharmaceutical care interventions among final-year pharmacy students, pharmacy residents, and clinical pharmacists is lacking. It might reasonably be hypothesized that the quality of patient care initiatives by the aforementioned pharmacy learners would be similar to that of clinical pharmacists, given that their interventions are performed in a manner consistent with, and under the supervision of, a pharmacist. Pharmacy learners are commonly assigned fewer patients than would be assigned to fully qualified pharmacists, because of challenges related to the complexity of cases and the management of a larger workload. Having a lower number of assigned patients often allows learners to develop comprehensive pharmaceutical care plans and to execute detailed patient care processes. Further research is encouraged to determine whether pharmacy learners' contributions to care are associated with improved patient outcomes.

Pharmacist preceptors were responsible for teaching foundational therapeutic knowledge, coaching pharmacy learners on particular activities (e.g., discharge patient education), and reviewing documentation performed by pharmacy learners. Despite these competing interests, the results of this study demonstrated that clinical productivity could be maintained while the pharmacist supervised final-year pharmacy students, with or without a pharmacy resident. There was a maximum of 3 pharmacy learners (all pharmacy students) during only one week of the entire study, with supervision by 2 pharmacists. Although not explicitly examined in our study, there may be a threshold number of pharmacy learners at which point clinical productivity declines because of increased devotion of pharmacist work hours to preceptor duties.

Another consideration that may need to be accounted for is whether pharmacists are staying after work hours in order to maintain overall clinical productivity during periods of preceptorship. This study did not reliably record or quantify whether the pharmacist preceptors worked extra hours during periods when learners were present. Subsequent ongoing institutional research aims to address this question within a similar context.

Because of the timing of planned PharmD student rotations, this study did not specifically examine a period when the pharmacy resident served as the sole pharmacy learner under the supervision of a pharmacist preceptor. More research is required to identify strategies to optimize the role of the pharmacy resident, who acts as a preceptor to pharmacy students, to maximize clinical productivity within the LLPM. These strategies should also meet the accreditation standards and educational needs of pharmacy residents within their clinical rotations.

CONCLUSION

At a practical level, the integration of pharmacy learners within an inpatient medical oncology service did not appear to impair clinical productivity. Although pharmacist contributions to patient care were reduced when pharmacy learners were present, overall patient care activities were maintained through delegation of these activities to the pharmacy learners. This study showed that the collaboration between pharmacists and pharmacy learners in a spectrum of the LLPM allowed provision of cpKPIs to similar proportions of patients and delivered comparable total numbers of cpKPIs relative to standard practice. Research is currently ongoing to identify strategies to optimize clinical productivity within an LLPM, which may include designation of specific roles to pharmacy students and enhanced delegation of teaching opportunities to pharmacy residents. Further studies are required to determine whether there are benchmarks for the proportion and number of completed cpKPIs that would affect patient outcomes at a population level.

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Assessment of Empiric Vancomycin Regimen in the Neonatal Intensive Care Unit

Ruthdol Ywaya and Brandi Newby

ABSTRACT

Background: Vancomycin is used to treat serious gram-positive infections in neonates. Currently, there is no consensus on the preferred empiric dosing regimen or target trough vancomycin levels for neonates. The current Fraser Health empiric dosing regimen, implemented in 2010, was designed to achieve target trough levels of 5 to 15 mg/L.

Objectives: To determine the percentage of neonates receiving vancomycin in whom target trough levels of 5 to 15 mg/L were achieved, to identify the times to negative culture result and clinical resolution, and to determine the incidence of nephrotoxicity.

Methods: A chart review was completed for patients who had received vancomycin in the neonatal intensive care unit of either Surrey Memorial Hospital or Royal Columbian Hospital from June 2012 to May 2017 and for whom at least 1 interpretable vancomycin level was available.

Results: A total of 87 vancomycin encounters (in 78 neonates) were identified in which the drug had been given according to the Fraser Health empiric dosing regimen. Target trough vancomycin level (5 to 15 mg/L) was achieved in 75% of these encounters. The mean times to negative culture result and clinical resolution were 5 and 6 days, respectively. There was no statistically significant correlation between vancomycin level and time to clinical resolution (r_s = 0.366, p = 0.072). Among cases in which the trough vancomycin level exceeded 15 mg/L, the incidence of nephrotoxicity was 22% (4/18).

Conclusions: The current Fraser Health empiric dosing regimen for vancomycin achieved target trough levels of the drug for most neonates in this study. Targeting trough levels less than 15 mg/L when appropriate to the infection type may limit nephrotoxicity associated with vancomycin in neonates. Further studies are needed to evaluate the clinical significance of various vancomycin levels.

Keywords: neonatal intensive care unit, newborn, vancomycin, pharmacokinetics, clinical effectiveness

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RÉSUMÉ

Contexte : La vancomycine est utilisée dans le traitement d'infections graves à bactéries à Gram positif chez le nouveau-né. Il n'y a pour l'instant pas de consensus quant à la posologie empirique ou aux concentrations minimales visées de vancomycine à privilégier chez le nouveau-né. La posologie empirique actuelle de la Fraser Health, instaurée en 2010, visait des concentrations minimales de 5 à 15 mg/L.

Objectifs : Déterminer le pourcentage de nouveau-nés ayant reçu les concentrations minimales visées de 5 à 15 mg/L de vancomycine, établir le temps nécessaire à l'obtention d'un résultat de culture négatif et celui nécessaire à la disparition clinique des symptômes et déterminer l'incidence de la néphrotoxicité.

Méthodes : Les investigateurs ont analysé des dossiers de patients ayant reçu de la vancomycine pendant leur séjour à l'unité de soins intensifs néonatals du Surrey Memorial Hospital ou du Royal Columbian Hospital entre juin 2012 et mai 2017, qui mentionnaient au moins une concentration de vancomycine interprétable.

Résultats : Ils ont répertorié 87 traitements de vancomycine (chez 78 nouveau-nés) administrés selon la posologie empirique de la Fraser Health. Les concentrations minimales visées de 5 à 15 mg/L ont été atteintes dans 75 % de ces traitements. Le temps moyen nécessaire à l'obtention d'un résultat de culture négatif ou à la disparition clinique des symptômes était respectivement de cinq et de six jours. Aucune corrélation statistiquement significative entre les concentrations de vancomycine et le temps nécessaire à la disparition clinique des symptômes n'a été relevée (r_s = 0,366, p = 0,072). Parmi les cas où les concentrations minimales de vancomycine dépassaient 15 mg/L, l'incidence de néphrotoxicité était de 22 % (4/18).

Conclusions : La posologie empirique de vancomycine actuellement en place à la Fraser Health a permis d'atteindre les concentrations minimales visées de médicament pour la plupart des nouveau-nés de la présente étude. Cibler des concentrations minimales de moins de 15 mg/L lorsque cela est pertinent en fonction du type d'infection pourrait limiter le nombre de cas de néphrotoxicité associés à la vancomycine chez les nouveau-nés. De plus amples études sont nécessaires pour évaluer la portée clinique de différentes concentrations de vancomycine.

Mots clés : unité de soins intensifs néonatals, nouveau-né, vancomycine, pharmacocinétique, efficacité clinique

INTRODUCTION

In the neonatal intensive care unit (NICU), vancomycin is used to treat serious gram-positive infections such as sepsis, meningitis, pneumonia, skin and soft-tissue infections, necrotizing enterocolitis, and osteomyelitis. The predominant gram-positive organisms of late-onset infections in the NICU are coagulase-negative *Staphylococcus* and *Staphylococcus aureus*.[1,2] These organisms have been shown to be sensitive to vancomycin when the minimum inhibitory concentration (MIC) is 2 mg/L or less.[3]

Time above the MIC or ratio of area under the curve to MIC has been used to assess vancomycin efficacy in adults, but there is lack of evidence for use of these measures in neonates. Vancomycin has been shown to exert bactericidal activity against *Staphylococcus* when the unbound levels are 4 to 5 times the MIC.[4-7] Because vancomycin is about 50% protein-bound, this translates to target levels of 4 to 5 mg/L for MIC of 0.5 mg/L, 8 to 10 mg/L for MIC of 1 mg/L, and 15 to 20 mg/L for MIC of 2 mg/L.

Other factors, including the type, location, and severity of infection, should also be considered when determining the target vancomycin level. For patients with infections at sites that are difficult to penetrate, such as the lungs or brain, adult guidelines suggest targeting higher serum levels, specifically 15 to 20 mg/L, regardless of MIC, to ensure adequate penetration of the vancomycin.[6,8] However, for less serious infections, such as uncomplicated infections of skin or soft tissue or infections of the urinary tract, lower targets may be adequate because of excellent clinical response rates with traditional vancomycin dosing.[8]

Pharmacokinetic data show that trough levels of 5 to 10 mg/L are sufficient to resolve infections with coagulase-negative *Staphylococcus* in neonates. By contrast, in adults, higher trough levels (10 to 20 mg/L) are associated with increased efficacy relative to lower trough levels (<10 mg/L), particularly in patients with methicillin-resistant *Staphylococcus aureus*.[6,9,10] However, in vitro studies have shown no difference in efficacy with concentrations above the MIC.[11] In addition, prolonged exposure to serum levels close to the MIC has been associated with increased risk of resistance.[12]

Currently, there is no consensus in the literature regarding the optimal vancomycin dosing regimen or target trough concentrations that are associated with better clinical outcomes in neonates. Some organizations have adopted the target levels for adults without evaluating the potential need for higher targets or the risks associated with those adult targets in the neonatal population. It is also not clear whether the recommended adult target levels are required to achieve desired clinical outcomes in neonates. A study by Barriere and others[13] suggested that higher vancomycin trough levels do not improve the clinical response but likely increase the incidence of nephrotoxicity. Relative to adults, neonates have a larger extracellular fluid volume, which could influence the distribution of vancomycin. Additionally, neonates have lower renal elimination and protein binding than adults, and vancomycin efficacy may be influenced by these pharmacokinetic differences.[10]

Following a local neonatal review in 2002 (unpublished data), the Fraser Health empiric vancomycin regimen was changed at one site in the health authority, and the revised neonatal regimen was then implemented regionally in 2010 (Table 1). This regimen was designed to generate trough levels of 5 to 15 mg/L for the majority of NICU patients. The current study was undertaken to evaluate the empiric regimen that had been in effect since 2010, to determine the percentage of neonates in whom target trough vancomycin levels of 5 to 15 mg/L were achieved, to identify the times to negative culture result and clinical resolution, and to determine the incidence of nephrotoxicity.

METHODS

Ethics approval for this study was obtained from the Fraser Health Research Ethics Board.

For this chart review, the pharmacy department of Surrey Memorial Hospital generated a list of neonates who received vancomycin in the NICU of either Surrey Memorial Hospital or the Royal Columbian Hospital between June 1, 2012, and May 31, 2017. Any neonate on this list for whom an interpretable vancomycin level was available and whose electronic chart was accessible was included in the study. An interpretable vancomycin

Table 1. Current Fraser Health Empiric Dosing Regimen for Vancomycin

Postmenstrual Age	Vancomycin Dosage	No. of Patient Encounters by Dose (*n* = 87)	Mean Vancomycin Level (Range) (mg/L)
< 30 weeks	10 mg/kg IV q12h	10 mg/kg: *n* = 42	11.0 (ND to 18.1)
≥ 30 weeks, 0–7 days of life	10–15 mg/kg IV q12h	10 mg/kg: *n* = 1	11.9 (NA)
		11 mg/kg: *n* = 1	12.2 (NA)
		15 mg/kg: *n* = 3	16.2 (8.5 to 29.5)
≥ 30 weeks, > 7 days of life	10–15 mg/kg IV q8h	10 mg/kg: *n* = 18	11.2 (ND to 21.3)
		11 mg/kg: *n* = 4	11.9 (10.2 to 15.4)
		12 mg/kg: *n* = 3	9.9 (7.5 to 12.3)
		13 mg/kg: *n* = 7	14.9 (8.6 to 21.2)
		14 mg/kg: *n* = 3	13.6 (10.1 to 19.1)
		15 mg/kg: *n* = 5	12.3 (7.4 to 17)

NA = not applicable, ND = not detectable.

level was defined by a serum sample for measurement of trough level drawn within 60 min before the third dose (or a later dose); alternatively, if 2 measurements had been done for a given patient, the serum trough level could be calculated from the 2 results, as described below. Patients were excluded if the postmenstrual age was greater than 45 weeks, if there was no electronic chart, if no vancomycin level had been recorded, or if vancomycin measurements had been inappropriately obtained.

For this study, the data collected included the following information about the patient; gestational age, birth weight, postmenstrual age, day of life and weight when vancomycin was started, baseline feeding status, urine output, concurrent vasopressor use, concurrent antibiotic use as well as antibiotic use within 48 h before initiation of vancomycin therapy, and infection type. In cases with a positive culture result, the MIC of the infective organism was recorded, if available. The vancomycin regimen, duration of therapy, and serum levels of vancomycin were also recorded. For patients who had received more than 1 course of vancomycin, all courses within the study period were included in the analysis, entered as separate encounters. For patients with multiple samples drawn during a single vancomycin course, only the first measured level obtained with the empiric regimen was assessed.

In cases where a serum trough level within 60 min of next dose was not available, but 2 interpretable levels had been obtained, pharmacokinetic calculations were used. The individual elimination rate constant (K) and extrapolated trough level were calculated according to the 2-point modified Sawchuk–Zaske method.[14]

Time to negative culture result was determined by analyzing data for patients with an initial positive culture result and then a subsequent repeat culture result; this analysis included only patients with an indication that required vancomycin therapy. Repeat culture was performed at the discretion of the attending physician. Results from repeat culture of endotracheal tube samples were excluded because of possible colonization. The time to negative culture result was defined as the number of days between initiation of vancomycin and the first negative result.

For clinical outcomes, the following information was collected: need for and type of respiratory support; oxygen requirements; recorded instances of apnea, bradycardia, or desaturation; vasopressor use; temperature of patient and isolette; feeding volume; any medical imaging reports; and complete blood counts. Baseline data were collected for the patients for the day before initiation of vancomycin for comparison with data collected throughout the vancomycin course. Clinical resolution was defined as a return to baseline clinical status. For determining whether patients had experienced nephrotoxicity, the following data were collected: serum creatinine, urine output, and concomitant nephrotoxic medications. Neonatal nephrotoxicity was defined on the basis of either of the following criteria: increase in serum creatinine of at least 26.5 µmol/L or at least 50%.[15]

Descriptive statistics were used to analyze the data in this study. The Spearman rho correlation coefficient was calculated to describe the relation between vancomycin level and time to clinical resolution. For this 2-sided test, $p < 0.05$ was deemed to represent statistical significance.

RESULTS

In total, 147 NICU patients received vancomycin during the study period (Figure 1), of whom 78 were included in the analysis and 69 were excluded. Several of the patients received more than 1 course of vancomycin therapy; as such, there were 87 encounters in which neonates received vancomycin according to the Fraser Health empiric regimen.

For the 87 patient encounters, the mean postmenstrual age was 30 weeks when vancomycin was started (Table 2). The most common infections that required vancomycin were coagulase-negative *Staphylococcus* bacteremia or sepsis (22 [25%]), suspected sepsis (23 [26%]), and necrotizing enterocolitis (19 [22%]). There were no cases of methicillin-resistant *Staphylococcus aureus*. For 29 cultures, the MIC was reported. Of these, 6 (21%) had MIC less than or equal to 0.5 mg/L, 16 (55%) had MIC of 1 mg/L, 7 (24%) had MIC of 2 mg/L, and none had MIC above 2 mg/L.

Among the 87 encounters, 43 involved an empiric vancomycin dosage of 10 mg/kg IV q12h, 1 involved a dosage of 11 mg/kg IV q12h, 3 involved a dosage of 15 mg/kg IV q12h, 18 involved a dosage of 10 mg/kg IV q8h, 5 involved a dosage of 15 mg/kg IV q8h, and 17 involved a dosage range of 11 to 14 mg/kg IV q8h (Table 1). The average duration of vancomycin therapy was 7 days. We did not evaluate the reasons why patients required prolonged courses of therapy, because all patients in this study had received antibiotics for the recommended duration for the presumed diagnoses.

Data for vancomycin levels were interpretable for all but 1 of the 87 patient encounters; for the sole exception, the pharmacokinetic calculation was performed. With the Fraser Health empiric regimen, 65 (75%) of the 87 vancomycin trough levels were within the target range (5 to 15 mg/L), and 14 (16%) were between 15.1 and 20 mg/L, for a total of 79 (91%) between 5 and 20 mg/L (Figure 2); 48 (55%) of the 87 measured trough levels were between 10 and 20 mg/L.

A positive culture result was obtained for 36 (41%) of the 87 encounters (Figure 3). For determination of time to negative culture result, 21 encounters were included. The other 15 encounters with an initially positive culture result were excluded for the following reasons: endotracheal tube sample ($n = 5$), no indication for vancomycin ($n = 4$), and no repeat culture performed ($n = 6$). The mean time to repeat culture and the time to negative culture result were 4 and 5 days, respectively (range 1 to 12 days for both). For 7 of the 21 encounters with repeat culture, the repeat result was positive; for all of these, negative results were eventually obtained on subsequent repeat culture.

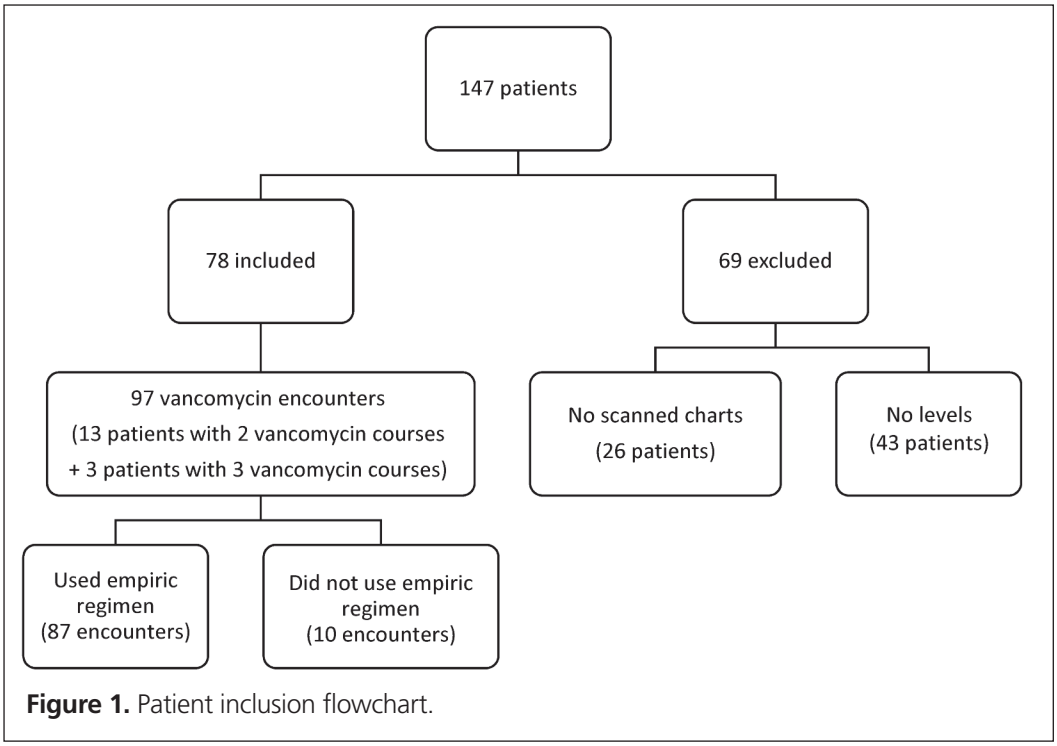

Figure 1. Patient inclusion flowchart.

For determination of clinical resolution, 4 encounters were excluded because there was no indication for vancomycin. No change from baseline clinical status was documented for 58 (70%) of the 83 vancomycin encounters included in this analysis. The other 25 encounters (30%) had a change from baseline clinical status followed by an eventual return to baseline status, with time to clinical resolution of about 6 days (range 2 to 17 days). For these 25 patients with a change in clinical status from baseline, there was no statistically significant correlation between vancomycin trough level and time to clinical resolution (r_s = 0.366, p = 0.072) (Figure 4).

There were a total of 26 encounters in which concurrent nephrotoxic medications were administered, specifically indomethacin, gentamicin, or furosemide. For 17 of these encounters, the vancomycin level was less than 15 mg/L. Neonatal nephrotoxicity occurred in 4 (5%) of the 78 patients included in this study. The mean time to nephrotoxicity from initiation of vancomycin was 3 days (range 1 to 5 days) (Table 3). For 3 of the 4 patients with nephrotoxicity, gentamicin was the only concomitant nephrotoxic medication administered. One of the patients receiving gentamicin also experienced septic shock requiring vasopressors. The incidence of nephrotoxicity was 22% (4/18) among patients with vancomycin level above 15 mg/L; none of the 60 patients with vancomycin level of 15 mg/L or below experienced nephrotoxicity.

