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Are We "Closing the Loop" on Meeting the Therapeutic Needs of Critically Ill Patients?

Marc M Perreault

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Health care professionals provide tremendous care to critically ill patients from the moment they are admitted to the emergency department, after transfer to the intensive care unit (ICU), and eventually upon transition back to the community. Fortunately for patients with critical illness, survival rates following care in the ICU have increased. However, many survivors do experience short- and long-term complications from their ICU stay. Post–intensive care syndrome (PICS) is characterized by a constellation of physical, cognitive, and psychosocial consequences of critical illness that prevent patients from returning to their former level of functioning, thus reducing their quality of life and causing significant distress among their caregivers.[1]

In 2016, the James Lind Alliance Priority Setting Partnership (United Kingdom) recognized this syndrome as one of two research priorities, not only for critical care clinicians, but also for ICU patients and their families.[2] Organizations such as the Society of Critical Care Medicine under the Thrive Collaboratives are developing initiatives to address the issue of ICU survivorship and to identify the most effective model for post-ICU care.[3]

PICS clinics and peer support groups have been implemented to respond to the needs of patients who survive critical illness, and pharmacists are starting to embrace this new role within multidisciplinary clinics. I believe critical care pharmacists are well positioned to contribute to the care of these now-ambulatory patients within these clinics. Not only do they know the patient and family members from their time in the ICU, but they also know the patients' ICU pharmacotherapies and the associated complications that individual patients may be at risk of experiencing.

What role would be expected from pharmacist involvement in such a clinic? First and foremost would be completing a thorough medication review and reconciliation.[4] A wide variety of medications are prescribed for patients during their ICU admissions, but after discharge from the ICU, many of these medications are no longer indicated. Unfortunately, they are often continued through transitions of care and may also remain in place at the time of hospital discharge. Examples include diuretics initiated to manage fluid overload, β-blockers used to prevent postoperative atrial fibrillation, or antipsychotics to cope with periods of ICU agitation. Participation of the pharmacist at the PICS clinic would allow all current medications to be reviewed, with those no longer necessary tapered and discontinued. The pharmacist would also reassess prior home medications that may not have been reinstituted during hospitalization and would resume those required to avoid further adverse events resulting in visits to the emergency department or readmission.

Interactions with the patient and the family at this ambulatory clinic would increase awareness among all health care professionals of the significant toll that patients face after a prolonged ICU stay. Deconditioning, muscle weakness, respiratory compromise, chronic pain, anxiety, sleeping difficulties and nightmares, and posttraumatic stress disorder are common and can present daily challenges for patients and family members. Management of these broad adverse consequences necessitate a multidisciplinary approach and justify the need for peer support groups in which patients and family members can break their isolation and share common concerns.

The COVID-19 pandemic has made such initiatives more difficult to organize and maintain; however, from the patient's perspective, the isolation resulting from confinement is a compelling reason to continue. I suspect that the growing number of patients known as "COVID long haulers", who suffer a variety of debilitating symptoms months after their initial infection and ICU stay, will become regular attendees at such clinics.

Implementation of PICS clinics, staffed by highly motivated individuals, currently occurs on a very small scale in Canada. Knowledge about patients' clinical outcomes associated with such initiatives is currently limited but is being addressed.[5,6] The involvement of a critical care pharmacist as an essential team member of the PICS clinic is crucial.

The most effective model for post-ICU care needs to be better defined. Through the PICS clinic, we may be closing the loop in terms of meeting the therapeutic needs of critically ill patients. However, until the role of these clinics is

better delineated and they become more widespread, let's make sure that a critical care pharmacist reviews all ICU medication discharge orders and develops a written plan to resume medications that are needed and stop those that are no longer required.

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ON THE FRONT COVER

Palestine Island, Georgian Bay, Ontario

This photograph of the setting sun was captured by Katrina Mulherin with a Canon Rebel XTi during her annual visit to Palestine Island (except for in 2020 and perhaps 2021 due to the pandemic). This location always compels her to run for her camera.

Katrina is currently the Deputy Registrar at the New Brunswick College of Pharmacists. In her spare time, she can be found outside mountain biking, swimming, skiing, skating, or hiking.

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Sommes nous en train de « boucler la boucle » pour répondre aux besoins thérapeutiques des patients des soins intensifs?

par Marc M. Perreault

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Les professionnels de la santé prodiguent des soins remarquables aux patients gravement malades, dès leur admission au service des urgences, jusqu'après leur transfert à l'unité des soins intensifs (USI) et, plus tard, au moment de leur retour dans la communauté. Heureusement pour ces patients, les taux de survie après un passage à l'USI ont augmenté. Nombre de patients souffrent toutefois de complications à court et à long terme à la suite de leur séjour dans une USI. Le syndrome post-soins intensifs (SPSI) se caractérise par une myriade de conséquences physiques, cognitives et psychosociales faisant suite aux maladies graves, qui empêchent les patients de retrouver leur capacité de fonctionnement antérieure, ce qui réduit leur qualité de vie et entraîne des détresses importantes chez les proches aidants[1].

En 2016, le James Lind Alliance Priority Setting Partnership (Royaume-Uni) a reconnu ce syndrome comme l'une des deux priorités de recherche, non seulement pour les cliniciens des USI, mais aussi pour les patients des USI et les familles[2]. Des organismes, comme la Society of Critical Care Medicine, sous l'égide de la Thrive Collaboratives, mettent au point des initiatives visant à aborder le problème de la vie après la sortie de l'USI et à déterminer le modèle de soins le plus efficace pour les patients ayant quitté les soins intensifs[3].

Des cliniques SPSI et des groupes de soutien par des pairs ont été mis en place pour répondre aux besoins des patients qui survivent à une maladie grave, et les pharmaciens commencent à assumer ce nouveau rôle au sein de cliniques multidisciplinaires. Selon moi, les pharmaciens spécialistes œuvrant en soins critiques sont bien placés pour contribuer aux soins de ces patients désormais ambulatoires dans ces cliniques. Ils connaissent non seulement le patient qui a séjourné à l'USI et les membres de sa famille, mais aussi les risques liés aux pharmacothérapies et aux complications, auxquels chaque patient pourrait être exposé.

Que pourrait-on attendre du pharmacien œuvrant dans une telle clinique? D'abord et avant tout, il pourrait effectuer un bilan comparatif exhaustif des médicaments[4]. Ces patients reçoivent une panoplie de médicaments lors de leur admission à l'USI, mais après leur congé, bon nombre de ces médicaments ne sont plus indiqués. Malheureusement, ceux-ci sont encore souvent administrés pendant les transitions de soins et continuent parfois à l'être au moment du congé de l'hôpital. On notera par exemple l'amorce d'un traitement diurétique pour gérer la surcharge liquidienne, l'utilisation d'antagonistes β-adrénergiques pour prévenir la fibrillation auriculaire postopératoire ou l'administration d'antipsychotiques pour faire face aux périodes d'agitation à l'USI. En tant que membre de l'équipe de la clinique de SPSI, le pharmacien pourrait revoir la médication en cours et cesser les médicaments qui ne sont plus indispensables. Il pourrait aussi réévaluer le traitement qui était auparavant suivi à domicile et qui aurait pu être abandonné pendant l'hospitalisation et réinstaurer les médicaments requis afin d'éviter d'autres effets indésirables responsables de visites ou de réadmissions aux urgences.