DISCUSSION

In this study, the current Fraser Health empiric vancomycin regimen led to vancomycin trough levels between 5 and 15 mg/L for 75% of patient encounters, with 91% of encounters having trough levels that fell between 5 and 20 mg/L. Given the broad range of neonates (postmenstrual age 24 to 42 weeks) included in this study and the anticipated interpatient variability, the empiric regimen generated acceptable vancomycin trough levels

Table 2. Patient Characteristics

Characteristic	Mean (Range) or No. (%) of Encounters*
Postmenstrual age (weeks)	30 (24–42)
Days of life	17 (1–68)
Birth weight (kg)	1 (0.38–4.25)
Weight at initiation of vancomycin (kg)	1.2 (0.44–4.25)
Urine output at initiation of vancomycin (mL/kg per hour)	3 (1.5 to 6.2)
NPO status	16 (18)
Vasopressor therapy	2 (2)
Received antibiotics 48 h prior	38 (44)
Infections	
CONS bacteremia/sepsis	22 (25)
Suspected sepsis	23 (26)
Necrotizing enterocolitis	19 (22)
Ventilator-associated pneumonia	13 (15)
Cellulitis	6 (7)
Other bacteremia (MSSA, *Bacillus cereus*, group *B Streptococcus*)	4 (5)

CONS = coagulase-negative *Staphylococcus*, MSSA = methicillin-sensitive *Staphylococcus aureus*, NPO = nothing by mouth.
*Mean values are based on 78 unique patients, some of whom had more than 1 course of therapy. Data for number (%) of encounters are based on a denominator of 87 encounters, with each encounter representing an individual course of vancomycin therapy.

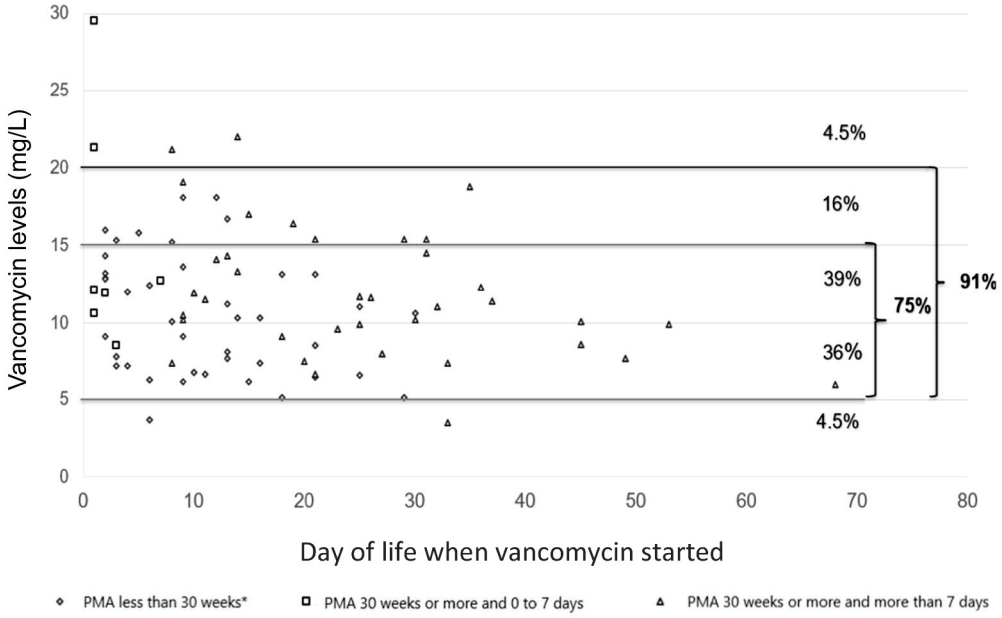

Figure 2. Scatter plot of vancomycin levels with current empiric regimen. For 2 patients, the vancomycin level was undetectable and data are therefore not shown in the scatter plot.

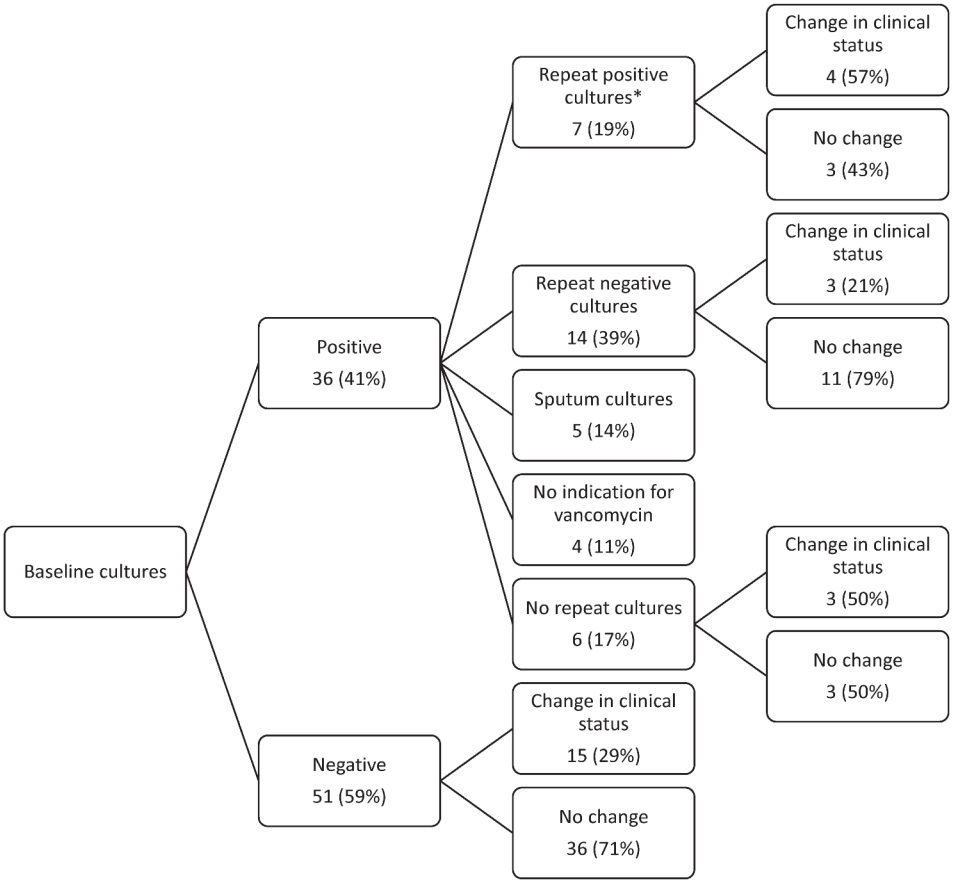

Figure 3. Culture results and clinical status. *All samples with repeat culture (following positive results on initial testing) were negative on subsequent culture.

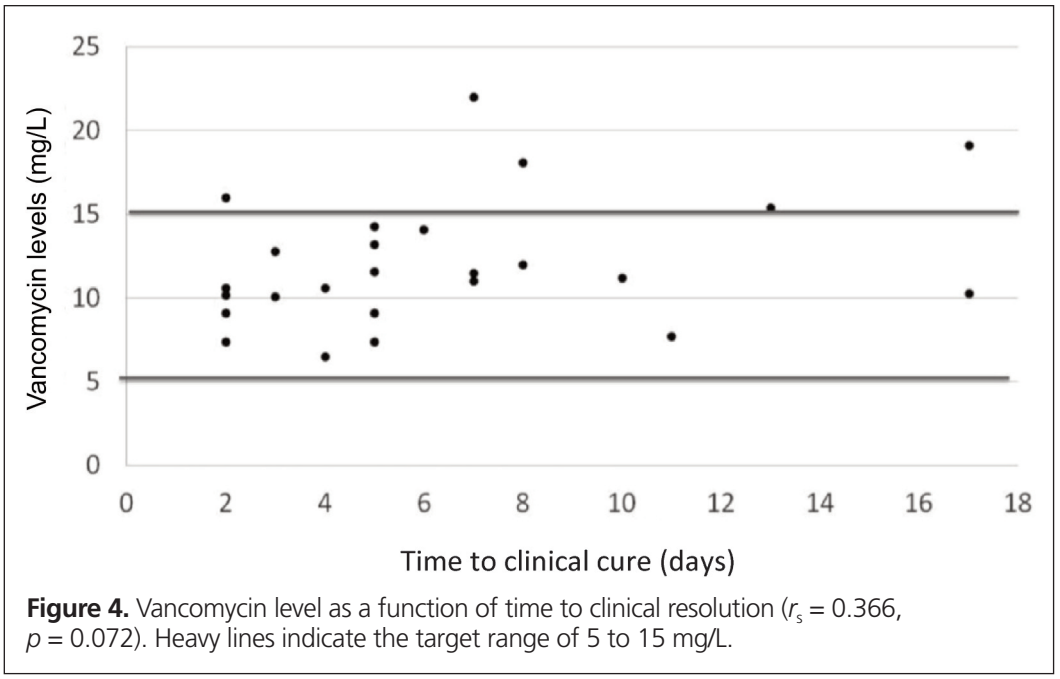

Figure 4. Vancomycin level as a function of time to clinical resolution (r_s = 0.366, p = 0.072). Heavy lines indicate the target range of 5 to 15 mg/L.

Table 3. Characteristics of Patients with Nephrotoxicity (n = 4)

PMA (weeks)	Day of Life when Vancomycin Started	Day of Life when Nephrotoxicity Documented	Urine Output* (mL/kg/h)	SCr (μmol/L)	Increase in SCr	Vancomycin Level (mg/L)	Concomitant Nephrotoxins
25+1	10	15	2.9	74 → 130	76%	13.6 → 22.4	Yes
27+4	13	14	2.2	74 → 126	70%	18.1	Yes
28+4	3	7	0.58	40 → 68	70%	15.3	No
34+1†	1	4	0	107 → 168	57%	21	Yes

PMA = postmenstrual age, SCr = serum creatinine.
*Lowest documented urine output during treatment.
†Patient had septic shock requiring vasopressors.

for a high percentage of encounters. Ringenberg and others[16] found that 25.1% of NICU patients achieved serum trough levels between 10 and 20 mg/L with a commonly used empiric vancomycin regimen given in *Neofax: A Manual of Drugs Used in Neonatal Care*.[17] Dersch-Mills and others[18] evaluated a different empiric vancomycin regimen and found that only 34% of patients achieved a trough level between 10 to 20 mg/L. In the study reported here, which used a simplified version of the *Neofax* regimen, 55% of trough levels fell between 10 and 20 mg/L.

The target trough vancomycin levels associated with efficacy are not known for neonates. Determination of the target trough level should take into consideration the MIC of the organism being treated and the location and severity of the infection.[4-7] In the current study, most of the patients with a positive culture result had organisms with MIC of 1 mg/L or less for vancomycin. Because most of the infections were bacteremia or sepsis-related, a trough level of 8 to 10 mg/L would be appropriate for the majority of these patients. The current empiric vancomycin regimen yielded acceptable trough levels for most of the patients. Therefore, for patients with organisms for which MIC is known, target vancomycin levels could be selected accordingly.

This study also evaluated the clinical significance of vancomycin levels in neonates, a topic that has not been addressed in previous studies. However, a limitation of this study was that the information about clinical status was collected retrospectively, and only 25 (30%) of patient encounters had a documented change from baseline clinical status after initiation of vancomycin. The mean time to clinical resolution for these 25 patients was 6 days (range 2 to 17). Various studies have shown time to clinical resolution of 3 to 7 days in adults with community-acquired pneumonia.[19-22] A study involving adults with sepsis and concurrent bacteremia showed a median time to clinical response of 2 or 4 days, depending on the type of blood culture identification test.[23] Clinical resolution in the neonatal population may be delayed because the source of infection is not always removed once the infection has been diagnosed. For example, central lines or

endotracheal tubes are often not removed until the patient has become clinically stable and can tolerate the necessary changes. No statistically significant correlation between vancomycin trough level and clinical resolution was found in this study. This finding may have been confounded by the small sample size, but it raises questions as to whether an increase in vancomycin levels increases efficacy and whether lower targets would be sufficient to achieve clinical resolution, while minimizing the risk of toxicity. With regard to microbiological cure, the collection of samples for repeat culture was at the discretion of the physician at the time of care; as such, the actual time to microbiological cure was not known and might have been earlier than what was found in this review, which would have been apparent only if culture samples had been collected earlier.

Lestner and others[24] reported that the incidence of vancomycin nephrotoxicity in neonates was 1% to 9%, similar to the overall incidence of nephrotoxicity in our study (5%). A review by Bhargava and others[25] evaluated the risk of acute kidney injury in NICU patients in relation to serum trough concentrations and showed that trough concentrations above 15 mg/L were associated with increased incidence of nephrotoxicity (18.2%) relative to trough concentrations between 10 and 15 mg/L (0%) and less than 10 mg/L (1.4%). The current study had similar findings, in that the incidence of neonatal nephrotoxicity was higher with vancomycin trough levels above 15 mg/L (22%) relative to levels of 15 mg/L or less (0%). However, it was difficult to determine whether the nephrotoxicity was a result of the vancomycin or other risk factors, including infection-related factors or concomitant nephrotoxins. Among the 4 patients with nephrotoxicity, the only additional risk factors identified were the use of concurrent gentamicin (for 3 patients) and septic shock requiring vasopressors (for 1 patient). Therefore, if trough vancomycin levels above 15 mg/L are targeted, it may be prudent to observe patients closely for signs and symptoms of nephrotoxicity and to assess, on a case-by-case basis, whether levels above 15 mg/L are truly needed.

Little appears to be known about the incidence of vancomycin-induced ototoxicity in neonates. Vancomycin-induced ototoxicity has not been consistently shown in animal studies, and clinical studies suggest that apparent vancomycin-induced ototoxicity may in fact be related to administration of impure fermented products and concomitant ototoxins.[26] We did not evaluate vancomycin-induced ototoxicity in this study because of its rare occurrence and inconsistent results in the available literature.

CONCLUSION

The current Fraser Health empiric vancomycin regimen generated trough levels within the target range of 5 to 15 mg/L for most patients in this study. All of the patients received vancomycin for the treatment duration appropriate for their diagnosis, and the mean times to microbiological and clinical resolution were 5 and 6 days, respectively. Of concern was the fact that 22% of patients with vancomycin trough levels above 15 mg/L experienced nephrotoxicity. Additional studies evaluating the clinical significance of vancomycin levels in neonates are needed to help identify the preferred vancomycin target levels for this patient population and thereby to ensure efficacy and minimize toxicity.

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ON THE FRONT COVER

Mont-Tremblant, Quebec

This photograph of the Mont-Tremblant Ski Resort was taken from the pier on Lac Tremblant in August 2018. Helena Trabulsi was enjoying a scenic drive during her summer holiday and used an iPhone 8s to capture the scene. Helena retired from her position as Director of Pharmacy with Halton Healthcare Services earlier that year.

The *CJHP* would be pleased to consider photographs featuring Canadian scenery taken by CSHP members for use on the front cover of the Journal. If you would like to submit a photograph, please send an electronic copy (minimum resolution 300 dpi) to publications@cshp.pharmacy.

Barriers and Strategies for Transition from Student to Successful Hospital Pharmacist

Jasminder Mourh and Brandi Newby

ABSTRACT

Background: Many health care professionals experience a process of transition when entering the workforce. Various barriers have been documented in the literature, including a lack of confidence, challenging interactions with patients and colleagues, workload, increased responsibility, and a fear of making mistakes. Strategies to overcome these barriers, such as orientation and support programs, have been proposed. However, evidence for the transition of students into successful hospital pharmacists is limited.

Objectives: To identify key barriers to the transition from student to successful hospital pharmacist and to outline strategies to overcome these barriers.

Methods: An electronic survey was distributed to Lower Mainland Pharmacy Services (LMPS) pharmacists, and subsequent one-on-one interviews were completed with a subgroup of new pharmacists.

Results: A total of 137 LMPS pharmacists (about 32% of potential respondents) responded to the survey, and 3 of these also participated in an interview. A performance score (used to quantify the transition experience) was calculated for 113 respondents, and there was a correlation between performance score and role satisfaction ($r = 0.550$, $p < 0.001$). Performance score was also correlated with years spent working as a hospital pharmacist ($r = 0.333$, $p < 0.001$) and with highest level of pharmacy education ($r = 0.210$, $p = 0.026$). Work in a specialty area and presence of an orientation program were additional factors associated with higher average performance scores. The greatest need for transitional support was during the first year of work, with trainers and social supports being identified as the most helpful resources. Various perspectives were offered during the interviews, with multiple barriers and strategies proposed.

Conclusions: Among respondents to this survey, the key barriers faced during the transition from student to successful hospital pharmacist were limited time working as a hospital pharmacist, lack of additional pharmacy education, lack of knowledge, rotation among multiple areas, uncertainty about role identity, and limited university preparation. Given that successful transition is associated with subsequent job satisfaction, workplace strategies such as limiting the number of practice areas, developing an orientation program, and providing continued support during the first year of work should be encouraged.

RÉSUMÉ

Contexte : Bien des professionnels de la santé passent par un processus de transition lorsqu'ils intègrent le marché du travail. Différents obstacles ont déjà fait l'objet d'études, notamment le manque de confiance, les interactions difficiles avec les patients et les collègues, la charge de travail, l'augmentation des responsabilités et la peur de faire des erreurs. Des stratégies visant à surmonter ces obstacles, comme des programmes d'orientation et de soutien, ont été mises de l'avant. Or il y a peu d'information sur la transition de l'étudiant vers le pharmacien d'hôpital accompli.

Objectifs : Repérer les principaux obstacles à la transition de l'étudiant vers le pharmacien d'hôpital accompli et décrire les stratégies permettant de surmonter ces obstacles.

Méthodes : Un sondage électronique a été envoyé aux pharmaciens du Lower Mainland Pharmacy Services (LMPS) (c.-à-d. les services de pharmacie des basses-terres continentales), puis des entrevues individuelles ont été réalisées auprès d'un sous-groupe de nouveaux pharmaciens.

Résultats : Au total, 137 pharmaciens du LMPS (environ 32 % des répondants potentiels) ont répondu au sondage et trois d'entre eux ont participé à une entrevue. Pour quantifier la transition vécue, les investigateurs ont calculé la cote de rendement de 113 répondants et ils ont établi une corrélation entre la cote de rendement et la satisfaction au travail ($r = 0{,}550$, $p < 0{,}001$). Ils ont également corrélé la cote de rendement au nombre d'années passées à travailler comme pharmacien d'hôpital ($r = 0{,}333$, $p < 0{,}001$) et à des niveaux plus élevés de scolarité en pharmacie ($r = 0{,}210$, $p = 0{,}026$). Un travail dans un domaine spécialisé et la présence d'un programme d'orientation représentaient des facteurs supplémentaires associés à une moyenne plus élevée des cotes de rendement. C'est au cours de la première année de travail que le besoin de soutien à la transition se faisait le plus sentir, et les formateurs ainsi que le soutien social se sont révélés comme étant les meilleures ressources. Différents points de vue ont été exprimés pendant les entrevues et de multiples obstacles et stratégies ont été abordés.

Conclusions : Selon les répondants au sondage, les principaux obstacles évoqués pendant la transition du rôle d'étudiant à celui de pharmacien d'hôpital accompli étaient : le peu de temps consacré au travail de pharmacien d'hôpital, l'absence de formation supplémentaire en pharmacie, des connaissances insuffisantes, la rotation entre différents domaines, les incertitudes concernant la définition du rôle et l'insuffisance de la prépa-

Keywords: students, pharmacy, hospital, work, professional practice, transition

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ration offerte par l'université. Étant donné qu'une transition réussie est associée à une plus grande satisfaction au travail, il faudrait encourager la mise en place de stratégies en milieu de travail, notamment limiter le nombre de domaines de pratique, établir un programme d'orientation et offrir un soutien continu durant la première année de travail.

Mots clés : étudiants, pharmacie, hôpital, travail, pratique professionnelle, transition

INTRODUCTION

Entry into clinical practice is a transition faced by many health care professionals. Transitions are situations that lead to changes in roles, relationships, and routines.[1,2] As suggested by Boychuk Duchscher,[1] professional transition can be envisioned as a 12-month progression of doing, when foundational skills are learned; being, when knowledge and skills are developed; and, finally, knowing, when the clinician becomes comfortable and confident in practice. Health care professionals have reported various challenges when transitioning from the role of a student to the role of a practitioner, including limited confidence and experience, unanticipated professional demands, challenging interpersonal interactions, lack of familiarity with the work environment, increased accountability and responsibility, inadequate support, gaps in knowledge, and a fear of making mistakes.[3-8]

Within the first year of work, individuals may progress from feelings of fear, anxiety, and excitement to an understanding of what is expected in practice and finally to a stage of adaptation.[3] Thus, transitions may pose challenges and require the use of coping resources and strategies, but they also allow for overall growth.[2] Literature analyzing the transition of hospital pharmacists into practice is limited. Noble and others[9] interviewed 15 hospital and community pharmacy interns regarding role identity and transition. Their findings were comparable to those from research involving other health care professionals, for whom entry into practice was challenged by limited experience, difficult interactions with physicians and patients, and misalignment of reality with school-based role identity.[9] Expectations of pharmacist roles were infrequently met when the interns progressed into the workplace, which suggested a need for undergraduate education to provide more opportunities to practise and observe realistic roles.[9-11] Another aspect of pharmacist transition involves modifications in learning styles. Loewen and others[12] reported that clinicians often shifted in and out of their dominant and/or secondary learning styles in the first year of work. Despite this instability in learning styles, most clinicians continued to be passive learners and assimilators overall. Awareness of learning styles and guidance of new staff toward more active learning techniques may be strategies to help facilitate the student-to-practitioner transition.[12]

Successful transition from student to practitioner affects patient care, staff retention, and role identity. Therefore, gaining insights into the perspectives of current hospital pharmacists is essential. The overall objective of this study was to investigate the transition from student to successful hospital pharmacist, specifically to identify key barriers to the transition process and to outline possible strategies for overcoming these barriers.

METHODS

Approval to conduct this study was obtained from the Fraser Health Research Ethics Board. This study was divided into 2 parts: an electronic survey and follow-up one-on-one interviews (by telephone or in person). A "student" was formally defined as any individual completing a pharmacy education program, such as a Bachelor of Science in Pharmacy (BSc(Pharm)) degree, a hospital pharmacy residency, or a Doctor of Pharmacy (PharmD) degree.

Survey

A literature review focusing on the transition of health care providers into practice was performed to create questions for the online survey. Most survey questions were adapted from a recent study involving new graduate nurses,[13] as well as the Casey–Fink Graduate Nurse Experience Survey,[14] a validated survey used to study the transition of graduate nurses into practice. The following themes were created to organize the questions used for the current survey: demographic characteristics, barriers to transition, strategies to facilitate transition, and role identity (see Appendix 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/190/showToc). The questions were first piloted by pharmacy staff members who did not participate in the study. The pretest assessed length and flow of the survey, ease of response, and acceptability to respondents.

Information about the project and a link to the anonymous survey (created with SurveyMonkey software; https://www.surveymonkey.com/) was sent by e-mail to all Lower Mainland Pharmacy Services (LMPS) pharmacists (about 430 individuals), including pharmacists with a dispensary, advisory, and/or clinically based practice who were providing care for inpatient and/or ambulatory patients. Only individuals who completed the survey were included in the analysis. The survey was distributed on November 21, 2017, and remained open for a total of 3 months (until February 13, 2018); 2 reminders were sent by e-mail during that period. After the survey was closed, data were imported from the survey software for analysis.

The various skills and activities that contribute to a hospital pharmacist's overall performance were used as the basis for assessing transition into practice. To quantify each respondent's transition, an overall "performance score" was calculated using 15 select questions from the online survey (see Appendix 1). These 15 questions were adapted from the Casey–Fink Graduate Nurse Experience Survey[14] and were modified for greater applicability to hospital pharmacists. The topics included confidence in communication and practice, knowledge, experience, preparation, and expectations, as well as task delegation and management. Responses to these questions were scored from 0 to 5 points or from 1 to 5 points (based on a Likert scale with 5 or 6 options), with a higher score indicating a higher level of performance for the particular task or skill set. Each respondent's scores for individual questions were summed; the maximum possible performance score was 75.

The performance score was used to compare the transition experience for respondents of different educational and professional backgrounds. Additionally, relationships between performance score and role satisfaction, as well as years of work, education, and work in a specialty area were analyzed. The survey did not explicitly define the concept of a specialty area; rather, participants indicated whether or not they considered their work to be in a specialty area. Lack of knowledge, opportunities for career advancement, need for support, orientation programs, helpful resources, and role of university programs were also assessed.

For questions that used a Likert scale, the following pairs of similar responses were grouped for question-specific analysis: "strongly agree" and "agree"; "disagree" and "strongly disagree"; "always" and "very often"; "rarely" and "never". Responses for "not applicable" were not combined with any other response.

Descriptive statistics were used for this study. IBM SPSS Statistics 21 (IBM, Armonk, NY) was used to calculate the Pearson correlation coefficient (r). A p value less than 0.05 was deemed to indicate statistical significance.

Follow-Up Interviews

The initial e-mail message about the online survey included an invitation to participate in a one-on-one interview. The invitation was limited to respondents who had started working as a hospital pharmacist within the past 5 years. Pharmacists who volunteered for this part of the study were interviewed once the online survey was closed. Responses to the interview questions were manually transcribed during the interview for analysis of themes, and all data were de-identified during the analysis. The participants were also asked to describe their views of a successful hospital pharmacist.

The interviews included a specific set of open-ended questions and focused on obtaining more details about themes explored in the online survey. Some questions were independently developed, whereas others were adapted from the existing literature[13,15] (see Appendix 2, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/190/showToc).

RESULTS

Survey

A total of 137 hospital pharmacists (about 32% of potential participants) responded to the online survey. Most (67 [48.9%]) of the participants had completed a hospital pharmacy residency as their highest level of pharmacy education (Table 1). Fifty (36.5%) of the respondents had been working for 5 years or less, and 91 (66.4%) reported that they were working in a specialty area.

The performance score was calculated for 113 respondents and ranged from 39 to 72. For the remaining respondents, the

Table 1. Characteristics of Survey Respondents

Characteristic	No. (%) of Respondents (n = 137)
Age (years)	
< 25	9 (6.6)
25–35	72 (52.6)
36–45	31 (22.6)
> 45	25 (18.2)
Highest level of pharmacy education	
BSc(Pharm)	15 (10.9)
Hospital pharmacy residency	67 (48.9)
PharmD	42 (30.7)
Other*	13 (9.5)
Experience as a hospital pharmacist (years)	
< 1	20 (14.6)
1–2	8 (5.8)
3–5	22 (16.1)
6–10	36 (26.3)
10–20	29 (21.2)
> 20	22 (16.1)
Work in a specialty area	
Yes	91 (66.4)
No	46 (33.6)

*These 13 respondents had completed a fellowship (3 [2.2%]), a Master of Pharmacy (2 [1.5%]), a postgraduate diploma in clinical pharmacy (2 [1.5%]) or a community pharmacy residency (1 [0.7%]) or were currently completing a residency or PharmD degree (5 [3.6%]).

performance score was not calculated because of missing data from incomplete surveys (n = 21) or because participants were completing a residency or PharmD at the time of the survey and had not yet worked as a hospital pharmacist (n = 3). There was a correlation between performance score and role satisfaction (r = 0.550, p < 0.001) (Figure 1). Among participants who were satisfied (n = 90) with their role, the average performance score was 70.1 (standard deviation [SD] 5.8), whereas among those who were dissatisfied (n = 6), the average score was 49.7 (SD 8.0). There was also a correlation between the performance score and years working as a hospital pharmacist (r = 0.333, p < 0.001), and between the performance score and highest level of pharmacy education (r = 0.210, p = 0.026) (Figure 2).

For these 113 respondents, the performance score was also analyzed in relation to self-reported type of practice (specialty or nonspecialty). The average score was greater among individuals who reported working in a specialty area than for those who reported working in a nonspecialty area (61.2 [SD 6.0], n = 81

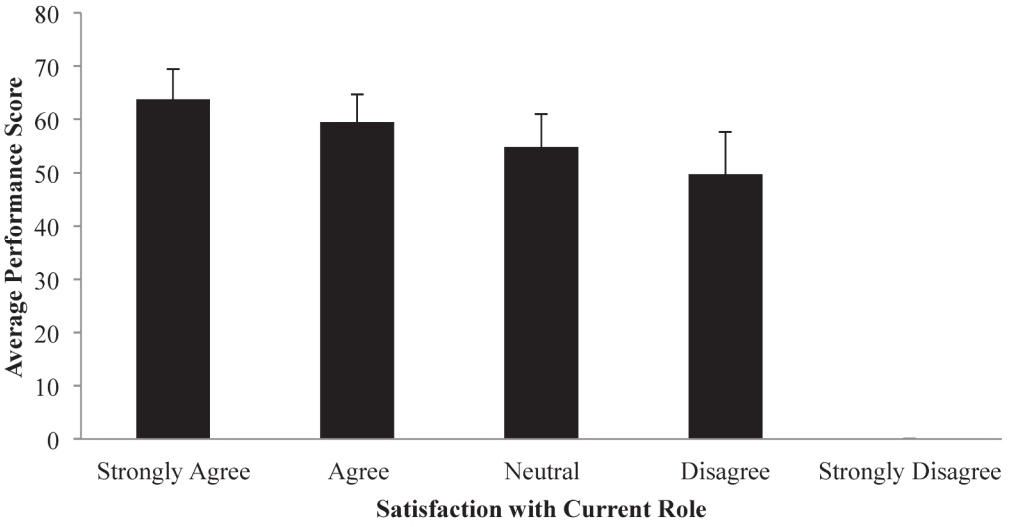

Figure 1. Average performance score in relation to role satisfaction (n = 110 respondents; r = 0.550, p < 0.001). The maximum possible performance score was 75, and the range of performance scores for individual respondents was 39 to 72.

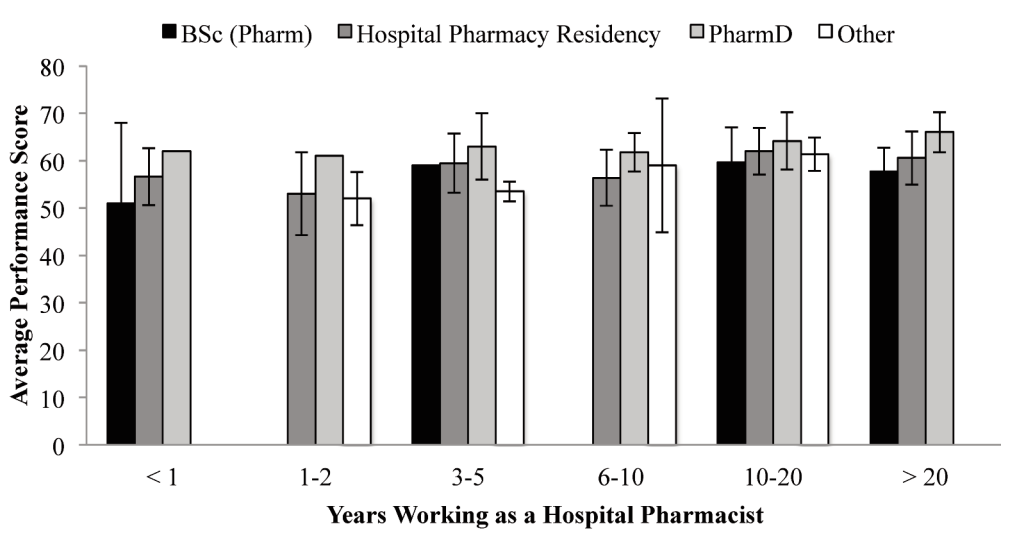

Figure 2. Average performance score in relation to years working as a hospital pharmacist and highest level of pharmacy education (n = 113 respondents). For performance score versus years of work, r = 0.333, p < 0.001; for performance score versus education, r = 0.210, p = 0.026.

versus 55.8 [SD 6.7], *n* = 32). Thirty-five of these 113 respondents had worked for 5 years or less, and for these respondents, the average performance score was also higher among those who reported working in a specialty area (61.0 [SD 4.9], *n* = 21 versus 51.6 [SD 6.4], *n* = 14).

Participants were asked whether they might provide less-than-optimal care to a patient because of their lack of knowledge. The percentage of participants who stated that they rarely or never felt that way increased with number of years working as a hospital pharmacist, from 21.4% (3/14) of those with less than 1 year of work experience to 71.4% (15/21) of those with more than 20 years of work experience. There was also a difference for staff with different educational backgrounds, with 43.3% (26/60) of those in the hospital pharmacy residency group and 72.5% (29/40) of those in the PharmD group reporting that they rarely or never felt that way.

When asked about their satisfaction with opportunities for career advancement, pharmacists who had worked for less than 1 year or for more than 20 years reported the highest level of satisfaction (69.2% [9/13] and 66.7% [14/21], respectively), whereas those who had worked for 1 to 2 years had the lowest level of satisfaction (28.6% [2/7]). When the study population was analyzed according to educational background, the PharmD group reported the highest satisfaction (68.4% [26/38) and the hospital pharmacy residency group reported the lowest satisfaction (45% [27/60]).

Participants from all educational backgrounds required support during their first year of work. In the overall population, the time of greatest need for support was identified as the first 3 months (27.7% [28/101]), the first 6 months (27.7% [28/101]), or the first 12 months (24.8% [25/101]). These results remained consistent when analyzed in relation to highest level of pharmacy education.

Of the 122 participants who answered questions about their orientation program, 90 (73.8%) reported that they had received an orientation specific to their institution's pharmacy as well as its patient care areas, and 87 individuals responded to questions regarding details of the orientation program (Table 2). In the analysis of performance scores in relation to orientation (*n* = 113), the average score was 59.3 (SD 6.7) for participants who had participated in an orientation program, 60.8 (SD 5.5) for those who did not receive orientation, and 60.2 (SD 7.3) for those who could not remember whether they had had any orientation. Among respondents who had been working less than 1 year (*n* = 11), the average performance score was higher for individuals who had participated in an orientation program than for those who did not participate in such a program or could not remember (57.3 [SD 6.0] versus 50.5 [SD 16.3]). Among participants who had worked for 2 years or less (*n* = 16), the duration of orientation did not appear to influence the performance score (Figure 3).

Table 2. Duration and Quality of Orientation Programs

Characteristic	No. (%) of Programs (*n* = 87)
Duration of orientation (weeks)	
< 1	20 (23.0)
1–2	16 (18.4)
2–4*	15 (17.2)
4–6	11 (12.6)
> 6	12 (13.8)
Do not remember	13 (14.9)
Quality of orientation in preparing for role	
Very good	22 (25.3)
Good	27 (31.0)
Acceptable	30 (34.5)
Poor	7 (8.0)
Very poor	1 (1.1)

*This category was presented in the survey as "more than 2 weeks but less than 4 weeks"; as such, the categories did not overlap.

Among the 116 participants who reported on which resources had been very helpful during their transition, 44 (37.9%) selected the trainer pharmacist, 43 (37.1%) selected social supports from other pharmacists, and 38 (32.8%) selected social supports from new graduates and peers (Figure 4).

When asked whether their university degree had prepared them to transition into the role of a hospital pharmacist, 27.8% (10/36) of participants who had completed the PharmD program, 17.9% (10/56) of those who had completed a hospital residency, and 20% (2/10) of those who had completed a BSc(Pharm) degree felt that the program had prepared them well. When asked about specific components of their university education program, 22.8% (26/114) identified practicums and 21.1% (24/114) identified case-based learning courses as being very helpful. In contrast, 28.1% (32/114) of respondents reported that simulation/labs were not very helpful, 26.3% (30/114) found that research activities were unhelpful, and 23.7% (27/114) found classroom/theory learning not very helpful.

Interviews

A total of 3 individuals volunteered to participate in one-on-one interviews (*n* = 1 for telephone interview; *n* = 2 for in-person interviews). Two of these participants had completed a hospital pharmacy residency, and one had completed a BSc(Pharm) degree as the highest level of education. The participants had been working as hospital pharmacists for 3 to 10 months. Two individuals had received a formal orientation program, one lasting 4 weeks and the other lasting 6 to 8 weeks. Overall, the participants had differing perspectives. The main barriers identified during these interviews were lack of knowledge, lack of confidence, and lack of comfort in the new role, in addition to impractical expectations and new responsibilities. Limited availability of hospital pharmacy rotations and inconsistency of role identity during university education were reported as additional barriers.

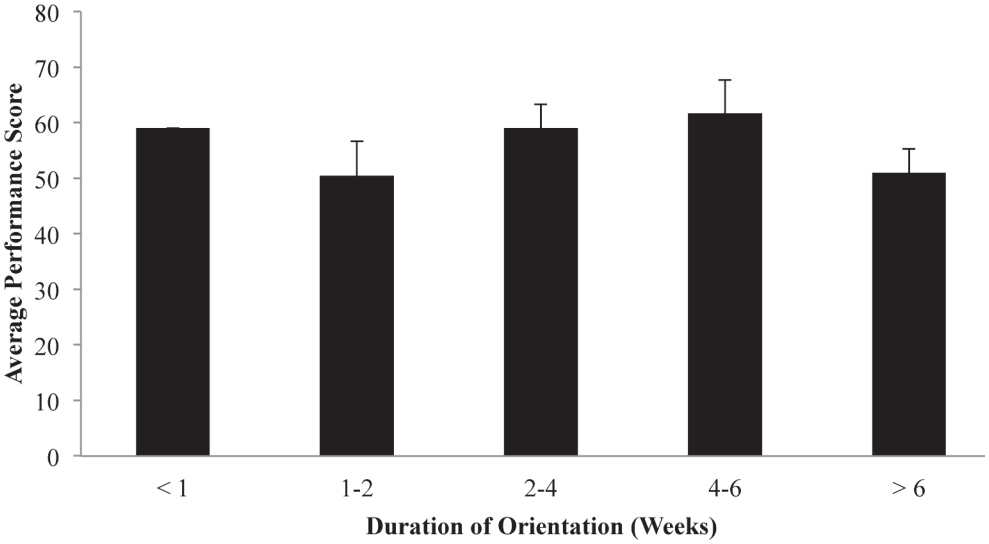

Figure 3. Average performance score in relation to duration of orientation among respondents who had been working for 2 years or less (*n* = 16). Note: The category shown here as "2–4 weeks" was presented in the survey as "more than 2 weeks but less than 4 weeks"; as such, the categories did not overlap.

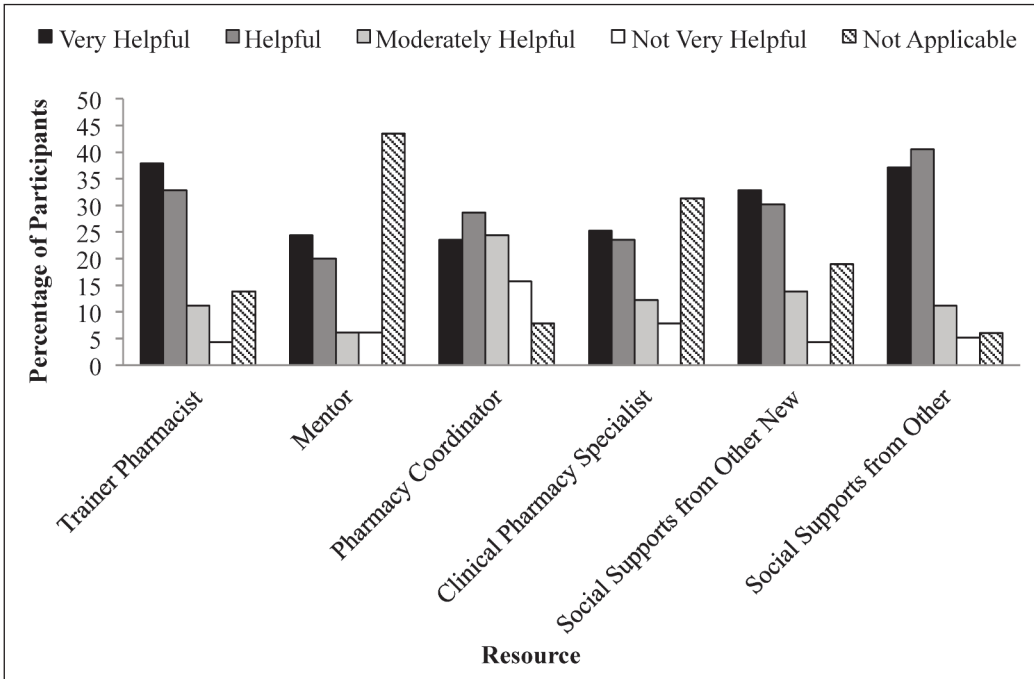

Figure 4. Helpfulness of "people resources" during transition period (*n* = 116 respondents).

Strategies to aid in the transition, either personally experienced or proposed by the participants, included orientation programs with a mentor that incorporated shadowing and independent learning, electronic communication with colleagues, small-group environments with frequent check-ins, and creation of quick reference resources specific to each ward.

Participants described a successful hospital pharmacist as an individual who was confident, willing to accept and overcome

knowledge gaps, willing to conduct research, effective at prioritizing and balancing tasks, and resourceful for the team. Increasing one's duration of work experience in the role of a hospital pharmacist and completing more education were proposed as strategies to facilitate transition into a successful clinician.

DISCUSSION

In this study, an association was found between the performance score and role satisfaction, with higher performance scores being correlated with greater job satisfaction. Given that higher performance scores indicated successful transition, it is important to ensure timely transition to promote pharmacist practice that is satisfying. Leveck and Jones[16] have shown that factors such as job satisfaction influence retention of staff nurses, as well as the quality of care they provide. In the current study, the following factors were incorporated in the performance score calculation, and they are therefore key areas on which to focus in order to maximize role satisfaction: confidence in communication and practice, prioritization of tasks to be performed, seeking of assistance, improvement in knowledge and experience, provision of acceptable preparation and expectations, and delegation of tasks.

Years of experience as a hospital pharmacist and highest level of education were other factors that influenced successful transition in this study. Given that work experience and education are related to knowledge and confidence, placing a greater emphasis on hospital pharmacy practice during university education may help students to develop a clear and realistic role identity and thus hasten their transition.[5,7,10] To help develop students' professional identity, curriculums need to focus on direct observation of role models, increased patient contact and responsibility, experimentation, and evaluation.[6,9-12] In the current study, implementing practicums and case-based learning courses with a particular focus on hospital practice was identified as a method to aid with transition. Encouraging hospital pharmacists to become preceptors would put them at the forefront of creating realistic expectations among students before graduation and would also provide further opportunities for career advancement.[5,7]

In an assessment of graduate nurses in a previous study, stress levels were found to be greatest during the initial 6 months of work, and subsequently decreased from the 9th to the 12th month of practice.[17] In contrast, the current study found that regardless of level of education, hospital pharmacists required support, especially during their first year of practice.