Les interactions avec le patient et la famille dans cette clinique ambulatoire permettraient de sensibiliser davantage tous les professionnels de la santé au lourd tribut auquel les patients sont soumis après un séjour prolongé dans une USI. Le déconditionnement, la faiblesse musculaire, la déficience respiratoire, les douleurs chroniques, l'anxiété, les troubles du sommeil, les cauchemars et les troubles de stress post-traumatique sont fréquents et peuvent présenter des difficultés au quotidien pour les patients et les membres de leur famille. La gestion de ces conséquences négatives au sens large nécessite une approche multidisciplinaire et justifie le besoin de groupes de soutien par les pairs au sein desquels les patients et les membres des familles peuvent briser leur isolement et partager des préoccupations communes.

La pandémie de COVID-19 a compliqué l'organisation et le maintien de telles initiatives; cependant, du point de vue du patient, l'isolement résultant du confinement est une raison convaincante de les poursuivre. Je soupçonne que le nombre croissant de patients atteints du « Covid long », qui

souffrent de divers symptômes débilitants des mois après leur infection initiale et leur séjour à l'USI, se rendront régulièrement dans de telles cliniques.

La mise en place de cliniques SPSI dotées d'un personnel hautement motivé s'effectue actuellement à très petite échelle au Canada. La connaissance des résultats cliniques des patients associés à de telles initiatives est actuellement limitée, mais cette lacune est en voie de résolution[5,6]. La collaboration d'un pharmacien spécialiste œuvrant en soins critiques au sein de l'équipe de la clinique SPSI est cruciale.

Il faut parvenir à une meilleure définition d'un modèle de soins plus efficace pour traiter les patients qui ont quitté les soins intensifs. Les cliniques SPSI nous permettraient de « boucler la boucle » pour répondre aux besoins thérapeutiques des patients gravement malades. Cependant, en attendant que le rôle de ces cliniques soit mieux cerné et qu'elles deviennent monnaie courante, assurons-nous qu'un pharmacien spécialiste œuvrant en soins critiques examine toutes les ordonnances de médicaments au moment du congé de l'USI, qu'il rédige un plan visant à reprendre ceux qui sont nécessaires et à abandonner ceux qui sont superflus.

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Comparison of Clinical Importance of Drug Interactions Identified by Hospital Pharmacists and a Local Clinical Decision Support System

Louise Lau, Harkaryn Bagri, Michael Legal, and Karen Dahri

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ABSTRACT

Background: Drug–drug interactions (DDIs) may cause adverse drug events, potentially leading to hospital admission. Clinical decision support systems (CDSSs) can improve decision-making by clinicians as well as drug safety. However, previous research has suggested that pharmacists are concerned about discrepancies between CDSSs and common clinical practice in terms of severity ratings and recommended actions for DDIs.

Objectives: The primary objective was to characterize the level of agreement in terms of DDI severity ranking and actions recommended between the local CDSS and pharmacists. The secondary objectives were to determine the level of agreement among pharmacists concerning DDI severity, to determine the influence of the CDSS on clinicians' decision-making, and to review the literature supporting the severity rankings of DDIs identified in the study institution's database.

Methods: This 2-part survey study involved pharmacists and pharmacy residents working at 1 of 4 health organizations within the Lower Mainland Pharmacy Services, British Columbia, who were invited to participate by email. Participants were first asked to rank the severity of 15 drug pairs (representing potential DDIs) on a 5-point Likert scale and to select an action to manage each interaction. Participants were then given the CDSS severity classification for the same 15 pairs and again asked to select an appropriate management action.

Results: Of the estimated 500 eligible pharmacists, a total of 73 pharmacists participated, for a response rate of about 15%. For DDIs of moderate severity, most participants chose to monitor. For severe and contraindicated interactions, the severity ranking and action proposed by participants varied, despite the same severity classification by the CDSS. There was poor agreement among respondents about the severity of the various DDIs. Moreover, knowledge of the CDSS severity ranking did not seem to change the actions proposed by most respondents.

Conclusion: This study identified a gap between the local CDSS and clinical practice. There were discrepancies in terms of severity rankings and actions proposed to manage DDIs, particularly for severe and contraindicated DDIs. The current CDSS did not appear to have a large impact on clinical decision-making, which suggests that it may not be functioning to its full potential.

Keywords: drug–drug interactions, clinical decision support system

RÉSUMÉ

Contexte : Les interactions médicamenteuses (IM) peuvent provoquer des réactions indésirables et entraîner potentiellement une admission à l'hôpital. Les systèmes d'aide à la décision clinique (SADC) peuvent améliorer le processus de prise de décision des cliniciens ainsi que la sécurité de l'usage des médicaments. Cependant, des recherches antérieures mentionnent que les divergences entre les SADC et la pratique clinique courante de l'évaluation de la gravité des IM ainsi que les mesures recommandées préoccupent les pharmaciens.

Objectifs : L'objectif principal consistait à caractériser le degré de concordance entre les SADC locaux et les décisions des pharmaciens en termes d'évaluation du degré de gravité des IM ainsi que des mesures recommandées. Les objectifs secondaires visaient quant à eux à déterminer le degré de concordance entre l'évaluation du degré de gravité de l'IM par les pharmaciens, à définir l'influence des SADC sur le processus de prise de décision des cliniciens et à examiner la documentation appuyant les critères d'évaluation de la gravité d'une IM, déterminés dans la base de données de l'institution où s'est déroulée l'étude.

Méthodes : Cette étude en deux volets, menée au moyen d'un sondage par courriel, impliquait les pharmaciens et les résidents en pharmacie travaillant dans l'un des quatre organismes de santé des Lower Mainland Pharmacy Services en Colombie-Britannique. On a tout d'abord demandé aux participants d'évaluer le degré de gravité de 15 paires de médicaments (représentant des IM potentielles) sur une échelle de Likert à 5 points et de choisir une mesure visant à gérer chaque interaction. Les participants ont ensuite reçu l'évaluation par les SADC de la gravité des mêmes 15 paires; on leur a ensuite demandé de choisir une mesure de gestion appropriée.

Résultats : Sur une estimation de 500 pharmaciens admissibles, 73 ont participé à l'étude et le taux de réponse s'est établi à 15 %. Concernant les IM dont le degré de gravité est modéré, la plupart des participants ont choisi la surveillance. L'évaluation du degré de gravité et les mesures proposées par les participants variaient lorsqu'il s'agissait d'interactions contre-indiquées et graves, et cela malgré une évaluation identique du degré de gravité par les SADC. On a relevé une mauvaise concordance entre les répondants quant à la gravité des diverses IM. De plus, la prise de connaissance par les répondants de l'évaluation du degré de gravité faite par les SADC ne semblait pas modifier les mesures proposées par la plupart d'entre eux.

Conclusion : Cette étude a mis en évidence un fossé entre les SADC locaux et la pratique clinique. On y a relevé des divergences entre l'évaluation du degré de gravité des IM et les mesures proposées pour les gérer, en particulier lorsque les IM sont graves et contre-indiquées. Le SADC utilisé couramment ne semble pas avoir d'impact important sur le processus de décision clinique, ce qui laisse supposer qu'il pourrait ne pas fonctionner au maximum de son potentiel.