Research involving new nurses, allied health professionals, and physicians has suggested that early support systems are needed to facilitate successful transition.[3,4,7,18-20] Examples of these strategies include clinical supervision, mentorship programs, and team assistance. Similarly, increasing accessibility to peer support and encouragement of peer teaching were suggested in this study as means to enhance transition. Mentorship programs are effective because they allow informal exchange of knowledge and experience between the mentor and mentee.[21] Mentorship benefits everyone involved by encouraging more reflection and greater acquisition of knowledge and skills, as well as job satisfaction.[18,21] Group environments are known to optimize the quality and quantity of learning.[22] Creating small-group learning environments for new graduates and encouraging regular meetings with hospital pharmacists who work in similar areas may aid transition. Team assistance with a small group may be a feasible way to maximize electronic communication between colleagues, and may allow the leader or mentor to facilitate regular check-ins, as well as providing opportunities for leadership development. In this study, it was unclear why most participants responded that the mentor was not applicable as a "people resource" during transition. Because formalized mentor assignment was not standard practice at all sites in LMPS, it is possible that participants did not recognize mentors as an official resource. The presence and quality of mentors and mentorship programs should thus be further explored in future studies.

Orientation programs are additional support systems known to hasten transition, decrease anxiety, and develop realistic expectations and job satisfaction.[23] In this study, there was very little difference between orientation programs less than 1 week in duration and longer programs (up to 6 weeks in duration). The presence of an orientation program was beneficial in terms of average performance score, even though the relationship to duration was inconsistent. Therefore, depending on the individual, site, and area of practice, longer orientation programs may not always be necessary, and it may be reasonable to provide shorter programs. The key is to extend provision of an effective support system well beyond the initial orientation, making such support available for the first 12 months of practice. Interestingly, Casey and others[17] also found that graduate nurses in acute care required support beyond their formal orientation period.

In addition to optimizing training, focus should be placed on limiting the number of practice areas, as the average performance score was higher among individuals working in a specialty area than among those in nonspecialty areas. Limiting the number of practice areas that a new hospital pharmacist is expected to cover would allow them to expand their knowledge and experience within select areas, which would assist with their transition. Fujino and Nojima[24] made a similar recommendation in their study analyzing the effects of ward rotation on clinical nurses. Those authors concluded that rotating among multiple wards increased role stress and emotional distress, and that the rotation experience needs to be optimized for confidence, professional advancement, and personal development.[24]

A limitation of the study presented here was the limited number of participants who were early in their career or had a BSc(Pharm) as their highest level of education. It would have been beneficial to have a larger number of these pharmacists to provide insight into the barriers and strategies they encountered. In

addition, the questions in the survey were not validated for use in a population of hospital pharmacists.

CONCLUSION

This study showed that the key barriers to the transition of students to successful hospital pharmacists were limited time working as a hospital pharmacist, lack of additional pharmacy education, lack of knowledge, rotation among multiple areas, uncertainty about role identity, and limited university preparation. The main strategies identified to assist with transition into the hospital setting were limiting the number of practice areas, developing an orientation program, and providing continued support from trainers and colleagues during the first year of work. Given that job satisfaction is linked to successful transition, it is important to continue studying how to improve the transition of staff into the role of hospital pharmacists. In addition, trialling innovative structures for orientation and mentorship programs would help in outlining key features that need to be optimized for successful transition.

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Efficacy and Safety of Infliximab in Pediatric Crohn Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Crohn disease is an inflammatory bowel disease with intermittent symptoms relating to damage to the gastrointestinal tract. Compared with adult-onset Crohn disease, the childhood-onset form is more likely to be severe. Infliximab has shown efficacy in adult patients.

Objective: To examine the efficacy and safety of infliximab in pediatric Crohn disease, by means of a systematic review.

Data Sources: Three databases (MEDLINE, Embase, and Cochrane Central Register of Controlled Trials) and regulatory documents were searched from inception to December 2017. Clinical trial registries, conference abstracts, and reference lists were searched to March 2018.

Study Selection and Data Extraction: Randomized controlled trials (RCTs) and prospective cohort studies that compared infliximab with active control were included in the analysis. Two reviewers independently performed screening, extracted data, and assessed risk of bias. The primary outcomes were induction and maintenance of endoscopic remission and severe adverse effects.

Data Synthesis: Three eligible RCTs comparing different dose regimens, 16 prospective cohort studies comparing infliximab with other therapies (adalimumab, exclusive enteral nutrition, or standard of care), and 3 prospective cohort studies comparing different infliximab regimens were identified. Meta-analysis of the RCTs showed no significant difference between infliximab every 8 weeks compared with longer intervals for maintenance of clinical remission (risk ratio [RR] 1.76, 95% confidence interval [CI] 0.98–3.19). Meta-analyses of the prospective cohort studies showed no significant differences between infliximab and adalimumab for maintenance of endoscopic remission (RR 1.07, 95% CI 0.60–1.92), between infliximab and exclusive enteral nutrition for induction of clinical remission (RR 1.09, 95% CI 0.82–1.45), or between infliximab and standard of care for maintenance of clinical remission at 6 and 12 months (RR 1.12, 95% CI 0.58–2.17, and RR 1.24, 95% CI 0.84–1.84, respectively).

Conclusions: Current evidence suggested comparable efficacy for infliximab and other therapies; however, the available literature was limited by risk of bias and small sample size. Further prospective studies are needed to confirm the efficacy and safety of this drug in pediatric Crohn disease.

RÉSUMÉ

Contexte : La maladie de Crohn est une maladie inflammatoire de l'intestin, dont les symptômes intermittents sont liés à des lésions du tractus gastro-intestinal. Comparativement à la maladie de Crohn se déclarant à l'âge adulte, celle qui se déclare dans l'enfance risque d'être plus grave. L'infliximab s'est avéré efficace chez l'adulte.

Objectif : Étudier l'efficacité et l'innocuité de l'infliximab chez l'enfant atteint de la maladie de Crohn à l'aide d'une analyse systématique.

Sources des données : Trois bases de données (MEDLINE, Embase, ainsi que le Registre central Cochrane des essais comparatifs) ont été interrogées et des documents réglementaires ont fait l'objet d'une recherche depuis leur création jusqu'en décembre 2017. Une consultation des registres d'essais cliniques, des résumés de conférences et des listes de références a eu lieu jusqu'en mars 2018.

Sélection des études et extraction des données : L'analyse a porté sur des essais cliniques à répartition aléatoire (ECRA) et des études de cohorte prospectives comparant l'infliximab au traitement actif. Deux examinateurs indépendants ont procédé à la sélection et à l'extraction des données ainsi qu'à l'évaluation des risques de biais. L'induction et le maintien d'une rémission endoscopique ainsi que les effets indésirables graves étaient les principaux paramètres d'évaluation.

Synthèse des données : Trois ECRA admissibles comparant différents schémas posologiques, 16 études de cohorte prospectives comparant l'infliximab à d'autres traitements (l'adalimumab, une alimentation exclusivement entérale et les soins d'usage) et trois études de cohorte prospectives comparant différents schémas posologiques d'infliximab ont été sélectionnées. Une méta-analyse des ECRA ne montrait aucune différence significative entre un traitement à l'infliximab toutes les huit semaines comparativement à des intervalles plus longs pour le maintien d'une rémission clinique (risque relatif [RR] de 1,76, intervalle de confiance [IC] à 95 % de 0,98–3,19). Des méta-analyses des études de cohorte prospectives ne montraient aucune différence significative entre l'infliximab et l'adalimumab pour le maintien d'une rémission endoscopique (RR de 1,07, IC à 95 % de 0,60–1,92), aucune différence non plus entre l'infliximab et une alimentation exclusivement entérale pour l'induction d'une rémission clinique (RR de 1,09, IC à 95 % de 0,82–1,45) ni entre

Keywords: inflammatory bowel disease, anti-tumour necrosis factor alpha, infliximab, Crohn disease

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l'infliximab et les soins d'usage pour le maintien d'une rémission clinique à six et douze mois (respectivement : RR de 1,12, IC à 95 % de 0,58–2,17 et RR de 1,24, IC à 95 % de 0,84–1,84).

Conclusions : Les données probantes actuelles laissaient entendre que l'efficacité de l'infliximab était comparable à celle des autres traitements; cependant, les articles disponibles étaient insuffisants en raison du risque de biais et de la faible taille de l'échantillon. De plus amples études prospectives sont nécessaires pour confirmer l'efficacité et l'innocuité de ce médicament chez l'enfant atteint de la maladie de Crohn.

Mots clés : maladies inflammatoires de l'intestin, inhibiteur du facteur de nécrose tumorale-alpha, infliximab, maladie de Crohn

INTRODUCTION

Crohn disease is an immune-mediated condition characterized by inflammation along the entire length of the gastrointestinal tract.[1,2] It is a chronic, progressive condition with a relapsing and remitting course.[3,4] The incidence of Crohn disease is increasing internationally, and it is estimated that 20% to 25% of cases present during childhood.[2,5] Childhood-onset Crohn disease is associated with higher disease activity and a more complicated disease course.[2,6]

The goals of treatment are to relieve symptoms, improve quality of life, and minimize drug-related adverse effects.[7] An additional goal specific to pediatric Crohn disease is to optimize the patient's growth, which may be impaired because of intestinal inflammation and inadequate nutrition.[2,8] Recently, there has been interest in mucosal healing or endoscopic remission as a treatment target.[1,2,4] In adults with inflammatory bowel disease, mucosal healing has been associated with sustained remission, decreased complications, and decreased corticosteroid use, relative to patients without mucosal healing.[4]

Infliximab is a chimeric monoclonal antibody that binds to and interferes with the activity of human tumour necrosis factor alpha (TNF-α). Current guidelines for pediatric Crohn disease, from both the European Crohn's and Colitis Organisation and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, recommend anti-TNF-α as a second-line therapy after failure of standard-of-care therapy, such as exclusive enteral nutrition and corticosteroids for induction of remission and immunomodulators for maintenance of remission.[7] This recommendation is in line with Health Canada's indications for infliximab in the pediatric population.[9] A consensus statement from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition has affirmed that anti-TNF-α agents have demonstrated benefit in induction and maintenance treatment of pediatric Crohn disease.[10]

This systematic review aimed to examine the efficacy and safety of infliximab, compared with conventional therapy, for inducing and maintaining endoscopic remission in pediatric patients with luminal or fistulizing Crohn disease.

METHODS

This systematic review was conducted in accordance with the PRISMA guidelines[11] and the *Cochrane Handbook for Systematic Reviews of Interventions*.[12] A protocol detailing the conduct of this systematic review and meta-analysis was registered a priori with PROSPERO (registration identifier CRD42016037820).

Eligibility Criteria

The initial search strategy was developed to identify randomized controlled trials (RCTs) examining participants less than 18 years of age who had moderate to severe luminal or fistulizing Crohn disease. Studies involving any dose and regimen of infliximab, compared with active controls or standard of care, were eligible. For the purpose of this review, the definitions of active control used by the authors of included studies were accepted. These active controls included but were not limited to corticosteroids, immunomodulators, aminosalicylates, exclusive enteral nutrition, and other biologics. In the event that no RCTs satisfying the eligibility criteria were found, the protocol allowed for inclusion of prospective comparative nonrandomized studies and studies comparing different regimens of infliximab. Language and publication status restrictions were not imposed.

Outcomes

The primary outcomes were induction of endoscopic remission by 14 weeks, maintenance of endoscopic remission at 6 months, and incidence of severe adverse effects. The definitions of endoscopic remission used by the authors of included studies were accepted. The secondary outcomes were induction and maintenance of clinical remission as measured by the Pediatric Crohn Disease Activity Index (PCDAI), maintenance of endoscopic or clinical remission at 1 year, change in PCDAI, change in height, serum infliximab antibodies, serum infliximab levels, corticosteroid use (in prednisone equivalents), corticosteroid-free remission, need for surgery, hospitalization, and

all-cause adverse effects. The incidence of each adverse effect, such as infections, malignancy, and infusion-related reactions, was individually examined.

Search and Study Selection

The search strategies were developed by 3 of the authors (S.L., C.R., and S.S.), with the assistance of a clinical librarian. Three databases (MEDLINE, Embase, and the Cochrane Central Register of Clinical Trials) and relevant regulatory documents were searched from inception to December 2017. Clinical trial registries, conference abstracts, and reference lists of included studies and systematic reviews were searched through to March 2018. The search strategies are provided in Appendix 1 (available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/190/showToc).

Duplicate citations were identified and removed using Mendeley software.[13] Multiple reports based on the same study were identified and linked. A screening tool was developed a priori and pilot-tested.

Data Collection and Risk-of-Bias Assessment

Before extraction of study characteristics and outcome data from eligible studies, an electronic data collection form, based on the Cochrane data extraction and assessment template,[12] was developed. For trials with missing, unclear, or discrepant information, an attempt was made to contact study authors. If clarification was unsuccessful, reviewers used their judgment to determine the trial's eligibility on the basis of available information. For RCTs, the risk of bias was assessed with the Cochrane risk-of-bias tool.[14] For nonrandomized studies, the risk of bias was assessed with the Ottawa–Newcastle scale.[15]

Screening, data collection, and risk-of-bias assessment were performed by the authors, in duplicate, in an independent, unbiased, and standardized manner. Disagreements were resolved by discussion and consensus among 3 authors, if necessary.

Synthesis of Results

A random-effects model (that of DerSimonian and Laird[16]) was used for the meta-analysis, with calculation of χ^2 and I^2 as indicators of heterogeneity. Values of P less than 0.10 and values of I^2 greater than 50% were used as thresholds defining significant heterogeneity.[17] Data from prospective cohort studies were analyzed separately from RCT data. Studies examining different comparators were analyzed separately, with grouping by comparator drug class or infliximab dosing regimen.

RESULTS

Summary of Study Characteristics

A total of 24 unique trials (some reported in multiple articles) were retrieved. Of the 24 trials included, 22 were complete (Figure 1, Table 1)[18-47] and 2 were still in progress at the time of our analysis (Table 2). Three of the studies were RCTs, and the remainder were prospective cohort studies. Most of the studies were conducted in North America,[18-21,44,46] Europe,[22-31,43,45] or both,[32-40] with only 2 studies from Asia.[41,42,47]

In 7 of the 22 completed studies, the mean or median PCDAI was above 30, signifying moderate to severe disease.[18,24,25,35-39,41,43,46] In 4 additional studies, only patients in the infliximab group had moderate to severe disease.[20,21,30,40,44] In 6 studies, the mean or median PCDAI was between 10 and 30, which indicated mild disease on average.[27,29,32-34,42,45,47] Five studies did not report disease severity.[19,22,23,28,31] Eight studies included patients with fistulizing disease,[18,24,26,29,35-39,40,43,45] although only 1 of these studies examined fistulizing disease in a separate analysis.[39]

The 3 RCTs compared different dose regimens of infliximab.[26,35-39] One study examined the efficacy of a single induction dose of 1 mg/kg, 5 mg/kg, or 10 mg/kg,[35-37] whereas the other 2 RCTs compared different maintenance regimens.[26,38,39]

Of the 19 prospective cohort studies, 2 studies compared infliximab with exclusive enteral nutrition,[18,42,47] 4 studies compared infliximab with adalimumab,[22-24,43,45] 3 studies compared different infliximab modalities (biosimilars versus originator,[25] standard versus intensified induction,[19] and early versus escalated therapy[41]), and 10 studies compared infliximab with other standard-of-care regimens.[20,21,27-34,40,44,46] These regimens included other biologics,[32-34] 5-aminosalicylate,[20,21,27,29,32-34] corticosteroids,[27,29,32-34,46] azathioprine,[20,21,27,29,31-34,44,46] 6-mercaptopurine,[20,21,32-34,44,46] methotrexate,[20,21,32-34,46] antibiotics,[32-34] and exclusive enteral nutrition.[20,21,29] Three studies did not define or report standard therapy agents.[28,30,40]

Common outcomes examined were endoscopic remission,[23,24,26,27,31,35,41-43] clinical remission,[18,20-22,24,26,27,35,38-42,44] and clinical response.[18,20,24,26,35,38-40,42] Other reported outcomes included partial endoscopic remission,[21,24] changes in PCDAI[27,45] or the Simple Endoscopic Score for Crohn Disease,[42] height for age,[20,27,44,46] body mass index for age,[20] weight for age,[20] quality of life,[18] malignancy,[32] serious infections,[33] and adverse reactions.[27,42] Studies varied in their outcome definitions (see Appendix 2, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/190/showToc): endoscopic remission or mucosal healing was defined using the Crohn Disease Index of Severity in 2 studies[31,42] and using the Simple Endoscopic Score for Crohn Disease in 2 studies.[24,41] One study used an endoscopic lesion severity score that involved a visual analogue scale,[35] and another defined endoscopic remission as disappearance of ulcerations, multiple erosions, bleeding and friability.[29] Clinical remission was defined as PCDAI ≤ 10 in 8 studies[18,20,21,24,35,40-42] and Physician Global Assessment of inactive disease in 2 studies.[22,40] Studies also varied in their definition of clinical response,[24,28,35,38-40,42] although this was most commonly defined as reduction in PCDAI ≥ 15 or final PCDAI ≤ 10.[18,42]

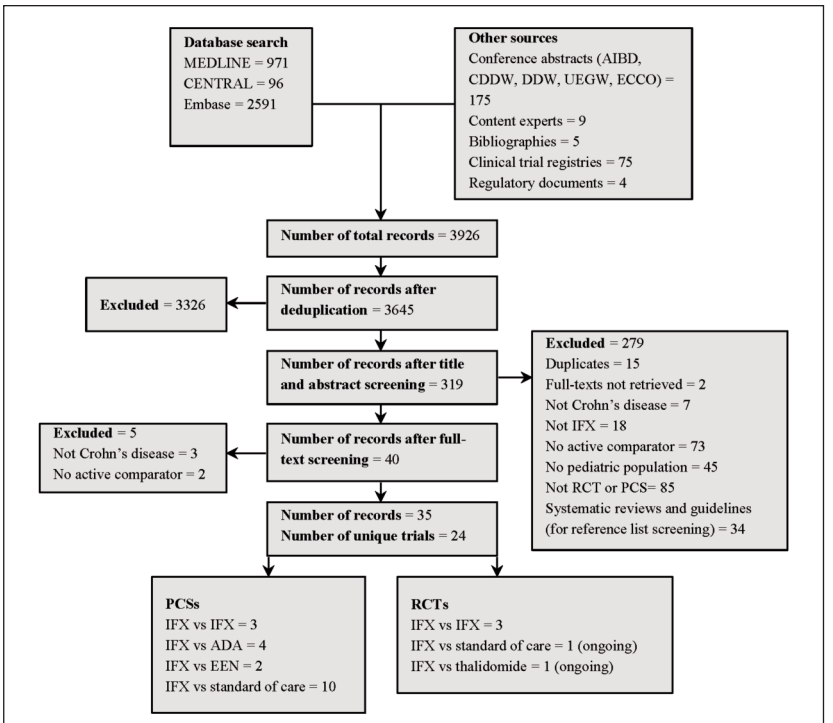

Figure 1. Flow chart of literature selection. ADA = adalimumab, AIBD = Advances in Inflammatory Bowel Disease, CDDW = Canadian Digestive Diseases Week, DDW = Digestive Diseases Week, ECCO = European Crohn's and Colitis Organisation, EEN = exclusive enteral nutrition, IFX = infliximab, PCS = prospective cohort study, RCT = randomized controlled trial, UEGW = United European Gastroenterology Week.

Follow-up time ranged from 8 weeks[18,42,47] to 5 years,[22,23] with the median follow-up time being 54 weeks. For 8 studies, only abstracts were available for data extraction.[19,22,23,25,28,31,44,45]

Risk of Bias

One of the RCTs was rated as having a low risk of bias,[35-37] whereas the other 2 RCTs were considered to have unclear risk of bias[26,38,39] (see Appendix 3, parts A and B; available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/190/showToc).

Of the prospective cohort studies, 5 studies were rated as having a low risk of bias,[20,21,24,32-34,40,41,43] 11 studies as having unclear risk of bias,[18,19,22,23,27,28,31,42,44-47] and 3 studies as having a high risk of bias[25,29,30] (see Appendix 3, parts C and D).

Meta-analyses

Maintenance of clinical remission at 1 year was reported by 2 RCTs.[26,38] There was no significant difference between regimens of infliximab every 8 weeks and infliximab given less frequently (risk ratio [RR] 1.76, 95% confidence interval [CI] 0.98–3.19, I^2 = 62%) (Figure 2).

Maintenance of endoscopic remission at 6 to 12 months was reported by 2 nonrandomized trials.[23,24] There was no significant difference between infliximab and adalimumab (RR 1.07, 95% CI 0.60–1.92, I^2 = 0%) (Figure 3).

Induction of clinical remission at 8 weeks, as measured by PCDAI, was reported by 2 nonrandomized trials.[18,42,47] There was no significant difference between infliximab and exclusive enteral nutrition (RR 1.09, 95% CI 0.82–1.45, I^2 = 0%) (Figure 4).

Clinical response at 8 weeks, as measured by PCDAI, was reported by 2 nonrandomized trials.[18,42,47] There was no significant difference between infliximab and exclusive enteral nutrition (RR 1.05, 95% CI 0.82–1.33, I^2 = 0%) (Figure 5).

Maintenance of remission at 6 months, as measured by PCDAI, was reported by 2 nonrandomized studies.[20,44] No significant difference was found between infliximab and standard of care (RR 1.12, 95% CI 0.58–2.17, I^2 = 95%) (Figure 6).

Maintenance of remission at 1 year, as measured by PCDAI, was reported by 2 nonrandomized studies.[20,29] No significant

Table 1 (Part 1 of 2). Characteristics of Included Trials

Source	Age, Mean* (years)	No. of Patients	Sex (% Male)	PCDAI, Mean*	Included Fistulizing Disease	Allowed Co-interventions	Intervention or Exposure	Comparator	Follow-up
Randomized controlled trials									
Ruemmele et al. (2009)[26]	13.9	31	55	7.6‡‡	Yes	Yes	IFX 5 mg/kg every 8 weeks	IFX 5 mg/kg on demand	60 weeks
Hyams et al. (2007),[38] Crandall et al. (2009)[39]†	13.3	103	58.9	41.2	Yes	Yes	IFX 5 mg/kg every 8 weeks	IFX 5 mg/kg every 12 weeks	54 weeks
Baldassano et al. (2003),[35] Hadigan et al. (1999),[36] Escher et al. (2000)[37]	Median 15	21	71.4	Median 43	Yes	Yes	IFX 1 mg/kg × 1 dose	Comparator 1: IFX 5 mg/kg × 1 dose Comparator 2: 10 mg/kg × 1 dose	20 weeks
Prospective cohort studies: IFX versus standard of care									
Hyams et al. (2017),[32] Escher et al. (2016),[33] Dubinsky et al. (2016),[34]‡§	IFX, 12.6 Biologics, 12.7 Non-biologics, 11.9	5766	IFX, 54.5 Biologics, 54.5 Non-biologics, 56.8	IFX, 11.3 Biologics, 11.4 Non-biologics, 9.8	NR	Yes	IFX	Comparator 1: biologics Comparator 2: non-biologics	Median 4.7 years
Muhammed et al. (2014)[31]	NR	57	NR	NR	NR	NR	IFX	AZA	NR
Olbjørn et al. (2014)[29]	Median 13	36	IFX, 55.6 Non-IFX, 55.6	Medians: IFX, 25 Non-IFX, 23	Yes	Yes	IFX§§	Non-IFX (CS, AZA, EEN, and/or 5-ASA)	2 years
Walters et al. (2014),[20] Hyams et al. (2013)[21]**††	Median age: Early anti-TNF, 13.8 Early IM, 12.6 No early IT, 12.1	552	Early anti-TNF, 68 Early IM, 62 No early IT, 61	PCDAI > 30 Early anti-TNF, 62% Early IM, 45% No early IT, 39%	No	Yes	Early anti-TNF	Comparator 1: Early IM Comparator 2: No early IT	1 year
Mangiantini et al. (2013)[28]‡	Median 14.1	33	NR	NR	NR	NR	NR	NR	NR
Bellizzi et al. (2011)[30]	IFX, 15 Standard therapy, 14	43	56	IFX, > 30 Standard therapy, 10–30	NR	NR	IFX 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks	Standard therapy (agents not specified)	1 year
Pfefferkorn et al. (2009)[46]	10.1	176	65	PCDAI > 30 in 57%	NR	Yes	IFX for ≥ 1 year§§	Comparator 1: IFX for < 1 year§§ Comparator 2: CS, MTX and/or 6MP or AZA	2 years
Keljo et al. (2009)[44]	NR	92	60	Moderate/severe IFX, 56% 6MP/AZA, 7.5%	NR	Yes	IFX	6MP/AZA	> 6 months
Hyams et al. (2009)[40]	IFX, 11.7 Non-IFX, 11.9	729	IFX, 63 Non-IFX,57	IFX, 35 Non-IFX, 29	Yes	Yes	IFX	Non-IFX (agents not specified)	≤ 3 years

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Table 1 (Part 2 of 2). Characteristics of Included Trials

Source	Age, Mean* (years)	No. of Patients	Sex (% Male)	PCDAI, Mean*	Included Fistulizing Disease	Allowed Co-interventions	Intervention or Exposure	Comparator	Follow-up
Paganelli et al. (2007)[27]	13.5	35	62.9	22.2	NR	Yes	IFX 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks§§	CS, AZA, and/or 5-ASA	> 6 months
Prospective cohort studies: IFX versus ADA									
Zárubová et al. (2017)[23]	14.8	14	57	NR	NR	NR	IFX	ADA	5 years
Wauters et al. (2016)[22]	Median 13.1	66	50	NR	NR	NR	IFX	ADA	5 years
Nuti et al. (2015),[43] Nuti et al. (2016)[24]	IFX, 13.4 ADA, 12.6	37	IFX, 72 ADA, 41.6	IFX, 31 ADA, 31.8	Yes	Yes	IFX	ADA	2 years
Nuti et al. (2011)[45]	IFX, 14.5 ADA, 16.4	69	NR	IFX, 22.7 ADA, 28.6	Yes	Yes	IFX	ADA	≤ 3 years
Prospective cohort studies: IFX versus EEN									
Luo et al. (2017),[42] Chen et al. (2016)[47]	IFX, 11.7 EEN, 11.9	26	IFX, 46.2 EEN, 69.2	IFX, 29.5 EEN, 26.0	No	NR	IFX	EEN	8 weeks
Lee et al. (2015)[18]††	anti-TNF, 13.9 EEN, 12.5 PEN, 12.0	90	anti-TNF, 46 EEN, 73 PEN, 88	anti-TNF, 30.2 EEN, 38.8 PEN, 37.6	Yes	Yes	anti-TNF	Comparator 1: EEN Comparator 2: PEN + ad lib diet	8 weeks
Prospective cohort studies: IFX versus other IFX modalities									
Chanchlani et al. (2017)[25]‡	14	278	IFX-B, 60 IFX-O, 61	Medians: IFX-B, 28 IFX-O, 36	NR	Yes	IFX-B	IFX-O	3 months
Crowley et al. (2017)[19]‡	Medians: Standard, 12.0 Intensified, 9.4	66	53	NR	NR	NR	Standard IFX induction	Intensified IFX induction	14 weeks
Kang et al. (2016)[41]	Early, 15.0 Escalated, 15.5	78	Early, 63 Escalated, 67	Median 35	No	Yes	Early IFX	Escalated IFX	54 weeks

5-ASA = 5-aminosalicylate, 6MP = 6-mercaptopurine, ADA = adalimumab, anti-TNF = anti–tumour necrosis factor, AZA = azathioprine, CS = corticosteroids, EEN = exclusive enteral nutrition, EN = enteral nutrition, IBD-U = unclassified inflammatory bowel disease, IFX = infliximab, IFX-B = infliximab biosimilar, IFX-O = infliximab originator, IM = immunomodulator, IT = immunotherapy, MTX = methotrexate, NR = not reported, PCDAI = Pediatric Crohn's Disease Activity Index, PEN = partial enteral nutrition.
*Unless otherwise specified.
†Data reported for total participant population, including patients with and without randomization.
‡Includes patients with ulcerative colitis and/or IBD-U.
§Data reported here were obtained from the study by Hyams and others[32]; the comparator groups were not mutually exclusive.
**Data from overall patient population (not a propensity score–matched cohort).
††Patients in the anti-TNF group received IFX, except for 1 patient who received ADA.
‡‡Harvey-Bradshaw Index.
§§Did not exclude the presence of standard-of-care agents.

Table 2. Characteristics of Trials That Were in Progress at the Time of Analysis

Study Name and Registry Identifier*	Study Design	Population	Intervention	Comparison	Primary Outcome
Top-down Infliximab Study in Kids with Crohn's Disease (TISKids) (NCT02517684)	Open-label RCT, estimated *n* = 100	Children with untreated moderate to severe CD (PCDAI > 40)	IInfliximab 5 mg/kg at weeks 0, 2, and 6, followed by 2 maintenance infusions every 8 weeks *AND* azathioprine 2–3 mg/kg once daily	Prednisolone 1 mg/kg oral (maximum 40 mg) once daily for 4 weeks followed by taper *OR* EEN with polymeric feeding for 6–8 weeks *AND* azathioprine 2–3 mg/kg once daily	Clinical remission at 52 weeks
Thalidomide versus Infliximab in New Onset Crohn Disease with Poor Prognostic Factors (NCT03221166)	Open-label RCT, estimated *n* = 124	Children with new diagnosis of CD and risk factors for poor prognosis	Thalidomide	IInfliximab	Endoscopic remission at 52 weeks

EEN = exclusive enteral nutrition, CD = Crohn disease, PCDAI = Pediatric Crohn Disease Activity Index, RCT = randomized controlled trial.
*ClinicalTrials.gov registry (https://clinicaltrials.gov/ct2/home).

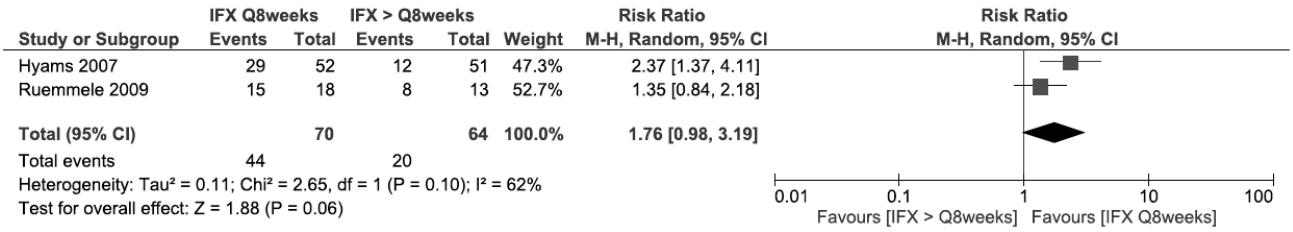

Figure 2. Forest plot examining maintenance of clinical remission in randomized controlled trials, as defined by Pediatric Crohn Disease Activity Index, at 1 year with infliximab (IFX) administered every 8 weeks compared with IFX administered less frequently.[26,38] CI = confidence interval, M-H = Mantel-Haenszel analysis.

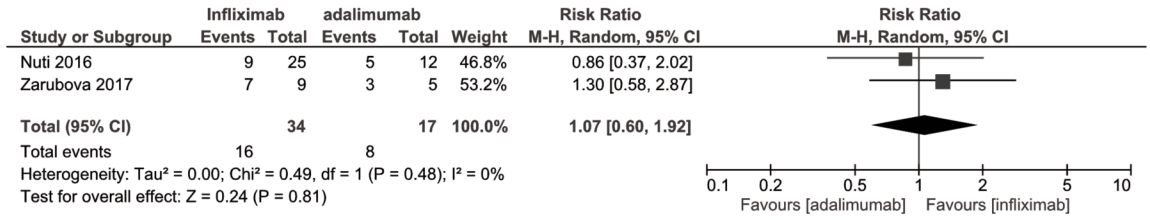

Figure 3. Forest plot of prospective cohort studies examining maintenance of endoscopic remission at 6 to 12 months with infliximab compared with adalimumab.[23,24] CI = confidence interval, M-H = Mantel-Haenszel analysis.

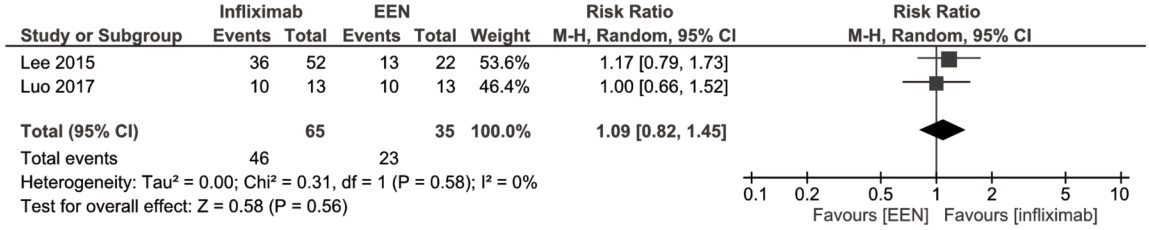

Figure 4. Forest plot of prospective cohort studies examining induction of clinical remission at 8 weeks with infliximab compared with exclusive enteral nutrition (EEN).[18,42,47] CI = confidence interval, M-H = Mantel-Haenszel analysis.

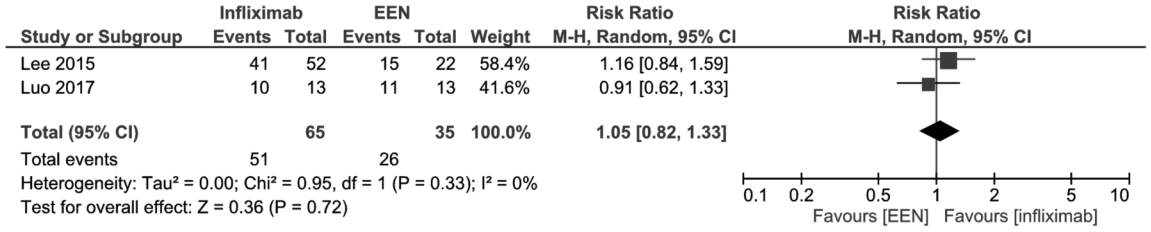

Figure 5. Forest plot of prospective cohort studies examining clinical response at 8 weeks with infliximab compared with exclusive enteral nutrition (EEN).[18,42,47] CI = confidence interval, M-H = Mantel-Haenszel analysis.

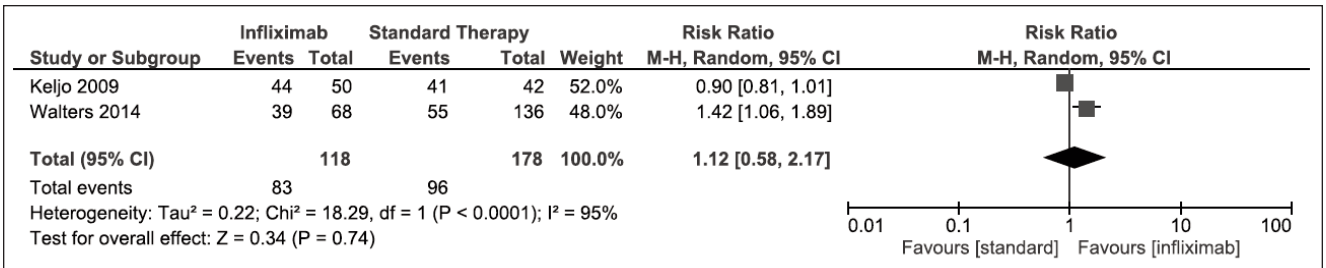

Figure 6. Forest plot of prospective cohort studies examining maintenance of clinical remission, as defined by Pediatric Crohn Disease Activity Index, at 6 months with infliximab compared with standard of care.[20,44]
CI = confidence interval, M-H = Mantel-Haenszel analysis.

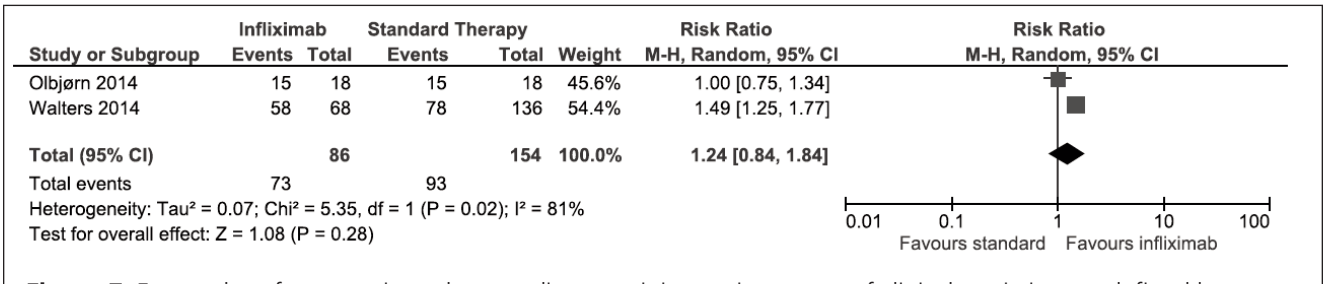

Figure 7. Forest plot of prospective cohort studies examining maintenance of clinical remission, as defined by Pediatric Crohn Disease Activity Index, at 1 year with infliximab compared with standard of care.[20,29]
CI = confidence interval, M-H = Mantel-Haenszel analysis.

difference was found between infliximab and standard of care (RR 1.24, 95% CI 0.84–1.84, I^2 = 81%) (Figure 7).

Notable Studies Not Included in Meta-analysis

One RCT randomly assigned 21 pediatric patients with moderate to severe luminal or fistulizing Crohn disease to receive 1 dose of infliximab 1 mg/kg, 5 mg/kg, or 10 mg/kg.[35-37] At week 4, the median decrease in endoscopic severity scores was 6.6%, 69.4%, and 52.2% in the 1 mg/kg, 5 mg/kg, and 10 mg/kg groups, respectively.[35] Sixty-one percent of all patients had a clinical response, and 16.7% of all patients were in clinical remission by week 12.[35] The study authors observed that the 5 and 10 mg/kg doses of infliximab were more effective than 1 mg/kg in achieving clinical remission.[35]

One nonrandomized study enrolled 78 pediatric patients with moderate to severe luminal Crohn disease of nonpenetrating, nonstricturing behaviour.[41] Patients received either escalated combined immunosuppression, in which corticosteroid induction and azathioprine were trialled before escalation to infliximab, or early combined immunosuppression, in which infliximab and azathioprine were initiated within 1 month after diagnosis without corticosteroid induction.[41] At week 14 from the first dose of infliximab, mucosal healing rates were higher in the early combined immunosuppression group, although no significant difference was observed between groups (32% versus 51%, p = 0.121).[41] At week 54, mucosal healing rates were significantly higher in the early combined immunosuppression group (42% versus 74%, p = 0.007), although rates of clinical remission and laboratory remission did not differ significantly between groups.[41] Z-scores for weight for age, height for age, and body mass index for age at weeks 15 and 54 did not significantly differ between groups.[41] No significant difference in adverse effects was observed between the 2 groups (p = 0.804).[41]

A multicentre cohort study enrolled 5766 pediatric patients with inflammatory bowel disease, including 4047 with Crohn disease.[32] When stratified by exposure to thiopurine agents, the infliximab cohort did not have an increased incidence (expressed in terms of events/100 patient-years) of malignancy compared with patients who received nonbiologic agents with thiopurines (0.53 [95% CI 0.14–1.35] versus 0.69 [95% CI 0.19–1.76]) and without thiopurines (0.31 [95% CI 0.01–1.75] versus 0.32 [95% CI 0.01–1.79]).[32] There were 5 cases of hemophagocytic lymphohistiocytosis, all of which occurred during active thiopurine therapy; none involved exposure to infliximab, adalimumab, or methotrexate.[32]

A second report from the same cohort study included a subset of 5402 pediatric patients with inflammatory bowel disease.[33] A greater cumulative incidence of serious infections (expressed in terms of events/100 patient-years) was reported in the infliximab cohort than the nonbiologics cohort (4.06 [95% CI 3.65–4.49] versus 2.25 [95% CI 1.92–2.61]), although the incidence of serious opportunistic infections was similar (0.35 [95% CI 0.24–0.5] versus 0.2 [95% CI 0.11–0.32]).[33] In patients with Crohn disease, monotherapy with infliximab or

corticosteroid and combination therapy including infliximab, immunomodulators, or corticosteroid were associated with increased risk of first serious infection.[33]

DISCUSSION

In the current analysis, the combined rates of clinical remission at 1 year were not significantly different between infliximab given every 8 weeks and infliximab given less frequently. This finding was interesting, given that the results of the individual trials were reported as statistically significant,[26,38] and could be due to the difference in statistical methods between the current review and the study by Ruemmele and others.[26] The heterogeneity in this outcome could be attributed to the different comparator regimens: whereas one study compared the standard regimen (5 mg/kg per dose every 8 weeks) to administration every 12 weeks,[38] the other used infliximab on demand as the comparator.[26]

There were no significant differences in maintenance of clinical remission at 6 months and 1 year when infliximab was compared with standard of care. Of note, the 3 studies that were combined in this meta-analysis varied in their definitions of the comparator regimen: in one study, standard therapy consisted of immunomodulators,[44] and in another, standard therapy was defined as corticosteroids, immunomodulators, aminosalicylates, and/or exclusive enteral nutrition.[29] In the third study, "early anti-TNF-α therapy" (defined as initiation of anti-TNF-α within 3 months of diagnosis) was compared with "early immunomodulators" and "no early immunotherapy groups".[20] The differences in comparator group definitions likely contributed to the high heterogeneity for this outcome. In 2 of the 3 studies, patients exposed to infliximab had features of higher disease severity than patients exposed to standard therapy.[29,44] In both studies, no adjustments were made to control for these differences in disease severity, which might have led to an outcome favouring the standard therapy group.[29,44] In 1 of the 3 studies included in this meta-analysis, propensity score analysis was used to control for differences in disease severity.[20] In this study, a significantly greater proportion of patients receiving early anti-TNF-α achieved clinical remission at 6 months and 1 year relative to patients receiving early immunotherapy or no early immunotherapy ($p = 0.0003$ and $p = 0.036$, respectively).[20]

The combined results of 2 prospective cohort studies demonstrated that infliximab was not significantly more effective than exclusive enteral nutrition in inducing clinical response or clinical remission at 8 weeks. This result was consistent with findings from the individual studies.[18,42,47] Of note, the 2 studies were conducted in 2 different geographic locations (China and North America), and the patient population in the study by Luo and others[42,47] had lower clinical disease severity than that of Lee and others.[18]

The combined results of 2 prospective cohort studies showed that infliximab was not significantly more effective than adalimumab in maintaining remission over a period of 6 to 12 months. This result was consistent with findings from the individual studies.[23,24,43] Of note, Zárubová and others[23] enrolled children with Crohn disease who had residual disease after ileocecal resection, whereas Nuti and others[24,43] excluded patients who needed immediate surgery.