Mots-clés : interactions médicamenteuses, système d'aide à la décision clinique

INTRODUCTION

Adverse drug events that arise from drug–drug interactions (DDIs) account for 2% to 3% of hospital admissions, despite most DDIs being predictable.[1] Since there are thousands of DDIs in existence, clinicians often depend on clinical decision support systems (CDSSs) to alert them to potential DDIs.[2] Many different types of CDSS have been designed to alert clinicians to potential DDIs, classify their severity, and suggest appropriate courses of action to reduce the risk of patient harm. A well-designed CDSS can improve decision-making and enhance patient care by making such care safer, more effective, and more efficient.[3] Unfortunately, CDSS use has also given rise to a phenomenon known as "alert fatigue", which results from repetitive exposure to irrelevant alerts.[4,5] Excessive numbers of inappropriate or clinically insignificant interactions are often flagged. Other complaints about CDSSs include lack of patient specificity, lack of clinical relevance, and lack of "actionable" recommendations.[6] Avoiding alert fatigue depends on obtaining pertinent, beneficial information without the burden of irrelevant alerts.

To further complicate matters, there is a lack of standardization of CDSSs because each vendor individualizes its approach to evaluating and classifying DDIs.[7] Therefore, the ability of different CDSSs to alert users to clinically important DDIs varies widely.[8-10] The major challenges of creating a suitable CDSS is knowing what information to transmit and how to display it.[3] Some studies have attempted to modify the program interface to make it more user-friendly (e.g., by simplifying screen displays and reducing the number of pop-ups).[11,12] Others have investigated the key pieces of information and functions that an ideal CDSS should incorporate.[13] In previous work conducted by our research group, pharmacists made various recommendations to increase the utility of the local system, such as colour coding alerts and eliminating duplicate alerts.[6] A common concern among these pharmacists was the substantial discrepancy in level of severity and recommended actions between the local CDSS and what they would do in practice.

To our knowledge, no studies to date have examined the level of agreement between pharmacists and a CDSS for specific drug interactions. Consistency between the CDSS and pharmacists using the system would suggest that the CDSS output is relevant and effective, whereas inconsistencies would indicate that the local CDSS can be further improved. Therefore, the primary objective of this research was to compare the level of agreement in DDI severity rankings and actions recommended between the local CDSS and clinical pharmacists. The secondary objectives were to determine the level of agreement among pharmacists about the severity of various DDIs, to determine the influence of the CDSS on clinical decision-making, and to review the evidence supporting the severity classification of DDIs identified in our database. The ultimate aim of this study was to help identify some of the gaps in creating an ideal CDSS by exploring the utility of the local CDSS with respect to its impact on clinical decision-making and its agreement with pharmacists' knowledge and experience and the current literature.

METHODS

Study Design

This study used survey methodology to examine the level of agreement between pharmacists' clinical decision-making and CDSS recommendations for a prespecified set of drug–drug combinations. The 2-part survey also explored the effect of the CDSS severity ranking and recommendations on pharmacists' decision-making. In addition, a literature review was completed to determine the severity level of the DDIs as listed in other databases and the evidence supporting the DDI severity classification, to assist in verifying the accuracy of the CDSS classification (where the latter is based on DDI information from a database managed by First Databank, August 2018 version).

The Behavioural Research Ethics Board at the University of British Columbia approved the study before recruitment began, and informed consent was obtained from all participants. The overall study period, including survey development and analysis, was November 2018 to June 2019.

Study Population

Pharmacists and pharmacy residents working across 4 health organizations (Fraser Health, Vancouver Coastal Health, Providence Health, and Provincial Health Services Authority) within Lower Mainland Pharmacy Services, in British Columbia, were invited to participate. Pharmacy personnel in the following roles were eligible to participate: dispensary pharmacists, nondispensary pharmacists, and pharmacy residents employed within the health authority. Dispensary pharmacists spend 100% of their shifts in the dispensary and do not work on any hospital ward. Nondispensary pharmacists and pharmacy residents spend at least some portion of their shifts working on a hospital ward. Pharmacists not employed by 1 of the 4 health organizations and pharmacy technicians were excluded from the survey.

Sampling Method

The invitation to complete the survey was sent to potential participants by pharmacy administrative assistants using group email lists. The survey was open for a total of 9 weeks (January 29 to April 6, 2019) and was housed within Qualtrics (Qualtrics Inc, version May 2019), a survey tool provided by the University of British Columbia.

The university's privacy impact assessment process has been applied to the survey tool, to assess the privacy and

security of the university's systems in relation to the tool. Information collected using the survey tool was kept secure by various measures, including data encryption. Participants had the opportunity to enter a draw for one of a pair of $20 gift cards by providing their email address at the end of the survey. To preserve the anonymity of responses, email addresses were unlinked from survey responses during the data analysis and kept in a separate document. Two weeks after the initial invitation, a reminder email was sent to potential participants.

Survey Development

The survey questions were based on a uniquely selected set of 15 DDIs (Figure 1). To generate the list of DDIs, the pharmacy information technology department at Vancouver General Hospital generated a list of DDIs flagged during clinical care in 2016, along with the frequency with which they were flagged and the severity classification category applied by the CDSS. From that list, the 20 most frequently flagged DDIs and those flagged only once were chosen. Duplicate DDIs that involved similar pharmacological mechanisms and had the same severity (e.g., CYP3A4 inhibition of moderate severity) as well as those with similar consequences and the same severity (e.g., QTc prolongation of moderate severity) were excluded. Each remaining DDI was assigned a number, and a final set of the 10 most frequently identified and 5 least frequently identified unique DDIs were selected by means of a random number generator. A larger number of DDIs from the most flagged category was chosen to reflect the DDIs most often encountered and likely contributing to alert fatigue, whereas a small sample of the least flagged DDIs was included with the aim of avoiding any potential bias because of participants already knowing the severity of DDIs that are commonly seen in practice. Among the 15 DDIs selected, 8 were of moderate severity, 5 were severe, and 2 were contraindicated, according to the CDSS severity ranking. The DDI selection process was presented to 10 relevant stakeholders (pharmacy residents and pharmacists with different years of experience, selected through convenience sampling) for further refinement. In addition, another group of 4 pharmacists, also selected through convenience sampling, reviewed the chosen DDIs and trialled the survey before it was finalized.

The survey consisted of 2 parts (survey questions available from the corresponding author by request). First, the participants were asked to rank the severity of each prespecified DDI on a Likert-type scale of 1 to 5, where 1 represented interactions of no consequence and 5 represented combinations that were contraindicated. Nondispensary pharmacists and pharmacy residents responding to the survey were asked to select 1 of 3 actions to manage the interaction, according to what they would do in practice: take no action; order appropriate laboratory tests to monitor for drug interaction and/or assess the patient for suitable monitoring; or contact the prescriber to discuss the interaction and/or propose an alternative recommendation. Dispensary pharmacists responding to the survey were given a related but somewhat different set of options because of differences in their scope of practice. These pharmacists had the following 3 options: take no action, flag the interaction for the clinical pharmacist to follow up the next day, or immediately contact the clinical pharmacist or the prescriber to discuss the interaction or make an alternative recommendation.