An older published systematic review of nonrandomized trials, including retrospective and noncomparative studies, summarized the risks of serious infection or lymphoma with anti-TNF-α agents in pediatric inflammatory bowel disease.[48] The authors concluded that the rate of serious infections among pediatric patients treated with anti-TNF-α agents was similar to that of pediatric patients who received immunomodulator monotherapy, but lower than the expected rate for pediatric patients treated with corticosteroids.[48] In contrast to these findings, the current systematic review found a recent prospective cohort study examining the risk of serious infections and malignancies in pediatric patients receiving infliximab over a median follow-up time of 4.7 years.[32-34] This study concluded that there was an increased risk of serious infections in pediatric patients receiving infliximab relative to those receiving nonbiologic agents, although there was no increase in the risk of serious opportunistic infection.[33]

Dulai and others[48] also found that the incidence of lymphoma was similar for pediatric patients receiving anti-TNF-α agents and the general pediatric population, but lower than for pediatric patients receiving thiopurine monotherapy. Hyams and others[32,34] confirmed that there was no increase in the incidence of malignancy among pediatric patients receiving infliximab, relative to those receiving nonbiologic regimens, with stratification by thiopurine exposure.

The question of whether the more aggressive "top–down" approach should be favoured in certain patient populations is a current topic of debate in the field of pediatric Crohn disease.[2,3] The top–down approach involves treatment with infliximab with or without concurrent immunomodulators early in the disease course, with the goal of attaining mucosal healing.[3] The current review retrieved 2 prospective studies that compared the top–down approach with the conventional "step-up" approach: Walters and others[20] demonstrated that in children newly diagnosed with severe Crohn disease, early monotherapy with anti-TNF-α agents (mainly infliximab) produced better clinical and growth outcomes at 1 year than early immunomodulators or no immunotherapy. Kang and others[41] demonstrated that in children with moderate to severe luminal Crohn disease of nonpenetrating, nonstricturing behaviour, initiation of infliximab within 1 month after diagnosis yielded improved mucosal healing at 1 year compared with initiation of infliximab after failure of conventional therapy with corticosteroids. An ongoing RCT will compare the efficacy of top–down and step-up therapy in children with newly diagnosed moderate to severe Crohn disease.[49]

The current guidelines of the European Crohn's and Colitis Organisation and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition recommend infliximab for induction and maintenance of remission in children with chronically active luminal Crohn disease despite prior optimized immunomodulator therapy, for induction of remission in children with steroid-refractory disease, or for primary induction and maintenance therapy for children with active perianal fistulizing disease.[7] The current systematic review found no significant differences in efficacy between infliximab and standard of care regimens, exclusive enteral nutrition, or adalimumab in pediatric patients with luminal Crohn disease. However, the risk of bias in the existing literature, the small sample size, and the low number of studies available limited strong conclusions about this association. Our review has confirmed the current role of infliximab as second-line therapy in pediatric patients with luminal Crohn disease for whom conventional treatment has failed, until further evidence from RCTs and prospective cohort studies becomes available.

Future research should examine the comparative efficacy of infliximab (including biosimilars) using prospective study designs. Given the challenges of conducting RCTs in children,[50] prospective comparative studies using registry data can be well designed to compare efficacy and safety between matched cohorts.[51] Although mucosal healing is the gold standard for evaluation of disease remission, the invasiveness of endoscopic assessment limits its feasibility.[8] The pediatric European Crohn's and Colitis Organisation committee accepts clinical remission as a primary outcome for induction and maintenance of remission for drugs with demonstrated efficacy in mucosal healing in adult trials, as for infliximab.[8] Primary outcomes should include induction and maintenance of endoscopic remission and corticosteroid-free clinical remission, and secondary outcomes should include growth, quality of life, and adverse effects over long-term follow-up.[8]

Limitations

Differences in study design and variability in definitions of standard therapy may have contributed to heterogeneity in some of the meta-analysis outcomes.

Unreported or incompletely reported outcomes and variability in outcome definitions limited the data available for meta-analysis. Although some trials reported endoscopic remission,[23,24,41,42] variability in comparator groups meant that only 2 trials could be combined to examine this outcome.[23,24]

The RCT is considered the most scientifically rigorous study design for evaluating effectiveness of interventions.[52] However, there was a lack of completed RCTs comparing infliximab with an active comparator for inclusion in this review. This could be explained by hesitancy to enroll pediatric patients in such trials, given their higher disease severity and ethical issues regarding consent.[50] Several organizations—the European Crohn's and Colitis Organisation; the European Society for Paediatric Gastroenterology, Hepatology and Nutrition; the Pediatric IBD Network for Research and Improvement; and the Canadian Children Inflammatory Bowel Disease Network—agree that placebo-controlled RCTs should not be conducted for a drug that has demonstrated superiority in adult studies.[50] Prospective trial designs in which the comparator would be an active arm of established standard treatment should be considered.[50]

Most of the prospective comparative cohort studies included in this systematic review were deemed to have unclear or high risk of bias: 10 of the 19 studies did not adjust for confounding variables between study groups,[19,23,25,29,30,31,40,42,44,45] which resulted in lack of comparability of cohorts at the start of the trial. Because 8 of the 19 studies were available only in abstract format,[19,22,23,25,28,31,44,45] outcome extraction and risk-of-bias assessment were limited. For many trials, length and adequacy of follow-up were unclear or were of concern.[18,19,22,23,25,27,30-32,40,42,44-46] The majority of the included studies were limited by small sample size: of the 9 studies included in the quantitative analysis, only 2 examined more than 100 patients.[20,38]

Combination therapy with immunomodulators was not addressed by this systematic review and meta-analysis. There were limited comparative data available to consider the efficacy of biosimilar products and the role of infliximab levels in pediatric Crohn disease.

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Advanced Strategies in Pharmacy Experiential Education

Michael Legal

INTRODUCTION

Pharmacy practice and pharmacy education in Canada continue to evolve.[1] In 2010, the Association of Faculties of Pharmacy of Canada and the Association of Deans of Pharmacy of Canada issued a position statement and joint resolution that, by 2020, the Doctor of Pharmacy degree would become the first professional pharmacy degree at all Canadian universities.[2] A major implication of this change is that, in contrast to Bachelor of Pharmacy degree programs, which include a minimum of 16 weeks of experiential education, entry-to-practice PharmD (EPPD) programs must include 40 weeks or more of experiential education.[3] At the same time, a traditional pathway for Canadian pharmacists to develop advanced practice expertise, the post-baccalaureate Doctor of Pharmacy degree, has been eliminated. Alternative pathways, such as advanced (year 2) pharmacy residencies, fellowship programs, and advanced practice or professional master's degrees, are in various stages of development and implementation.

Experiential education is the central component of all these programs. The increased emphasis on experiential education relative to the bachelor degree programs is a positive development that has the potential to strengthen the practice skills of future pharmacists. Indeed, a major rationale for the adoption of EPPD programs is to ensure that graduates are capable of fulfilling increasingly advanced pharmacy practice roles.[2] However, it is critical that the traditional approach to experiential education also evolve, to ensure that learners derive maximum benefit. In addition, solutions are needed to address the capacity challenges created by the rapid expansion in the number and duration of experiential rotations.

This article highlights innovative models and novel approaches to pharmacy experiential education that can help in addressing these challenges and better prepare pharmacy learners to be the advanced practitioners of the future.

BACKGROUND

Experiential education has been a part of pharmacy training since the early days of the profession, when the 1:1 apprentice–master model was the norm. As the profession advanced, formal experiential education was incorporated into university-level pharmacy curricula. In these programs, learners received relatively limited exposure to practice, and it was expected that they would further refine their learning on the job after graduation. This expectation was one of the major reasons that residency programs began to flourish in the 1980s. These residency programs provided the extra training needed to practise in the hospital setting and remained the dominant approach until the 1990s in the United States and until the late 2000s in Canada. Throughout this time, the 1:1 learner–preceptor model remained the primary configuration for pharmacy experiential education.

In 2012, Hall and colleagues[4] highlighted the need for pharmacy programs to produce "confident graduates who are able and willing to assume responsibility and accountability for drug therapy management." They identified a number of key barriers to achieving this goal, including rotations of limited duration; rotations at multiple sites, necessitating repeated orientation; and limited opportunities for independent practice. The result, according to these authors, was pharmacy rotations that amounted to "observerships" rather than patient care experiences.[4] They proposed a variety of potential solutions, including initiating experiential education early in the pharmacy program, instituting extended rotations at a limited number of sites, providing opportunities for students to assume increasing responsibility for patient care, incorporating peer or near-peer learning methods, expanding interprofessional learning opportunities, and establishing a set of patient care activities that students could assume at different levels of training.[4]

The implementation of EPPD programs has addressed some of these concerns. In the EPPD programs, students are required

to complete experiential rotations (including hospital rotations) at an early stage. Advanced Pharmacy Practice Experience (APPE) rotations are typically longer in duration (5–8 weeks) than those in bachelor degree programs (4 weeks), and interprofessional education is embedded in the curriculum. Finally, it is expected that the substantial increase in the total amount of experiential education in EPPD programs will increase PharmD graduates' level of competence, relative to that of bachelor degree graduates.

Despite these positive developments, challenges remain. Pharmacy preceptors, leaders, and educators have been slow to change their approach to experiential education. The most common learner–preceptor model remains the 1:1 model.[5] Rotation capacity continues to be a concern for many practice sites, a challenge that has intensified as more EPPD programs have been implemented. Finally, it is not certain that the switch to EPPD programs alone will result in graduates who are confident and ready for future practice. The US experience supports these concerns. Despite the implementation of EPPD programs in the United States in the late 1990s, it has been suggested that pharmacy students remain inadequately engaged in impactful direct patient care.[6,7] Rotation capacity in the United States is also major issue.[8,9] Thus, in both Canada and the United States, there is a need to consider new approaches to pharmacy experiential education.

INNOVATIVE APPROACHES TO EXPERIENTIAL EDUCATION

Nontraditional Learner–Preceptor Models

It has been suggested that pharmacy adopt nontraditional learner–preceptor models, such as the "medical model", as a strategy to address rotation capacity issues and to enhance the learning experience.[8-10] Although the traditional (1:1) learner–preceptor model affords ample interactions between preceptors and learners and support of learners, it does have drawbacks. From a capacity perspective, it is inefficient and inflexible, because it permits only as many learners on site as there are preceptors. It also requires significant preceptor time, may inhibit independent practice, and does not allow peer-assisted learning.[11]

Nontraditional learner–preceptor models may offer advantages. Assigning multiple learners to a single preceptor allows sites to host greater numbers of learners, alleviating capacity issues. Also, these models leverage the concept of peer-assisted learning,[11] a system that involves "people from similar social groupings who are not professional teachers helping each other to learn and learning themselves by teaching".[12] Peers or near-peers have cognitive congruence with each other, meaning that they share a similar knowledge base and can more easily teach each other new concepts in ways that will be readily understood.[13] The influence of peers or near-peers seems to have an important and positive effect on how these models are perceived by learners.

Several accounts of peer-assisted learning and near-peer models in pharmacy experiential education have been published.[14-17] Lindblad and others[14] implemented peer-assisted learning in the form of a pilot clinical teaching unit for student pharmacists on a 36-bed stroke and medicine unit in Red Deer, Alberta. Five fourth-year pharmacy students participated in 9-week rotations, which had staggered starts. At any give time, between 2 and 5 students were working on the unit, with a single attending pharmacist. The students took patient histories, developed care plans, and made recommendations in collaboration with the preceptor and the multidisciplinary team. At the end of the rotation, the students reported being satisfied with the experience and felt that it contributed to their learning. Preceptors also reported being satisfied or very satisfied with the experience. The presence of students on the unit resulted in a 5-fold increase in pharmacy interventions relative to baseline.[14]

Kan and others[15] described another variant on the peer-assisted learning model, which was implemented on a general medicine unit at Toronto Western Hospital in Toronto, Ontario. Over a 2-year period, 10 fourth-year EPPD students were scheduled into 2 sequential 5-week blocks each, with 2 students overlapping each month in a staggered fashion. Each pair of students was supervised by a single preceptor, who assigned patients from his or her medical team to the students. Patient case discussions and therapeutic topic discussions were conducted jointly. After each rotation, the preceptors and the learners provided feedback via electronic survey. Overall, the students reported a positive experience, focusing especially on the value of interacting and learning from peers. They also appreciated being exposed to a greater variety of cases during shared patient case discussions. Although a few students felt that the preceptor's time and attention were split between learners, 83% agreed that they would participate in the model again, given the opportunity.[15]

Leong and others[16] employed a near-peer "hierarchical model" that involved learners at different levels of training working with an attending pharmacist on a hemodialysis unit. The main objective was to document and qualitatively evaluate the interactions between participants over the month-long rotation. The learners included a postbaccalaureate PharmD student and a pharmacy resident, who acted as senior learners, as well as 2 pharmacy students, the junior learners. All of the students participated in patient care activities, rounds, and didactic discussions. Two major themes that emerged from observation and analyses were the concepts of cognitive congruence and legitimate peripheral participation.[16] The junior learners appreciated having frequent opportunities to seek advice from the senior learners and ask them questions. The junior learners were initially noted to participate less but became more engaged as they gained comfort in their surroundings. The authors concluded that a hierarchical model was viable even in a specialty area such as hemodialysis.[16]

Another near-peer model, described by Tsang and others,[17] explored the perceptions of 15 second-year pharmacy students completing brief early hospital experiences at Sunnybrook Health Sciences Centre in Toronto (12 h total, split over 2 or more

visits).[17] Four students had a staff pharmacist alone as their preceptor, 9 students were directly mentored by fourth-year pharmacy students currently on rotation at the site, with a pharmacist as backup, and 2 students had a pharmacy resident as their preceptor. After the experience, the participants provided feedback via an electronic survey. The model was well received by all participants, who also felt that all of the learning objectives of the rotation had been met. The second-year students preferred having fourth-year pharmacy students or the pharmacy resident as mentors. These senior learners were felt to be more accessible to the learners and more familiar with the curriculum and career options than pharmacist preceptors.[17]

A recent systematic review of different learner–preceptor models employed in nursing, medicine, and allied health (including pharmacy) corroborated many of findings described above.[18] Models that employed various forms of peer-assisted learning (e.g., 2:1 or 3:1 models, with 2 or 3 learners, respectively, at the same level of training being assigned to a single preceptor) yielded a number of perceived benefits. Learners reported a sense of increased social support and decreased anxiety, shared knowledge and teamwork, and greater independence. Preceptors reported opportunities for richer discussion and greater efficiency relative to the 1:1 model.[18]

Near-peer models are sometimes referred to as tiered learning, hierarchical models, or the medical model. In these models, a preceptor supervises 2 or more learners who are at different levels of learning, with the senior learner providing learning support to the junior learner.[18] A variation of this model, referred to as the layered learning model,[9] is discussed in detail later in this paper. The benefits of these models are that the junior learner receives mentorship and support from the senior learner, and the senior learner gains experience as a preceptor. In addition, learners may be more independent than is the case with the 1:1 model, and the teaching and patient care workload can be split among the team members. As with peer-assisted learning, near-peer models provide increased capacity for learners at the practice site.[18]

The disadvantages of peer-assisted learning and near-peer models include limited physical space for learners to work, multiple assessments for the preceptor to complete, difficulty in supporting struggling learners, and, for the near-peer model, role confusion among other disciplines, as well as mismatched expectations around supervision and reporting.[18]

In summary, there appear to be a number of benefits associated with nontraditional learner–preceptor models, and these models are viewed favourably by the participants. Nonetheless, there has been limited uptake outside of a few centres and pilot studies, and broader adoption of these models is necessary if their benefits are to be fully realized.

Engagement of Students in High-Value, Mutually Beneficial Patient Care Activities

As stated above, student involvement in impactful patient care activities is an important part of the learning process. In addition, the satisfaction of both individual preceptors and facility administrators is enhanced when learners are integrated into the work of the department.[19] Several investigators have explored the potential of pharmacy students to contribute to patient care in a general way or through targeted student-delivered services.

Mersfelder and Bothillier[20] conducted a comprehensive literature review in an attempt to quantify the impact of pharmacy students on patient care. The authors identified 29 studies conducted in the United States and published between 1990 and 2011 that involved pharmacy students on rotations in community, ambulatory, and acute care settings. Overall, during rotations that ranged from 4 to 6 weeks, students made an average of 6 interventions per week, with the number of interventions increasing over the course of the rotation. Students' activities ranged from general patient care activities to targeted services such as IV-to-oral stepdown, deprescribing of acid-suppressive therapy, warfarin dose adjustment, and medication reconciliation. In the studies that included economic analyses, pharmacy students' involvement in care was associated with cost savings or cost avoidance. The authors concluded that students improved the clinical productivity of pharmacy departments and that schools of pharmacy and practice sites should work together to optimize the scheduling of learners so that they can participate in these activities.[20]

More recently, Champion and others[21] conducted a systematic review of medication reconciliation facilitated by technicians or pharmacy students. The authors identified a total of 32 studies, 10 of which involved pharmacy students. Eight of the student-focused studies took place in inpatient settings, whereas 2 occurred in community settings. In these studies, the students obtained medication histories and were involved in medication reconciliation; in some they also provided patient counselling. Overall, students' medication histories were more accurate than those of physicians or nurses, and the rate of medication reconciliation increased when students were involved.[21] Another recent medication reconciliation study demonstrated that patients whose cases were reviewed by a combined team consisting of 2 APPE pharmacy students and 2 pharmacy technicians had a lower rate of readmission than those not seen by the team.[22] In this study, students identified more medication discrepancies than pharmacy technicians.[22]

Another innovative student service was described by Wentzell and others,[23] who piloted a student-facilitated program for reporting adverse drug reactions (ADEs) at a tertiary care hospital in Ottawa, Ontario. The baseline rate of pharmacy reporting of ADEs to Health Canada in the 6 months before implementation was low (only 2 reports submitted). After implementation of the student-facilitated service, 27 ADEs were reported in the 6-month study period. A follow-up survey involving students and pharmacists indicated strong support for the program to continue.[23]

Student services have also been implemented in the outpatient setting. Kim and others[24] described a student-run program

for monitoring direct-acting oral anticoagulants (DOACs) for patients attending an internal medicine outpatient clinic. Students reviewed the health care records and refill histories of patients for whom DOACs had been prescribed in the previous 6 months, and made recommendations and performed interventions when necessary. A total of 136 interventions were performed for 90 patients, including assisting with medication access and coverage, providing adherence counselling, and recommending additional laboratory monitoring. The authors concluded that pharmacy students are valuable team members who can help to ensure the safe use of DOACs.[24]

Although most of the emphasis here has been on pharmacy students, it should be noted that pharmacy residents can also make significant contributions to patient care. Pharmacy residents provide service to health care organizations through direct patient care activities, research projects, and targeted services.[25] Examples of innovative pharmacy resident services include providing weekend antimicrobial stewardship services, assisting patients with medication access or coverage, providing after-hours on-call services, and participating on the cardiopulmonary resuscitation team.[25-27] Increasingly, residents are also fulfilling the role of senior learners in near-peer or layered learning models.

In summary, there are numerous ways in which pharmacy learners can provide care that is mutually beneficial to patients, the practice site, and their own learning. Although much of the literature reviewed here is from the United States, there is no reason to believe that these approaches would not work in Canada.[23] The most extensively studied student activities are medication history taking, medication reconciliation, and patient counselling. Even students who are relatively early in their training can contribute to these activities. Advanced learners can enhance or extend the quality or scope of pharmaceutical care provided to patients, or they can serve as copreceptors for junior learners. Learner involvement in these activities has the potential to increase facilities' willingness to host learners and to allow the learners to develop independence and a sense of responsibility for patient care.

A Combined Approach: The Layered Learning Practice Model

The layered learning practice model (LLPM) arose out of a need to increase clinical pharmacy services and address rotation capacity challenges without additional resources.[28-30] This model is a variant on the near-peer model and has the built-in expectation that the learners provide tangible service to the organization. The LLPM was pioneered at the University of North Carolina (UNC) Medical Center, in collaboration with the UNC Eshelman School of Pharmacy, and is now gaining widespread interest and acceptance at other sites across the United States.[29,30]

Implementation and evaluation of the LLPM at the UNC Medical Center was described in a series of publications.[28,31,32] The model was deployed in multiple acute care areas, including critical care, medicine, cardiology, pediatrics, and oncology, as well as in ambulatory care. The model involves teams of participants, specifically a clinical pharmacy specialist (the attending pharmacist), a postgraduate year 1 or year 2 resident, a fourth-year APPE pharmacy student, and, in some cases, a clinical generalist pharmacist. Members of the layered learning pharmacy team work together to provide pharmacy care for all of the assigned patients. Key responsibilities of learners include obtaining medication histories, reconciling medications during care transitions, providing patient medication education, and facilitating patients' access to medications on discharge.[28] Factors thought to be important for successful implementation of the LLPM include a systematic approach, good communication, flexibility for the attending pharmacist to adapt the model to the practice area, adequate resources, the commitment of all participants to ensuring the model's success, and evaluation after implementation.[31]

Bates and others[31,32] published 2 studies that evaluated the impact of the LLPM on the oncology units at UNC Medical Center. In the first study, they found that after implementation of the LLPM, 51% of patients received personalized medication education at discharge,[31] whereas before implementation, no patients in the clinical area had received such education. The authors also noted that most of the discharge counselling was conducted by either the pharmacy resident or the pharmacy student.[31] The second study, which attempted to evaluate the educational impact of the LLPM, indicated that learners had a positive experience.[32] Residents reported that they learned to be more independent and organized, and students reported feeling less intimidated when working with the resident. Students also felt that the experience helped them to prepare for a residency.[32]

Soric and others[29] described an LLPM on an intensive care and internal medicine service in a 126-bed community hospital. The participants were an attending pharmacist, 2 postgraduate year 1 residents, and 2 pharmacy students. The model was designed to run continuously with each successive rotation block (11 months per year). The learners performed patient workup and made recommendations, provided medication education, and participated in multidisciplinary rounds. Units where the LLPM was implemented experienced a 22% reduction in medication expenditures. In addition, the frequency of medication education at discharge increased by nearly 20%, and patient satisfaction scores in all categories relating to medication education increased.[29]

Delgado and others[30] described a model that incorporated a single layer of learners (specifically, fourth-year APPE students), who worked with an attending pharmacist in a learning and service delivery model at Cleveland Clinic Florida hospitals. The stated goal of the model was to obtain "pharmacy-generated medication histories and discharge counselling for all patients in a cost-neutral manner." Before implementation of the model, preceptors hosted 1 or 2 pharmacy students per rotation. After implementation, each preceptor was assigned 5 or 6 students per block. The model resulted in improvements in patient satisfaction

scores, an increase in pharmacy interventions, and an increase in patients receiving bedside delivery of discharge medications.[30]

The LLPM represents an innovative approach that combines near-peer learning opportunities with an emphasis on learner contributions to patient care and service delivery. LLPMs appear to be associated with increases in interventions and productivity, and the limited published data that exist suggest that they are regarded positively by learners. LLPMs also address rotation capacity issues and may prove attractive for Canadian hospitals. When implementing such models, it will be important to ensure that assigned activities provide clear value to the students' learning, and ongoing assessment of the impact of such models on learning will be essential.

FUTURE DIRECTIONS

In many of the examples described above, the novel models and approaches were implemented on a single ward or at a single practice site or were temporary pilot projects. In the future, it will be necessary to permanently implement a combination of these approaches alongside broader system changes such as redesigned learner schedules and local workflows aimed at better integrating learners. Ideally, these changes will occur across multiple practice sites or across the entire health system.

Cameron and others[33] described a system-wide approach. In 2010, the University Health Network hospitals in Toronto partnered with the local faculty of pharmacy to strategize in advance of upcoming increases in placement demands associated with a new EPPD program.[33] Several goals were established for experiential education rotations, including the need to maximize capacity and the learner experience through novel models of preceptorship. It was also agreed that learners should perform work that is "meaningful to learning and to patient care."[33] To accomplish these goals, a variety of strategies were implemented, including year-round student placements, extended duration of rotations, integrated near-peer and peer-assisted learning models, a streamlined student onboarding process, a validation process to confirm learners' ability to independently conduct medication reconciliation, and preceptor guidelines outlining teaching expectations. Together, these strategies successfully increased the rotation capacity by 3.5-fold over a period of 4 years.

In British Columbia, the AGILE project (Advancing Experiential Learning in Institutional Pharmacy Practice) outlined a series of approaches, such as strengthening the partnership between the university and the health authority, using non-traditional learner–preceptor models, establishing mutually beneficial patient care activities to be performed by students, and implementing site-based faculty support liaisons, referred to as experiential education facilitators.[5] These experiential education facilitators have now been deployed at multiple sites across the province, helping to build rotation capacity and fuel teaching innovation at a local level.

It is also important to assist preceptors and practice sites as they embark on the changes described above. Reports from the Canadian Experiential Education Project for Pharmacy (also known as CanExEd) provide a series of recommendations related to promoting and supporting the implementation of novel strategies in experiential education.[34] The Priority 2 report, which focuses on learner–preceptor models, highlights the need to customize the approach to each practice site, to provide adequate education to preceptors and model-related orientation for learners, and to establish preceptors with expertise in using the models.[35]

Preceptor education may also be necessary, given that many current preceptors have little or no direct experience in a peer-assisted learning or near-peer model. To promote these models, the University of British Columbia, the University of Alberta, and the Association of Faculties of Pharmacy of Canada jointly developed a series of guidebooks.[36-38] These guidebooks provide practical advice and guidance for preceptors who are considering rotations involving peer-assisted learning, near-peer models, or co-preceptorship. They highlight best practices from the literature and convey advice from preceptors who have experience with each of these models. As such, they may be useful resources in helping preceptors transition away from the status quo.

There are a number of potential approaches to increasing preceptor comfort with greater student involvement in and responsibility for patient care activities. Specific student training or validation processes similar to those outlined by Cameron and others[33] for medication reconciliation could be developed. In addition, close collaboration between practice sites and the faculty of pharmacy can ensure that on-campus learning activities realistically simulate activities that the learners will be expected to perform at the practice site. Conversely, if preceptors have a good understanding of the curriculum and expected levels of student performance, they can more easily determine which patient care activities may be appropriate to assign.

CONCLUSION

A number of significant changes have occurred recently in the structure and duration of pharmacist training programs in Canada. Overall, these changes are intended to produce pharmacy practitioners who are prepared to advance the profession and take pharmacy practice to the next level. However, to achieve this result the current approach to experiential education must be re-evaluated, and new approaches investigated and applied. This paper has outlined a variety of innovative approaches to experiential education along with considerations for their implementation. If the profession is to continue evolve, it will be essential for the pharmacy practitioners of the future to be fluent in these approaches.

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Rivaroxaban Treatment for Left Ventricular Thrombus

Jayesh Changela and Maria Anwar

INTRODUCTION

Rivaroxaban, a direct oral anticoagulant (DOAC), is a factor Xa inhibitor indicated for treatment and prevention of deep vein thrombosis and pulmonary embolism, as well as for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[1] No large randomized controlled trials have been performed to formally study the use of rivaroxaban for treatment of left ventricular (LV) thrombus, and there is limited information available about the efficacy and safety of any DOAC for managing LV clots. Currently, the recommended pharmacological treatment for LV thrombus in patients who have experienced transient ischemic attacks (TIAs) or stroke is vitamin K antagonist therapy.[2] We report a case in which rivaroxaban was prescribed for LV thrombus in a patient with heart failure secondary to systemic lupus erythematosus and history of TIA.

CASE REPORT

A 40-year-old patient presented to the emergency department on October 8, 2014, with dysarthria lasting 2 min and left-sided facial numbness lasting 1 h; the diagnosis was TIA.* The medical history was significant for remote alcohol abuse (> 15 years previous) and systemic lupus erythematosus, diagnosed 3 years previous. Pre-admission medications for the latter diagnosis included prednisone, hydroxychloroquine, azathioprine, and methotrexate. The patient was an active smoker, but did not have hypertension, dyslipidemia, or a family history of premature coronary artery disease.

*Informed consent could not be obtained from the patient or family. Potentially identifying details not pertinent to the patient's diagnosis and treatment course have been omitted from this report.

The patient had experienced a similar TIA episode 1 month before (on day –35, in relation to the date of index presentation to the emergency department), presenting with dysarthria, left-arm weakness, and facial paralysis lasting 5 min. Magnetic resonance imaging (MRI) of the brain at that time revealed punctate watershed infarcts in the right frontal lobe; acetylsalicylic acid (ASA) 81 mg daily was initiated. Transthoracic echocardiography was performed 3 weeks later (on day –14) to investigate the possibility of cardioembolic stroke. The imaging showed moderate to severe eccentric LV hypertrophy and systolic dysfunction, with 31% LV ejection fraction and LV apical dyskinesia, which together suggested the presence of an LV thrombus. The patient was subsequently referred to a cardiologist, and anticoagulation therapy, consisting of warfarin overlapped with low-molecular-weight heparin (LMWH), was recommended. However, the patient did not wish to receive injections or to undertake regular testing of international normalized ratio and therefore declined this therapy.

The risks of forgoing the recommended therapy, including the increased risk of further embolic events, were explained by the cardiologist, with support from a cardiology pharmacist. The patient continued to decline the preferred treatment option, so non-indicated options for treating LV thrombosis were considered. The patient appeared to understand the information provided about these options and elected to proceed with off-label use of rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg daily, with the therapy starting on day –10. Repeat transthoracic echocardiography was planned for 3 months after initiation of rivaroxaban, to allow reassessment of the need for continuing therapy on the basis of LV function and resolution of the LV thrombus.

At the time of this case (in 2014), evidence regarding the use of any DOAC for treatment of LV thrombus was very limited,

and there was no compelling evidence favouring one DOAC over another. The patient had no prior history of major bleeding, and the hemoglobin level and platelet count were within normal ranges. Given the availability of provincial drug benefit coverage for DOAC therapy and the absence of evidence for any specific DOAC in this setting, rivaroxaban was chosen. The dosing strategy selected was similar to what would be used for treatment of deep vein thrombosis with the goal of mimicking, to the extent possible, the most comparable indication-specific dosing available. Cardiac MRI performed 4 days after the start of rivaroxaban therapy (on day –6) confirmed the presence of the LV thrombus; repeat outpatient imaging was planned for 3–6 months later, to check for thrombus resolution.

Less than a week later, and 1 day before a planned hospital admission for renal biopsy, the patient presented to the emergency department (day 0 of this case report) with new TIA symptoms. The biopsy had been scheduled on short notice to investigate ongoing microscopic hematuria and possible lupus nephritis. At the time of this presentation, ASA had been held since day –6 and rivaroxaban since day –1, as part of the plan for periprocedural management, to minimize the risk of bleeding during the biopsy (such that ASA and rivaroxaban would be held for a total of 7 days and 48 h, respectively, before the biopsy, which was planned for day +1). Computed tomography angiography of the head and neck, performed on day 0, ruled out intracranial hemorrhage. It was suspected that the TIA was secondary to emboli from the previously documented LV thrombus, so treatment with heparin by IV infusion was initiated, and all other antithrombotic medications remained on hold. The planned renal biopsy was postponed to day +2, but on that date, while awaiting the procedure, the patient experienced worsening left-arm weakness and speech difficulties. Repeat MRI of the brain revealed new acute right hemispheric infarcts. The left renal biopsy was performed anyway (on day +2), with the heparin infusion held just before the procedure. The partial thromboplastin time was 29.8 s at the time of the procedure, which indicated that the anticoagulant effects of IV heparin were no longer present. Upon consultation, the hematology service speculated that the TIA symptoms were likely hemodynamically related; as a result, the patient's antihypertensive medications were held. The following day (day +3), the treatment-dose heparin infusion was resumed, and clopidogrel was started with a 300-mg loading dose, followed by 75 mg daily.

The patient's hospital stay was further complicated by progressively worsening abdominal pain, as well as decreases in blood pressure, respiratory rate, and responsiveness. The patient's hemoglobin decreased progressively, from 133 g/L at the time of the biopsy (on day +2) to 79 g/L (on day +6). The patient was eventually intubated and transferred to the intensive care unit, where cardiac arrest occurred (on day +6). Ultimately, resuscitation was unsuccessful, and the final autopsy report declared retroperitoneal hemorrhage, accounting for about 2000 mL of clotted blood, as the cause of death.

DISCUSSION

The usual treatment for LV thrombus in patients with TIA who have normal sinus rhythm is anticoagulant therapy with a vitamin K antagonist for 3 months or longer.[2,3] In patients with TIA complicated by LV thrombosis and LV ejection fraction less than 40%, and in the setting of myocardial infarction, treatment with LMWH, dabigatran, rivaroxaban, or apixaban for 3 months may be considered as an alternative to vitamin K antagonist therapy for prevention of recurrent stroke or TIA.[2]

Since the original presentation to the emergency department of the patient described in this case report (in late 2014), new literature has emerged regarding the use of DOAC for treatment of LV thrombus. In a recent review, Ghaffarpasand and others[4] identified 31 cases in which rivaroxaban was used to treat intracardiac thrombi, 16 of which were LV thrombi. The dosing regimens varied and included 10 mg daily (1 patient), 10 mg twice daily (1 patient), 15 mg daily (5 patients), 15 mg twice daily (1 patient), 20 mg daily (6 patients), and a combination of 15 mg twice daily followed by 20 mg daily (2 patients). The duration of anticoagulation ranged from 7 to 436 days. In 15 of the patients with LV thrombi, echocardiography after completion of anticoagulation treatment showed that the thrombus had resolved; 1 patient was lost to follow-up. None of the 15 patients with follow-up experienced a thromboembolic event; however, bleeding events were not reported.

Determining the ideal rivaroxaban dosage and duration of treatment is difficult, given the large variation in regimens described in the review by Ghaffarpasand and others.[4] For the patient described here, MRI of the left ventricle showed no resolution of the thrombus after 4 days of treatment with rivaroxaban 15 mg twice daily, and no repeat imaging was done (because the patient died). Whether extended therapy might have resulted in dissolution of the thrombus is difficult to determine; however, the information compiled by Ghaffarpasand and others[4] indicates that longer therapy is likely required to achieve this outcome, given that patients whose thrombi resolved generally had longer treatment duration.

According to the bleeding risk stratification based on type of operation presented in the guidelines of the American College of Chest Physicians,[5] renal biopsy is considered to pose a high risk of bleeding. Thrombosis Canada recommends that rivaroxaban should be held for at least 2 days before a major procedure, such as a renal biopsy.[6] In the case reported here, the patient's rivaroxaban therapy conformed with the Thrombosis Canada recommendation and with guidelines of the American Heart Association[7] and thus appeared to be appropriately managed to minimize the risk of bleeding in association with the renal biopsy. The last dose of rivaroxaban was taken on October 7, about 72 h before the biopsy was done (on day +2). Given the patient's estimated creatinine clearance at the time (109 mL/min, as calculated by the Cockcroft–Gault equation) and the half-life of

rivaroxaban in non-elderly patients (reported as 7–11 h[1]), a period of more than 5 drug half-lives had passed between the patient's last dose and the biopsy, and adequate clearance of rivaroxaban would therefore have been expected. In addition, given that the patient's partial thromboplastin time was normal at the time of biopsy (29.8 s), it can be concluded that the anticoagulant effects of heparin therapy had also worn off.

The contribution of the pharmacodynamic interaction between ASA and rivaroxaban to bleeding outcomes in this patient is difficult to quantify. The patient had most recently received rivaroxaban 24 h before and ASA 6 days before presentation to the emergency department. Thus, we assumed that 75%–87.5% of the rivaroxaban had been eliminated (with passage of 2–3 drug half-lives) and that for most platelets, inhibition of aggregation was unaffected by ASA (given that the normal lifespan of a platelet is 8–9 days).[8] Both the American Heart Association[7] and Thrombosis Canada[9] recommend holding ASA before a major procedure unless the patient has high cardiovascular risk, in which case the cardiovascular risk must be weighed against the risk of bleeding and the continuation of ASA may be appropriate. There are no explicit guidelines for the perioperative management of antiplatelet agents in patients with increased cerebrovascular risk. However, the guidelines of the American College of Chest Physicians suggest that in patients with moderate to high risk of a cardiovascular event, ASA should be continued around the time of the procedure.[5]

In the patient described here, the comparative risk of cerebrovascular attack and risk of bleeding was not documented. Detailed consult service notes were not available, as the hospital patient chart was unobtainable, which is a limitation of our report. The patient's course was further complicated by recurrent TIAs 2 days after admission. Whether continuing ASA in the lead-up to renal biopsy would have prevented these ischemic attacks is unknown. Other confounders included the administration of therapeutic heparin and clopidogrel for the management of recurrent TIA starting 1 day after the renal biopsy, which likely increased the risk of bleeding.

The complexity of this case warrants further examination. Specifically, should clinicians be more hesitant to apply therapies for off-label use in patients with complex comorbidities? What other patient- and drug-specific factors may play a role in adverse events? Balancing a patient's preferences with evidence-based practice can lead to challenging clinical conundrums. In this case, patient preference was the defining determinant for the use of off-label therapy. However, when considering the use of any medication for off-label indications, patient preferences, potential risks, and anticipated benefits must be carefully weighed, and any decisions must be made on a case-by-case basis. We propose the following framework, based on our clinical experiences, to help clinicians determine the appropriateness of off-label use of DOACs for LV thrombus:

1) Identify preferred therapeutic alternatives with more robust evidence for treatment of LV thrombus.
2) Identify the patient's preference in favour of or against these preferred alternatives.
3) If considering off-label anticoagulation therapy for treatment of LV thrombus, identify patient-specific risks of bleeding.
4) Determine whether the patient is taking other medications that might increase the risk of bleeding.
5) Discuss with the patient the advantages, disadvantages, and unknowns associated with off-label use of anticoagulants.

CONCLUSION

We have described a patient with presumed LV thrombus who preferred not to use warfarin bridged with LMWH injections and was treated instead with rivaroxaban 15 mg twice daily. The LV thrombus was confirmed by imaging 4 days after initiation of rivaroxaban. Renal biopsy to investigate other symptoms was performed several days later, despite the presence of multiple complicating factors (including additional medications known to increase the risk of bleeding); the patient experienced fatal bleeding shortly afterward. Because of the patient's complicated course, no imaging was done beyond the fourth day of rivaroxaban therapy, and it is therefore unclear whether the prolonged therapy had any effect on dissolution of the thrombus. Given the lack of robust evidence for the use of rivaroxaban to manage LV thrombus, vitamin K antagonists continue to be the therapy of choice. The efficacy and appropriate dosing strategy for off-label use of rivaroxaban in the treatment of LV thrombus are unknown, and this off-label use may increase the risk of bleeding. Further studies are warranted to confirm the efficacy and safety of rivaroxaban in this specific patient population.

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Should All Patients 75 Years of Age or Older Receive Intensive Management for Hypertension?

THE "PRO" SIDE

> It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.
>
> —Sir William Osler (1849–1919)

The Canadian population is aging, with an estimated one-quarter of Canadians reaching 65 years of age or older by 2036, and 25% of those individuals being 80 years and older.[1] Among the leading causes of death in Canada for those aged 75–84 are cardiovascular and cerebrovascular diseases.[2] Globally, high blood pressure is the leading risk factor for death and disability.[3]

To evaluate whether lower targets for systolic blood pressure (BP) could further protect against cardiovascular disease, SPRINT (the Systolic Blood Pressure Intervention Trial) compared a standard systolic BP target of 140 mm Hg with an intensive target of 120 mm Hg. The overall trial, which enrolled almost 10 000 participants, showed that treating to an intensive systolic BP target reduced fatal and nonfatal cardiovascular events from 6.8% to 5.2% (hazard ratio 0.75, absolute risk reduction [ARR] 1.6%, number needed to treat [NNT] 63) over 3.3 years. All-cause mortality was also reduced (ARR 1.2%, NNT 84 over 3.3 years).[4]

A closer look at the design of SPRINT reveals that it was intended to examine high-risk populations and to specifically recruit individuals within those groups, including individuals aged 75 or older. Patients were eligible to participate if they met one of the following inclusion criteria: history of clinical or subclinical cardiovascular disease, chronic kidney disease, 10-year Framingham cardiovascular disease risk of 15% or more, or age 75 or older. Patients were excluded if they had systolic BP less than 110 mm Hg following a minute of standing, expected survival of less than 3 years, diabetes mellitus, or heart failure, or if they lived in a nursing home. Frailty and lower functional status were not specified as exclusion criteria. In total, 28% of participants recruited (n = 2636) met the inclusion criteria of age 75 and older, with an average age of about 80 years in this subgroup. Of these, more than 80% were characterized as "less fit" (about 55%) or "frail" (about 31%) according to a validated frailty index. The results, including outcomes based on frailty, were evaluated separately. Importantly, the results for this prespecified subgroup were more impressive than the results of the overall trial. The NNT over 3.3 years for the primary outcome (a composite of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes) was lower within this group than for the overall trial (27 versus 63, respectively), and the NNT for all-cause mortality was also lower (41 versus 84, respectively). These benefits were consistent regardless of frailty status, with the frail patients and slowest walkers benefiting as much as younger, fitter participants.[5] Additionally, this outcome was achieved with an average of 3 antihypertensive medications, compared with 2 in the standard treatment arm, which indicated that this population had hypertension that was responsive to treatment (i.e., nonresistant hypertension).