The second part of the survey was administered immediately after the first. Participants were presented with the same 15 DDIs, along with the severity level of each DDI as ranked by the CDSS and the action recommended by the CDSS. The CDSS recommendations were as followed: for mild interactions, monitor and take no action; for moderate interactions, assess the risk to the patient and take action as needed; for severe interactions, take action as required to reduce the risk of severe adverse interactions; and for interactions that were contraindicated, avoid administering the drug combination. The participants were then asked

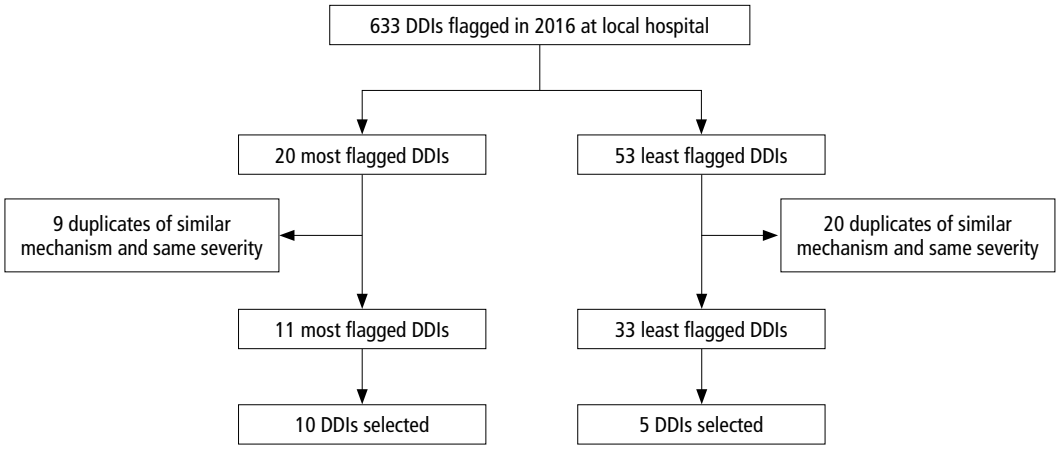

FIGURE 1. Selection of drug–drug interactions (DDIs) for the survey.

to again select how they would manage the interaction, without having access to their responses in the first part of the survey, to determine the impact of the CDSS on pharmacists' decision-making. In addition, they were asked to rate, on a scale of 0 (none) to 5 (extremely large), how seeing the severity ranking of the CDSS altered their approach. Finally, participants were asked to list, in an open-text field, other factors or assumptions they made while completing the survey.

Literature Review

A literature search was conducted for the prespecified DDIs to examine the evidence related to each DDI and the severity level assigned by the CDSS. First, a commercial database, *Lexicomp® Drug Interactions* (UpToDate, Inc, © 2019) was viewed to determine the severity of the interaction. A literature search was then conducted within MEDLINE Ovid (1946 to November 2019) and Embase Ovid (1974 to November 2019) using search terms that included the specific drug pair involved (e.g., "quetiapine" and "citalopram") and the term "interaction" or "adverse effects". The references used in the commercial database were also reviewed for additional information. The literature search was completed by one of the co-investigators (L.L.) and verified by another researcher on the team (K.D.).

Statistical Analysis

Descriptive statistics were used to report baseline characteristics and to assess the primary and secondary outcomes of the study. A Fleiss kappa value was calculated to determine the inter-rater agreement among participants on the overall severity ranking and actions proposed for each DDI. The respective totals for each severity category and each action category for each DDI were summed manually and entered into a Fleiss kappa calculator (http://justusrandolph.net/kappa/). The actions proposed by the dispensary pharmacists were excluded from calculation of the Fleiss kappa, because the options presented to them were different from the options presented to nondispensary pharmacists and pharmacy residents.

RESULTS

Demographic Characteristics

An estimated 500 pharmacists and pharmacy residents were invited to participate, and 73 fully completed responses were collected (response rate about 15%), 51 (70%) from ward/dispensary pharmacists, 4 (5%) from dispensary-only pharmacists, and 18 (25%) from pharmacy residents.

Part 1: Respondent Ranking and Proposed Actions

DDIs ranked as "moderate" by the CDSS were most commonly ranked by participants as 2 or 3 out of 5 on the Likert-type scale (Table 1). There was greater variability in ranking for both the severe and the contraindicated DDIs. Two of the severe DDIs (clozapine–rifampin and mebendazole–metronidazole) were ranked as 4 or 5, whereas the other severe DDIs (citalopram–quetiapine, clozapine–lorazepam, fluoxetine–metoclopramide) were commonly ranked as 2 or 3, despite their classification as "severe" by the CDSS. A similar discrepancy was found for the 2 contraindicated DDIs: the carbamazepine–voriconazole combination was considered more severe than clopidogrel–pioglitazone by many of the participants. Overall, the inter-rater agreement for severity ranking of all DDIs, among nondispensary pharmacists and pharmacy residents, was 35%.

In terms of proposed actions, most participants selected "monitor" to manage 11 of the DDIs, which were most frequently ranked as either 2 or 3 on the severity scale. Among the remaining DDIs, "contact prescriber" was the most frequently selected option for 3 of the DDIs (2 classified as severe and 1 contraindicated by the CDSS). These 3 DDIs were most commonly ranked as 4 or 5 on the severity scale by participants. There was only 1 DDI, involving paroxetine and pravastatin, for which the most frequently selected response was "no action". This DDI was ranked as having moderate severity by the CDSS and was most commonly ranked as 2 on the severity scale by participants. The overall inter-rater agreement in terms of actions proposed, among nondispensary pharmacists and pharmacy residents, was 57%.

Part 2: Pharmacists' Decision-Making Based on CDSS Information

Table 2 shows the proportions of participants who did and did not change the action proposed for each DDI after learning the CDSS severity classification and recommendation. Most participants did not change their response with this additional information. More specifically, on average, only 15.8% of participants proposed a different action to manage the DDI in part 2 of the survey. Interestingly, when asked "on a scale of 0 (none) to 5 (extremely large), to what degree did seeing the severity ranking by the computer system [CDSS] alter your approach", the largest proportion of participants selected 2 (30.1%) and 3 (26.0%), with only 4 participants selecting 0 (5.5%). As such, it appears that participants felt the CDSS had some degree of influence on their actions, although this was not entirely reflected in the comparison of responses shown in Table 2.