The intensive systolic BP achieved in those 75 years and older was slightly higher (123.4 mm Hg) compared to that achieved with intensive treatment in all trial participants (121.4 mm Hg); these values can be compared to the systolic BP target achieved with standard treatment (134.8 mm Hg). Furthermore, within the intensive treatment group, mean systolic BP during follow-up was slightly higher for participants classified as less fit (123.3 mm Hg) or frail (124.3 mm Hg) than for those considered to be fit (121.4 mm Hg). Overall, the difference in systolic BP between treatment groups ranged from 10.8 to 13.5 mm Hg. These BP values were obtained with an unattended automated cuff, also called an automated office blood pressure device.[4] For clinicians using a BP measurement device that is attended and/or manual, the systolic BP reading may be 5 to 10 mm Hg higher. Achieving these BP targets is contingent on using a similar method for BP measurement.[6]

To explore a preventive role in cognitive impairment, a subgroup analysis was planned a priori to evaluate the effect of intensive lowering of systolic BP on probable dementia and mild cognitive impairment.[7] The incidence of probable dementia was not decreased significantly (although the trend was toward reduction), but there was a significant 19% relative risk reduction (RRR) in mild cognitive impairment, with an RRR of 15% for the composite end point of probable dementia or mild cognitive impairment. Although concerns have previously been expressed that lower BP causes hypoperfusion of the brain, leading to negative effects, this problem was not observed. It is promising that, over 3.3 years of intervention and just over 5 years of follow-up, mild cognitive impairment was reduced. The trial was stopped early (after 3.3 years) because of positive cardiovascular effects in the intensive arm, truncating the ability to assess these cognitive outcomes, which typically manifest slowly over many years.[7]

Importantly, the oldest subgroup tolerated the intensive treatment to the same degree as the standard treatment. Serious adverse events were defined as events that were fatal or life-threatening, resulting in significant or persistent disability, requiring or prolonging a hospitalization, or being significant enough to require intervention. The outcomes evaluated included hypotension, syncope, electrolyte abnormalities, and acute kidney injury or renal failure. The incidence of serious adverse events was virtually identical in the 2 treatment arms (48.4% versus 48.3% in the standard treatment arm), with none of the individual outcomes having a statistically significant difference. There was also no difference in injurious falls between the groups, a finding that was independent of frailty status. Typically, risks of orthostatic hypotension and falls are cited as reasons for not intensifying hypertension management, and these findings provide reassurance that these outcomes did not differ with the BP target. While there was an overall increase in the rate of adverse events, they were mostly events that could be addressed and that should not have long-term consequences. For this reason, a monitoring plan is important, so that adjustments, like deprescribing, can be made on the basis of treatment response.[5]

On the basis of results from the Hypertension in the Very Elderly Trial, Hypertension Canada previously recommended that those over 80 years of age be treated to a target of less than 150 mm Hg. In response to SPRINT, Hypertension Canada has adopted BP targets based on risk level, and has abandoned recommendations based on age alone.[8] Other countries have done the same. The US guidelines were changed in 2018 to recommend a lower systolic BP target—less than 130 mm Hg—for all high-risk patients.[9]

Ultimately, these results show meaningful benefit in those aged 75 and above, and were achieved with relative ease, by adding one more antihypertensive medication to their regimen. Moreover, the results were obtained with a side effect profile that was no different from that associated with standard BP treatment targets. As with many treatment decisions for elderly patients, the benefits (specifically, decreases in cardiovascular disease and mortality that are not achieved with many therapies for this age group) need to be weighed against the risk tolerance for additional monitoring and medications. To maximize treatment benefit and minimize harms, the goal should be to work in partnership with patients (especially those 75 years of age or older) to treat their hypertension to evidence-based guideline recommendations, with a monitoring plan in place. It seems reasonable to give this strategy a try in patients who are willing and able.

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See page 251 for the "Con" side of this debate.

THE "CON" SIDE

Optimal blood pressure (BP) has been debated since hypertension was first identified more than 100 years ago as a cardiovascular risk factor. Previous trials have shown that reducing BP in elderly patients is beneficial.[1-3] However, contrary to what golfers and limbo enthusiasts alike strive to achieve, lower—in the context of BP—is not always better. Two trials involving elderly Japanese patients (mean age 74 and 76 years, respectively) with a systolic BP above 160 mm Hg both demonstrated that "strict" BP control (systolic BP < 140 mm Hg) was not superior to "moderate" control (systolic BP 140–159 mm Hg) with respect to adverse cardiovascular and renal events.[4,5] A subsequent meta-analysis assessed a BP target of <160/<90 mm Hg versus <140/<90 mm Hg in adults 65 years of age or older who had hypertension and found no difference in all-cause death and cardiovascular serious adverse events.[6] The latest contribution to this debate is the Systolic Blood Pressure Intervention Trial (SPRINT), the seminal contemporary hypertension trial that has brought about countless metaphorical presentation titles at conferences worldwide. In that spirit, when it comes to intensive hypertension management in older adults, I would argue that we should walk rather than "SPRINT" toward a benefit.

In SPRINT, an "intensive" systolic BP target (< 120 mm Hg) was compared with a "standard" target (< 140 mm Hg) in 9361 patients (mean age 68 years, 25% women) with initial systolic BP between 130 and 180 mm Hg.[7] After 3.3 years, patients in the group with intensive systolic BP target had a lower rate of the primary composite end point of cardiovascular death, acute coronary syndrome, stroke, and heart failure (absolute reduction 1.6%; number needed to treat [NNT] 63). Although intensive treatment also lowered the risk of all-cause death (NNT 84), heart failure (NNT 125), and cardiovascular death (NNT 167), it did not reduce myocardial infarction or stroke. Intensive treatment was not without risk—it increased certain serious adverse events, including acute kidney injury or renal failure (number needed to harm [NNH] 56), hypotension (NNH 100), electrolyte abnormalities (NNH 125), and syncope (NNH 167). It is important to note that each of these was a serious adverse event, defined as "an event that was fatal or life-threatening, resulting in significant or persistent disability, requiring or prolonging a hospitalization, or was an important medical event that the investigator judged to be a significant hazard or harm to the participant."

A preplanned subgroup analysis of SPRINT[8] included 2636 patients 75 years of age or older (mean age 80 years, 38% women), which constituted only 28% of the overall population. The results were similar to those of the overall trial: intensive treatment reduced the primary end point (NNT 29), all-cause death (NNT 39), and heart failure (NNT 67), yet did not lower the risk of cardiovascular death, myocardial infarction, or stroke. Interestingly, the primary end point was not reduced in the subgroup of patients younger than 75 years of age.[7] In the subgroup of patients 75 years of age or older, treatment-related serious adverse events were numerically (though not significantly) higher with intensive treatment.[8] From an evidence-based purist perspective, a subgroup analysis—one that excluded 72% of the study population—should be viewed with skepticism.[9] One could argue that such an analysis should be used only to generate future research, not to dictate clinical practice. With respect to other prespecified subgroups, the primary end point was lower in patients without (but not with) chronic kidney disease, in those without (but not with) cardiovascular disease, in men (but not women), and in patients with a baseline systolic BP of 132 mm Hg or below (but not 133–144 mm Hg or ≥ 145 mm Hg). As any angler will agree, if you go fishing enough times, you're bound to catch something.

I concede that the results of SPRINT are impressive. Notwithstanding, the argument against intensive BP management in older persons is less about critical appraisal and more about the pragmatic application of these data in practice. It is not so much about, "What does the evidence show?" but rather, "How does this evidence apply to my patient?"

The SPRINT was conducted in a relatively healthy population. It excluded patients with diabetes mellitus or previous stroke, as well as many frail older patients, specifically those with a 1-min standing systolic BP below 110 mm Hg, proteinuria (24-h urinary protein excretion ≥1 g/day or similar), estimated glomerular filtration rate (eGFR) below 20 mL min^{-1} 1.73 m^{-2} or end-stage renal disease, left ventricular ejection fraction below 35%, life expectancy less than 3 years, dementia, or residence in a nursing home. Even among those aged 75 years or older, only 25% had a history of cardiovascular disease and only 16% had eGFR below 45 mL min^{-1} 1.73 m^{-2}. At baseline, mean BP was 142/71 mm Hg, and patients were taking an average of 2 antihypertensive agents. Also, it was challenging to achieve systolic BP below 120 mm Hg even with a trial protocol: mean systolic BP in the intensive treatment group over the follow-up period was 123 mm Hg. Furthermore, given that the trial was discontinued prematurely, the long-term effect of intensive BP management remains unknown. There was no difference in the rate of injurious falls (i.e., falls that resulted in hospital admission or evaluation in an emergency department), but the total number of falls was not reported. However, in older persons, a non-injurious fall or even the fear of falling may have a negative impact on quality of life. In addition, although the rate of syncope was similar between groups, data were not reported for symptomatic lightheadedness, which also can have a subtle deleterious effect on patients' daily activities.

Some clinicians may argue that intensive BP treatment has an overall net clinical benefit. However, this conclusion disregards the values that patients assign to those outcomes. Many older persons value quality over quantity of life. Thus, some patients may place more value on avoiding the possible adverse effects of antihypertensive therapy than on the relatively small reduction in all-cause mortality. Furthermore, health literacy may be low among elderly patients. Therefore, it is imperative to employ novel ways of engaging patients and their families in shared decision-making to determine whether intensive BP management aligns with their health goals. Other

practical considerations include the risk of nonadherence, potential contribution to polypharmacy, and cost.

I believe that the SPRINT results should have a meaningful impact on clinical practice, but would encourage clinicians not to let any bias favouring the efficacy data to negate consideration of patients' values and preferences. In my own admittedly anecdotal experience, when I have engaged in shared decision-making with select patients in my practice who meet the SPRINT criteria, most have declined to pursue a systolic BP target of less than 120 mm Hg. When it comes to BP control in older patients, the best advice is likely the often quoted, yet seldom followed medical axiom: treat the patient, not the number.

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Clinical Handbook of Psychotropic Drugs for Children and Adolescents, 4th edition

Elbe D, Black TR, McGrane IR, Procyshyn RM, editors. Hogrefe Publishing Corp., 2019. Softcover, 396 pages. ISBN-13 978-0-88937-550-5. $137.95 ($117.26 for CSHP members).

The *Clinical Handbook of Psychotropic Drugs for Children and Adolescents* is well established as one of the essential references for medical professionals practising in the field of pediatric mental health. It is a comprehensive resource that combines evidence from scientific research with knowledge from leading clinical experts, presenting the material clearly and in a highly accessible format. Extensive information about topics such as the frequency of adverse effects and dosing considerations is conveniently condensed into well-organized tables. This feature, along with the use of colour coding, icons, and bullet-point format, makes navigation quick and easy.

As in the third edition, the latest handbook begins with brief overviews of the various psychiatric disorders that occur in children and adolescents, including up-to-date summaries on the following subjects: epidemiology, risk factors, comorbidities, presentation and symptoms, diagnosis, associated outcomes, and treatment. Then, clinically relevant information is presented separately for each class of psychotropic medication. Along with standard content such as indications and interactions, the insight provided in the "nursing implications" and "general comments" sections can be particularly useful in improving care plans and the patient experience.

It is worthwhile to highlight the chapter on antipsychotic-induced extrapyramidal side effects and their management. This chapter will be valuable in distinguishing among the many types of symptoms and syndromes and in considering the most appropriate therapeutic adjustments. Also, the charts listing the pharmacological effects of antidepressants and antipsychotics on various neurotransmitters and receptors are innovative and can be helpful in understanding a patient's response to a particular agent. Another advantage of this reference is the detailed information on augmentation strategies provided at the end of each drug class section.

Several significant updates appear in this latest incarnation of the handbook. The recommendations on switching antidepressants have been fully revised, and now include more specific wash-out durations for each class of these medications. Switching methods (direct switches, stops, and cross-tapering) are further detailed, and there is increased emphasis on gradual, individualized tapering plans. The pharmacology section for second-generation antipsychotics has been expanded to include the proposed theory involving rate of dopamine receptor dissociation. Other changes include a comparison chart of treatments for nicotine use disorder and an updated section on unapproved treatments for psychiatric disorders, which summarizes recent studies involving agents such as *N*-acetylcysteine for cannabis use disorder and irritability in autism. Also, key material related to lithium toxicity and monitoring parameters for antipsychotics has been revised and nicely reorganized into charts.

The fourth edition includes many new agents that have come to market since the last revision, in 2014. Among those currently approved for use in Canada, one third-generation antipsychotic, brexpiprazole, and a serotonin modulator and stimulator, vortioxetine, are notable additions.

Some practitioners will find that they need to consult other resources, to complement the valuable information in this volume. For example, anyone who is looking for supplemental information related to pharmacology may find a reference such as *Stahl's Essential Psychopharmacology* (4th edition, Cambridge University Press, © 2008 or online edition) beneficial. For switching strategies for antidepressants and antipsychotics, the free online resource switchRx.ca may be helpful, as it allows users to create specific, detailed, and visually appealing handouts useful for counselling patients and communicating recommendations to prescribers.

The *Clinical Handbook of Psychotropic Drugs for Children and Adolescents* is an exceptionally useful resource with which all clinicians and trainees involved in pediatric psychiatry should be familiar. A complete list of the updates included in the fourth edition, as well as preview pages, can be found on the publisher's website (https://us.hogrefe.com/). An electronic version of the resource is also available by subscription.

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Passer de la parole aux actes : résoudre la crise des opioïdes au Canada

par Douglas Doucette

Il est primordial que les dirigeants utilisent les bons mots, mais il est plus important encore qu'ils posent les bons gestes — qu'ils passent de la parole aux actes — particulièrement lorsqu'ils s'attaquent à un problème, tel que la crise des opioïdes. Le nombre de surdoses et de décès liés aux opioïdes au Canada représente une crise nationale de santé publique. La Société canadienne des pharmaciens d'hôpitaux (SCPH) est signataire de la Déclaration conjointe sur les mesures visant à remédier à la crise des opioïdes au Canada, qui dresse la liste des engagements concrets pris par les gouvernements, les associations et d'autres décideurs. Dans ce commentaire présidentiel, j'aimerais faire le point sur les progrès accomplis par la SCPH en ce qui concerne le respect de la Déclaration d'action conjointe.

L'un des engagements qu'a pris la SCPH au sujet des substances contrôlées consistait à sonder ses membres dans le but de déterminer les outils et les ressources nécessaires. Les résultats de ce sondage, mené vers la fin de l'année 2017, servent à guider l'élaboration d'outils de pratique et de programmes de formation continue en gestion responsable des opioïdes (le rapport d'enquête est disponible en anglais à l'adresse https://www.cshp.ca/opioid-crisis).

En février 2019, la SCPH a publié le *Controlled Drugs and Substances in Hospitals and Healthcare Facilities: Guidelines on Secure Management and Diversion Prevention*, une ressource en libre accès offerte aux praticiens aussi bien qu'au public (à l'adresse https://www.cshp.ca/guidelines). Ces lignes directrices aident les établissements de santé canadiens à développer de nouveaux systèmes de prévention, de détection et d'intervention en cas de détournement de substances contrôlées en plus de leur fournir des pistes d'amélioration une fois ces systèmes instaurés. Le groupe qui a établi ces lignes directrices comprenait des membres de la SCPH ainsi que des représentants d'autres groupes signataires de la Déclaration d'action conjointe, notamment d'associations médicales et infirmières, de Santé Canada, de SoinsSanté*CAN* et de l'Institut pour la sécurité des médicaments aux patients du Canada. Une consultation a également eu lieu auprès du public. Cette collaboration à grande échelle a débouché sur des lignes directrices applicables dans les établissements de santé de partout au Canada. Quant au détournement de substances en milieu de santé, nous sommes passés d'une culture du blâme à un sentiment de responsabilité partagée, de déclaration universelle et d'amélioration des systèmes. Les lignes directrices de la SCPH ainsi que le présent journal (par les articles de cette publication) offrent un encadrement en matière de détournement de substances.

Pour soutenir les pharmaciens s'occupant de patients exposés à des risques de problèmes liés aux opioïdes, la SCPH a conçu un briefing pour l'optimisation des médicaments au Canada, baptisé *Safe Transitions of Care for Patients Taking Opioids* (auquel les membres de la SCPH peuvent accéder à l'adresse https://www.cshp.ca/canadian-medication-optimization-briefing-0). La SCPH tient à jour une bibliothèque virtuelle offrant des ressources éducatives et pratiques sur l'utilisation des opioïdes (voir https://www.cshp.ca/opioid-use). Elle fournit aussi une rétroaction des révisions du document *Usage abusif et détournement de substances désignées : guide pour les professionnels de la santé* rédigé par Santé Canada (dont la version actuelle est disponible à l'adresse http://publications.gc.ca/site/fra/9.667412/publication.html) en plus de soumettre des recommandations pour la mise à jour du document *S'abstenir de faire du mal : Répondre à la crise liée aux médicaments d'ordonnance au Canada* (dont la version actuelle est disponible à l'adresse http://www.ccdus.ca/fra/topics/prescription-drugs/pages/default.aspx).

Nos membres devraient être heureux // satisfaits du travail accompli par la Société pour respecter ses engagements fixés par la Déclaration d'action conjointe. Évitons néanmoins de tomber dans la complaisance. Nous devons plutôt utiliser ces nouvelles lignes directrices pour joindre la parole aux actes dans le cadre de notre pratique et ainsi soutenir nos patients et nos collègues qui abusent (ou risquent d'abuser) des opioïdes ou d'autres substances contrôlées.

[Traduction par l'éditeur]

Douglas Doucette, B. Sc. (Pharm.), Pharm. D., FCSHP, est président et agent de liaison externe de la Société canadienne des pharmaciens d'hôpitaux.

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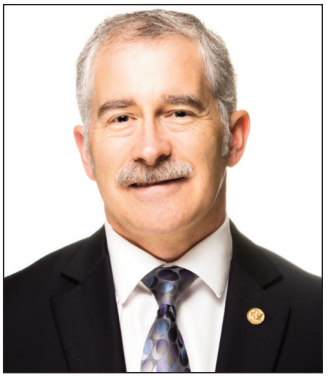
Walking the Talk: Actions to Resolve Canada's Opioid Crisis

Douglas Doucette

It is critical that leaders not only say the right things but also, more importantly, do the right things—that they "walk the talk"—especially when addressing difficult problems such as the current opioid crisis. The number of overdoses and deaths attributed to opioid abuse and misuse in Canada is a national public health emergency. The Canadian Society of Hospital Pharmacists (CSHP) is a signatory to the Joint Statement of Action to Address the Opioid Crisis, which lists specific commitments made by governments, associations, and other decision-makers. In this presidential commentary, I'd like to provide an update on CSHP's progress toward fulfilling our commitments under the Joint Statement of Action.

One of CSHP's commitments was to survey its members to identify their needs for tools and resources concerning controlled substances. The results of this survey, which was conducted in late 2017, are being used to guide the development of practice tools and education programs for opioid stewardship (survey report available through https://www.cshp.ca/opioid-crisis).

In February 2019, CSHP released *Controlled Drugs and Substances in Hospitals and Healthcare Facilities: Guidelines on Secure Management and Diversion Prevention*, an open-access resource that is freely available to both practitioners and the public (through https://www.cshp.ca/guidelines). These guidelines offer direction to Canadian healthcare facilities on developing a system to prevent, detect, and respond to the diversion of controlled substances, and on continuously improving such a system once it has been established. The guideline development group included CSHP members and representatives of other signatories to the Joint Statement of Action, including medical and nursing associations, Health Canada, HealthCare*CAN*, and the Institute for Safe Medication Practices Canada. Input was also sought from the general public. The final result of this broad collaboration is a set of guidelines suitable for implementation in healthcare institutions across Canada. Discussion about and action on drug diversion in healthcare are changing from a culture of "blame and shame" to a sense of shared responsibility, universal reporting, and systems improvement. Both CSHP (through its guidelines) and this Journal (through articles elsewhere in this issue) are offering leadership in the area of drug diversion.



To support pharmacists caring for patients who are at risk of opioid-related problems, CSHP developed a Canadian Medication Optimization Briefing entitled "Safe Transitions of Care for Patients Taking Opioids" (available to members through https://www.cshp.ca/canadian-medication-optimization-briefing-0). CSHP maintains an online library of educational and practice-related resources on opioid use (see https://www.cshp.ca/opioid-use), is contributing feedback on revisions to Health Canada's *Abuse and Diversion of Controlled Substances: A Guide for Health Professionals* (current version available at http://publications.gc.ca/site/eng/289299/publication.html), and is submitting recommendations for an update to *First Do No Harm: Responding to Canada's Prescription Drug Crisis Strategy* (current version available at www.ccdus.ca/Eng/topics/Prescription-Drugs/Pages/default.aspx).

Our members should be proud of the Society's work toward fulfilling its commitments under the Joint Statement of Action. Now is not the time for complacency. Rather, it is time for us to use the new guidelines and other resources to "walk the talk" in our own practices, to support both patients and colleagues who are (or are at risk of) abusing and misusing opioids and other controlled substances.

Douglas Doucette, BSc(Pharm), PharmD, FCSHP, is President and External Liaison for the Canadian Society of Hospital Pharmacists.

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