Literature Review

For each DDI included in this study, the level of severity identified by the tertiary reference (*Lexicomp Drug Interactions* database) was either moderate or major (Table 3). Even when differences in terminology were taken into account, there was a lack of agreement in severity classification between the CDSS and the tertiary reference (Table 3). For example, for the 8 DDIs categorized as moderate by the

TABLE 1. Respondents' Severity Ranking of Drug–Drug Interactions and Proposed Actions

Combination[a]	Respondent's Severity Ranking[b]; % of Respondents[c] (*n* = 73)					Respondent's Proposed Action; % of Respondents[c] (*n* = 73)		
	1	2	3	4	5	No Action	Monitor	Contact
Moderate								
ASA and prednisone	20.5	**43.8**	30.2	5.5	0.0	40.6	**55.1**	4.3
Citalopram and trazodone	12.3	**42.5**	36.9	8.3	0.0	31.9	**63.8**	4.3
Clopidogrel and warfarin	6.8	17.8	**38.4**	35.6	1.4	11.6	**73.9**	14.5
Furosemide and ramipril	32.9	**39.7**	26.0	1.4	0.0	24.6	**75.4**	0.0
Glyburide and propranolol	19.2	**49.3**	26.0	4.1	1.4	30.4	**60.9**	8.7
Hydromorphone and prochlorperazine	21.9	**41.1**	32.9	4.1	0.0	42.0	**55.1**	2.9
Paroxetine and pravastatin	27.4	**50.7**	20.5	1.4	0.0	**47.8**	43.5	8.7
Ramipril and potassium chloride (PO)	4.1	**47.9**	42.5	5.5	0.0	7.2	**91.3**	1.4
Severe								
Citalopram and quetiapine	6.8	**43.8**	**43.8**	4.1	1.4	23.2	**73.9**	2.9
Clozapine and lorazepam	15.1	23.3	**35.6**	24.7	1.4	26.1	**55.1**	18.8
Clozapine and rifampin	1.4	1.4	12.3	**45.2**	39.7	1.4	26.1	**72.5**
Fluoxetine and metoclopramide	9.6	28.8	**45.2**	15.1	1.4	21.7	**59.4**	18.8
Mebendazole and metronidazole	5.5	2.7	8.2	19.2	**64.4**	7.2	8.7	**84.1**
Contraindicated								
Carbamazepine and voriconazole	0.0	1.4	6.8	31.5	**60.3**	0.0	17.4	**82.6**
Clopidogrel and pioglitazone (>15 mg)	17.8	**34.2**	31.5	12.3	4.1	27.5	**56.5**	15.9

ASA = acetylsalicylic acid.
[a]Categorized according to severity of interactions, as per the local clinical decision support system.
[b]Likert-type scale, ranging from 1 (no consequence) to 5 (combination contraindicated).
[c]For each drug combination, the most common response is highlighted in bold.

CDSS, the tertiary reference categorized 5 as "moderate" and 3 as "major". Similar discrepancies occurred for the DDIs categorized by the CDSS as severe and contraindicated, further highlighting the lack of consistency among various databases.

In terms of the primary evidence discovered in the literature search, the best evidence for most of the DDIs was often of low quality (i.e., cohort studies and case reports). Furthermore, not all of the studies identified were specific to the drug pair involved; instead, many were based on drugs from the same class.

DISCUSSION

A previous study by our research group showed that pharmacists believed there was a discrepancy between the local CDSS and what they would do in practice in terms of DDI severity classification; they also believed that the current system was performing suboptimally in the identification of clinically important DDIs.[6] An effective CDSS should provide clinicians with useful information and recommendations that are applicable to practice. As such, a CDSS that is performing optimally could be expected to make recommendations that are aligned with how pharmacists manage DDIs in practice. The results of the current survey study highlight inconsistencies in severity rankings of DDIs between the CDSS and practising pharmacists and also differences in the evaluation of DDIs among different pharmacists. Such results may stem from the lack of strong evidence supporting the severity rankings and management of DDIs, as was found in our literature search. Overall, there is a limited body of evidence to guide the best course of action in specific clinical situations.

DDIs are prevalent even in highly monitored settings, such as hospitals. One meta-analysis showed that 33% of general medicine patients and 67% of intensive care patients experienced a potential DDI while in hospital.[14] The larger the number of drugs that a patient is receiving, the greater the likelihood of potential DDIs. Adverse drug reactions are the most concerning outcomes of DDIs, and such reactions are well documented in literature. In a single-hospital retrospective study, 63% of the study population had experienced at least 1 DDI.[15] More importantly, the authors found that the presence of 3 or more interactions and the duration of exposure to the interaction were independently associated with mortality. Given the prevalence of DDIs seen in the hospital setting and their potential consequences, there is a need for better evidence and a clearer decision framework within the CDSS to help guide clinicians in optimizing patient care.

One notable result from this survey was that the severity rankings by participants were higher on the Likert scale, at

TABLE 2. Comparison of Action Proposed[a] to Manage DDIs before and after Learning the Relevant CDSS Severity Ranking and Recommendation

Combination[b]	Influence of CDSS on Response; % of Respondents (n = 73)	
	Changed Response	Did Not Change Response
Moderate		
ASA and prednisone	15.9	84.1
Citalopram and trazodone	15.9	84.1
Clopidogrel and warfarin	13.0	87.0
Furosemide and ramipril	13.0	87.0
Glyburide and propranolol	15.9	84.1
Hydromorphone and prochlorperazine	15.9	84.1
Paroxetine and pravastatin	29.0	71.0
Ramipril and potassium chloride (PO)	13.0	87.0
Severe		
Citalopram and quetiapine	13.0	87.0
Clozapine and lorazepam	17.4	82.6
Clozapine and rifampin	11.6	88.4
Fluoxetine and metoclopramide	23.2	76.8
Mebendazole and metronidazole	5.8	94.2
Contraindicated		
Carbamazepine and voriconazole	10.1	89.9
Clopidogrel and pioglitazone (>15 mg)	24.6	75.4

ASA = acetylsalicylic acid, DDI = drug–drug interaction, CDSS = clinical decision support system.

[a]The choices of management options for nondispensary pharmacists and pharmacy residents were no action, monitor, or contact prescriber; the choices of management options for dispensary pharmacists were no action, flag clinical pharmacist, or immediately contact clinical pharmacist or prescriber. The data presented in this table are based on whether, for a particular DDI, the respondent's proposed action to manage the DDI changed between part 1 and part 2 of the survey, where part 2 entailed the respondent having knowledge of the CDSS recommended action.

[b]Categorized according to severity of interactions, as per the local CDSS.

4 or 5, for DDIs that involved antimicrobials: carbamazepine–voriconazole (contraindicated), clozapine–rifampin (severe), and mebendazole–metronidazole (severe). Moreover, for all 3 of these interactions, most of the participants stated that they would contact the prescriber rather than monitor or take no action. These results suggest that the acuity of the clinical situation often influences a pharmacist's decision in the management of DDI. Perhaps a useful approach in designing a CDSS would be to ensure that the system takes into consideration various patient-specific factors when making recommendations for its users, rather than simply classifying each DDI by severity. For example, for DDIs that might increase the risk of bleeding, factors such as the patient's age, history of bleeding, and hemoglobin level could be taken into consideration. An algorithm approach that incorporates patient-specific parameters can help to better stratify individualized risks and could potentially be more applicable in practice. Moreover, one of the most frequent actions proposed by participants in this study was to "monitor". A useful feature to increase the utility of a CDSS would be to outline specific monitoring parameters for each DDI.

This study had a few limitations related to the survey design. First, participants were asked to use a Likert-type scale of 1 (interaction of no consequence) to 5 (combination contraindicated) to rank the severity of each DDI, rather than terminology such as "mild", "moderate", "severe", or "contraindicated", as used by the CDSS. Our intention was to avoid potential bias, given that participants might have been familiar with the CDSS ranking before answering the survey, and this familiarity might have influenced their responses. The challenge of using a Likert-type scale in this survey was the inability to reconcile and quantify the level of agreement between the CDSS and participants. If the survey were to be conducted at other hospitals that use different CDSSs with different terminology and classifications, the results might be different. In addition, the Likert scale was not validated, which limits the reliability of the survey responses.

Another limitation to the survey design was administration of part 2 immediately after part 1. The participants might have recalled their responses from the first part of the survey, which could have affected their responses in the second part, resulting in an underestimate of the impact of the CDSS on clinical decision-making. Furthermore, no clinical context was provided, so responses might have varied depending on the area of practice and expertise of the individual participants. The dose, duration, and frequency for each DDI were also not provided to participants, because the CDSS often does not take into consideration the dosing regimens. For almost all DDIs in the survey, the CDSS severity ranking would be the same, regardless of dose, duration, or frequency. One exception is the DDI involving clopidogrel and pioglitazone, which is categorized as contraindicated if the dose of pioglitazone is greater than 15 mg. In the open-text field at the end of the survey, a number of participants expressed that frequency, dose, and duration of therapy would greatly affect their approach to managing each DDI. For consistency, we did not provide dosing information for any of the DDIs. Therefore, the results may vary depending on assumptions about dosing regimens that participants made while completing the survey. Our rationale for this aspect of survey design was to allow our results to be generalizable and to reflect the reality of the CDSS, which does not take into consideration the clinical context, dosing regimen, or patient-specific factors.

TABLE 3. Results of Literature Evidence Supporting Selected Drug–Drug Interactions

Combination	Ranking as per CDSS	Ranking as per Tertiary Reference[a]	Best Evidence[b]
ASA and prednisone	Moderate	Moderate	5A
Citalopram and trazodone	Moderate	Major	5B
Clopidogrel and warfarin	Moderate	Major	3B
Furosemide and ramipril	Moderate	Moderate	3B
Glyburide and propranolol	Moderate	Moderate	3B
Hydromorphone and prochlorperazine	Moderate	Major	3B
Paroxetine and pravastatin	Moderate	Moderate	3A
Ramipril and potassium chloride (PO)	Moderate	Moderate	3B
Citalopram and quetiapine	Severe	Moderate	3B
Clozapine and lorazepam	Severe	Major	5A
Clozapine and rifampin	Severe	Major	5A
Fluoxetine and metoclopramide	Severe	Moderate	6A
Mebendazole and metronidazole	Severe	Major	4A
Carbamazepine and voriconazole	Contraindicated	Major	5A
Clopidogrel and pioglitazone (>15 mg)	Contraindicated	Moderate	6A

ASA = acetylsalicylic acid, CDSS = clinical decision support system.
[a]*Lexicomp® Drug Interactions* database (2019).
[b]Evidence types (not all types occurred in this study): 1 = systematic review, 2 = randomized controlled trial, 3 = cohort study, 4 = case-controlled study, 5 = case report, 6 = pharmacokinetic study, 7 = animal study, A = involves the listed drug pair, B = involves drugs in the same class(es) as the listed drug pair.

A final major limitation of the study was the low response rate. An estimated 15% of survey recipients participated; therefore, the responses may reflect only a portion of the pharmacists who practise in our region.

CONCLUSION

A CDSS that is applicable in practice has the potential to be an invaluable tool for improving patient safety and reducing the workload of clinicians. However, there remain challenges in identifying and addressing gaps between the CDSS currently in use at the study institution and one that is operating at its full potential. The purpose of this study was to determine if various DDIs and their respective severity classifications in the CDSS aligned with the assessment of practising pharmacists. We identified a gap between the local CDSS and current clinical practice. Furthermore, the current CDSS did not have a large impact on clinical decision-making. The consequences of unidentified or improperly managed DDIs emphasize the need for an effective and applicable CDSS. Further research focused on determining and implementing approaches to improving the CDSS to enhance patient outcomes is warranted.

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Patient Factors Associated with Pharmaceutical Interventions for Inpatients at a Brazilian Teaching Hospital

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ABSTRACT

Background: Pharmaceutical interventions aim to correct or prevent a drug-related problem (DRP) that might lead to negative clinical consequences and increase health care costs.

Objective: To identify variables associated with the provision of pharmaceutical interventions by clinical pharmacists during hospitalization.

Methods: In this retrospective cohort study, adult inpatients of the medical ward of the University Hospital of the University of São Paulo in São Paulo, Brazil, were followed from admission to discharge. Logistic regression models were used to evaluate the association between occurrence of at least 1 pharmaceutical intervention and the following baseline characteristics: sex, age, Charlson comorbidity index, renal failure, electrolyte imbalance, hemoglobin, platelet count, and use of a nasoenteric tube, as well as the number, second-level Anatomical Therapeutic Chemical (ATC) code, and administration route of prescribed medications.

Results: A total of 148 patients were included in the study, of whom 75 (50.7%) were men. The mean age was 62.8 (95% confidence interval [CI] 59.9–65.8) years, and the mean length of the hospital stay was 10.7 (95% CI 8.4–13.1) days. Analgesics (ATC code N02), the most common type of medication, were prescribed to 144 (97.3%) of the patients. Pharmaceutical interventions were performed for only 49 (33.1%) of the patients. One out of every 4 of these interventions was intended to obtain information not provided in the prescription, to allow the prescription to be completed and dispensing to proceed. According to the multivariate analysis, the odds ratio (OR) of occurrence of at least 1 pharmaceutical intervention increased for patients with electrolyte imbalance (OR 2.68, 95% CI 1.09–6.63; $p = 0.033$), patients using 5 to 8 medications (OR 8.73, 95% CI 1.07–71.36; $p = 0.043$), patients using 9 or more medications (OR 10.39, 95% CI 1.28–84.05; $p = 0.028$), and patients using at least 1 systemic antibacterial (ATC code J01; OR 2.76, 95% CI 1.30–5.84; $p = 0.008$).

Conclusions: The findings of this study could allow the identification, at the time of admission and possibly before the occurrence of a DRP, of patients at higher risk of requiring a pharmaceutical intervention later during their hospital stay. To optimize patient care, clinical pharmacists should closely follow inpatients with electrolyte imbalance, polypharmacy, and/or use of systemic antibacterials.

Keywords: anti-infective agents, drug-related side effects, adverse reactions, patient safety, medication therapy management, pharmaceutical services

RÉSUMÉ

Contexte : Les interventions pharmaceutiques visent à corriger ou à prévenir un problème lié aux drogues (PLD), qui pourrait entraîner des conséquences cliniques négatives et accroître les coûts des soins de santé.

Objectif : Déterminer les variables associées aux interventions pharmaceutiques des pharmaciens cliniques lors d'une hospitalisation.

Méthodes : Dans cette étude de cohorte rétrospective, les patients adultes hospitalisés au Service de médecine de l'Hôpital universitaire de São Paulo au Brésil ont été suivis dès leur admission et jusqu'à leur sortie. Des modèles de régression logistique ont été utilisés pour évaluer l'association entre au moins une intervention pharmaceutique et les caractéristiques de base suivantes : sexe, âge, indice de comorbidité de Charlson, insuffisance rénale, déséquilibre électrolytique, hémoglobine, numération plaquettaire et utilisation d'un tube nasoentérique, et l'ensemble du groupe a subi une évaluation selon le nombre de médicaments prescrits au deuxième niveau des classifications du Système de classification anatomique thérapeutique chimique (ATC) et leur voie d'administration.

Résultats : Cent-quarante-huit (148) patients ont été inclus dans cette étude; 75 d'entre eux (50,7 %) étaient des hommes. L'âge moyen était de 62,8 ans (95 % intervalle de confiance [IC] 59,9 - 65,8), et la durée moyenne du séjour à l'hôpital était de 10,7 jours (95 % IC 8,4 – 13,1). Des analgésiques (code ATC N02), type de médicament le plus répandu, ont été prescrits à 144 patients (97,3 %). Seuls 49 patients (33,1 %) ont fait l'objet d'une intervention pharmaceutique. Une de ces interventions sur quatre avait pour but d'obtenir des informations absentes dans la prescription mais indispensables à l'obtention de la validation de la prescription et de l'autorisation de distribution des médicaments. Selon l'analyse multivariée, le rapport de cotes (RC) de la nécessité d'au moins une intervention pharmaceutique augmentait pour les patients ayant un déséquilibre électrolytique (RC 2,68, 95 % IC 1,09 - 6,63; $p = 0,033$), les patients prenant entre cinq et huit médicaments (RC 8,73, 95 % IC 1,07 - 71,36; $p = 0,043$), les patients prenant au moins neuf médicaments (RC 10,39, 95 % IC 1,28 - 84,05; $p = 0,028$) et ceux utilisant au moins un antibactérien systémique (code ATC J01; RC 2,76, 95 % IC 1,30–5,84; $p = 0,008$).

Conclusions : Les résultats de cette étude pourraient permettre d'identifier, à l'admission à l'hôpital et probablement avant l'apparition d'un PLD, les patients présentant des risques plus élevés, qui pourraient nécessiter une intervention pharmaceutique plus tard lors de leur séjour. Pour optimiser les soins aux patients, les pharmaciens cliniques doivent suivre étroitement les patients hospitalisés ayant un déséquilibre électrolytique, ceux qui nécessitent une polypharmacie et ceux qui utilisent des antibactériens systémiques.

Mots-clés : agents anti-infectieux, effets secondaires liés aux drogues, effets indésirables, sécurité du patient, gestion de la pharmacopée, services pharmaceutiques

INTRODUCTION

A pharmaceutical intervention is defined as an action that could be taken at the prescriber, patient, or medication-use level, aimed at preventing or correcting a drug-related problem (DRP) and thus contributing to the optimization of pharmacotherapy outcomes.[1] DRPs are events involving drug therapy with the potential to negatively affect the desired health outcome.[2] This definition encompasses medication errors, adverse drug reactions, and adverse drug events (ADEs).[3]

The negative effects of DRPs on health outcomes have been previously reported. For example, a meta-analysis showed that 10% of hospital admissions among older adults were due to adverse drug reactions.[4] A German prospective observational study reported that 16.2% of hospital admissions were related to 1 or more community-acquired ADEs.[5] Furthermore, older adults with ADEs during hospitalization had 25% and 9% higher odds of readmission and in-hospital mortality, respectively, relative to those without ADEs. Hospitalization with an ADE was associated with a 2.2-day increase in length of stay, at an additional cost of US$3782.[6] In the United Kingdom, it has been estimated that medication errors cause 12 000 deaths per year, contributing to an additional £0.75 billion to £1.5 billion in health care expenditures.[7] A systematic review, including studies conducted in primary care and hospital settings, found mean costs per medication error ranging from €2.58 to €111 727.08.[8]

DRPs may be due to factors such as previous or current diseases, decreased renal function, advanced age, sex, body weight and fat distribution, allergy history, and genetic predisposition.[4,9,10] They can also be related to social factors such as alcohol drinking, race or ethnicity, and smoking.[10] In addition, there are some drug-related factors that could increase the risk of a DRP, such as the IV route of drug administration, the use of 5 or more medications, and drug dose and frequency.[9,10] Predicting the risks of ADEs can facilitate pharmacovigilance and targeted interventions for high-risk inpatients by the multidisciplinary health care team.[11,12] Interventions to reduce medication errors and improve the quality of care in the health sector are required to increase effectiveness from both clinical and cost perspectives.[8]

Given that DRPs can substantially affect the health care system, there is a clear need for their prevention in clinical practice.[13] Accordingly, pharmaceutical strategies to prevent DRPs include the identification and reporting of medication errors and adverse drug reactions, monitoring of drug interactions, dose individualization for patients with renal or hepatic dysfunction, and the investigation of IV compatibility and dilution stability of drugs.[14]

Given the clinical and economic impacts of DRPs, the aim of this study was to identify patient characteristics associated with the occurrence of at least 1 pharmaceutical intervention during the hospital stay.

METHODS

A retrospective cohort study was carried out using data for inpatients of the medical ward of the University Hospital of the University of São Paulo, a 196-bed secondary level public teaching hospital in São Paulo, Brazil, that offers medium-complexity clinical services to students and staff, as well as to the local community. The medical ward has 38 beds and a clinical staff of 6 physicians, 13 nurses, and 2 clinical pharmacists, namely 1 clinical pharmacology specialist, who is responsible for the ward and mentorship of the residency program, and 1 resident pharmacist. In this ward, the clinical pharmacists perform thorough follow-up of all inpatients, from admission to discharge. The hospital's pharmacy team is responsible for preventing, identifying, and resolving DRPs through the design and implementation of pharmaceutical interventions, which are documented in a pharmacy database on a daily basis. The main activities of this team include medication reconciliation, assessment of patients' needs and the effectiveness and safety of drug therapy, screening of medical prescriptions, evaluation of drug interactions and physicochemical compatibility, determination of the adequacy of pharmaceutical forms, monitoring of serum levels of drugs, participation in medical rounds, pharmacovigilance, discharge guidance, and assistance to the multidisciplinary team.

Patients aged 18 years or older who were admitted to the medical ward from October 1 to November 30, 2018, and not released within the first 24 hours, were included in this study. Patients receiving palliative care, those who died, and those who were transferred before occurrence of the first pharmaceutical intervention were excluded. Prescribed medications and clinical and laboratory data recorded in the first 24 hours of admission (baseline) were collected from each patient's medical record (hard copy) by one of the authors (D.B.F.). All pharmaceutical interventions performed during the hospitalization period, and the corresponding acceptance ratio (rate rate at which recommendations for a pharmaceutical intervention were accepted by the health care team), were obtained from the pharmacy database (Excel, Microsoft Corporation). Information about pharmaceutical interventions was paired with patient characteristics by means of each patient's identification number.

Data for the study, which were limited to patients' characteristics, were collected using a form designed specifically for this purpose. The following definitions were used. Renal failure was defined as creatinine clearance less than 30 mL/min/1.73m^2, as estimated by the Chronic Kidney Disease Epidemiology Collaboration formula.[15] Electrolyte imbalance was defined as at least one of the following:

hyponatremia (Na^{2+} < 136 mEq/L), hypernatremia (Na^{2+} > 145 mEq/L), hypokalemia (K^+ < 3.5 mEq/L), or hyperkalemia (K^+ > 5.1 mEq/L). Hemoglobin reference values were 13.5 to 17.5 g/dL (135 to 175 g/L) for men and 12.0 to 16.0 g/dL (120 to 160 g/L) for women. For platelet count, the reference value was 150 000 to 400 000/µL (140 to 400 × 10^9/L).

Medications were categorized according to second-level codes of the Anatomical Therapeutic Chemical (ATC) classification system[16]; patients were then dichotomized as users or non-users of medications defined by each code. Only the most frequently prescribed ATC codes were used to calculate the regression models.

Each pharmaceutical intervention was designed to resolve or correct one or more DRPs, and these interventions were categorized according to the DRP they were most likely intended to resolve. The Pharmaceutical Care Network Europe (PCNE) classification scheme for DRP causes (version 9.00) was used for this purpose.[2] Characteristics not related to patients that might also affect the occurrence of a pharmaceutical intervention, such as factors related to the pharmacists performing the intervention, were not collected or evaluated.

Statistical analyses were carried out using SPSS software, version 22.0 (IBM Corporation). Categorical data were described as absolute and relative counts. Seventeen logistic regression models were calculated to estimate the dependent variable, which was the occurrence of at least 1 pharmaceutical intervention during the hospitalization period (as a dichotomous variable, relative to the absence of such an intervention). The independent variables were sex (male, female); age (< 65 years, ≥ 65 years); Charlson comorbidity index[17] (0–3, ≥ 4); renal failure (no, yes); electrolyte imbalance (no, yes); hemoglobin (within reference range, altered); platelet count (within reference range, altered); use of nasoenteric feeding tube (no, yes); number of prescribed medications (< 5, 5–8, ≥ 9); medications from ATC codes B01 (non-user, user), A03 (non-user, user), A10 (non-user, user), A04 (non-user, user), C10 (non-user, user), and J01 (non-user, user); and use of at least 1 IV medication (no, yes). Variables with p values less than 0.10 in univariate models were included in the multivariate analysis in a single block. Pairs of variables were checked for associations by means of χ^2 tests before the multivariate analyses were run, to avoid collinearity; out of 2 significantly associated variables, only the variable with the most clinical and conceptual relevance was included in the analysis. The level of significance was set at $\alpha = 5\%$, $p < 0.05$.

Regarding the number of prescribed medications, we obtained the most effective cut-off point to distinguish between admissions with and without a pharmaceutical intervention by analysis of the receiver operating characteristic curve. Since the most effective cut-off was a considerably low value, we created another cut-off using the median of the remaining higher values. Medians of age and Charlson comorbidity index were used to dichotomize these values, because the p values related to area under the receiver operating characteristic curve were not significant.

Post hoc analyses were performed to verify the association between the variables retained in the multivariate regression model and the types of pharmaceutical intervention, by means of likelihood ratio χ^2 tests. Since each PCNE code is encompassed in a primary domain, we considered these as the pharmaceutical intervention types.

The research ethics committees of the University Hospital (ID 3422497) and the School of Pharmaceutical Sciences (ID 3358233) of the University of São Paulo approved this retrospective study. These committees waived the need for informed consent from patients.

RESULTS

Overall, 153 patients were eligible for the study, of whom 5 (3.3%) were excluded because they died before a pharmaceutical intervention occurred. The analyses therefore included 148 patients, with 128 (86.5%) referred from primary care and 20 (13.5%) admitted in the emergency unit. The mean age was 62.8 (95% confidence interval [CI] 59.9–65.8) years, and 75 patients (50.7%) were men. Half of the patients (n = 74) were 65 years of age or older. The hospitalization period ranged from 1 to 102 days, with a mean of 10.7 (95% CI 8.4–13.1) days.

Pharmacists proposed a total of 124 pharmaceutical interventions for 49 (33.1%) of the patients (Table 1). A total of 120 (96.8%) of these interventions were accepted by the medical team. Twenty (40.8%) patients had 1 intervention, 15 (30.6%) had 2 interventions, and 14 (28.6%) had 3 or more interventions. The most common interventions were intended to resolve DRPs related to the logistics of the prescribing and dispensing process. Of note, 1 of every 4 pharmaceutical interventions was intended to obtain information not provided in the prescription, to allow the prescription to be completed and dispensing to proceed.

Of the 40 second-level ATC codes identified, analgesics (N02) were the most frequently prescribed (97.3% of patients), followed by antithrombotics (B01; 68.2%) and drugs for functional gastrointestinal disorders (A03; 52.7%) (Table 2).

Both univariate and multivariate analysis (Table 3) revealed 3 patient characteristics at the time of admission that increased the odds of at least 1 pharmaceutical intervention during the hospital admission: presence of electrolyte imbalance, more than 4 prescribed medications, and prescription of at least 1 antibacterial for systemic use (ATC code J01).

Given that almost every patient had a prescription for a medication with ATC code N02 (analgesics), mainly represented by non-opioid analgesics such as dipyrone, this

TABLE 1. Reasons for Pharmaceutical Interventions during Hospital Admission, According to PCNE Classification Scheme of DRP Causes (version 9.00),[2] Grouped by Primary Domain

Primary Domain and Reason for Intervention	No. (%) of Interventions (n = 124)	
Dispensing		
Necessary information not provided	31	(25.0)
Prescribed drug not available	8	(6.5)
Dose selection		
Drug dose too high	17	(13.7)
Dosage regimen too frequent	7	(5.6)
Drug dose too low	6	(4.8)
Dosage regimen not frequent enough	3	(2.4)
Instructions for dose timing wrong, unclear, or missing	1	(0.8)
Drug selection		
No or incomplete drug treatment in spite of existing indication	14	(11.3)
No indication for drug	8	(6.5)
Inappropriate drug according to guidelines or formulary	2	(1.6)
Too many drugs prescribed for indication	1	(0.8)
Drug form		
Inappropriate drug form	12	(9.7)
Drug-use process		
Inappropriate timing of administration or dosing intervals	10	(8.1)
Other		
No or inappropriate outcome monitoring	3	(2.4)
Patient transfer–related		
No medication reconciliation at transfer	1	(0.8)

DRP = drug-related problem, PCNE = Pharmaceutical Care Network Europe.

variable was not considered for the regression analysis. The ATC code C10 (lipid-modifying agents) was not included in model 17 (multivariate) because it was associated with ATC code J01 (antibacterials for systemic use, $p = 0.004$).

Post hoc analyses revealed that the types of pharmaceutical intervention (as primary domains) were evenly distributed across the categories for electrolyte imbalance ($p = 0.18$), number of prescribed medications ($p = 0.35$), and antibacterials for systemic use ($p = 0.053$). The primary domains are listed in Table 1.

DISCUSSION

In this study, we identified several characteristics of patients that might contribute to the occurrence of a pharmaceutical intervention. Given that such interventions are intended to correct or prevent DRPs, this finding may allow identification of patients at increased risk of DRPs. Hence, the

TABLE 2. Frequency of Medications Prescribed at Baseline, Categorized by Second-Level ATC Codes

ATC Category	ATC Code	No. (%) of Patients (n = 148)	
Analgesics	N02	144	(97.3)
Antithrombotic agents	B01	101	(68.2)
Drugs for functional gastrointestinal disorders	A03	78	(52.7)
Drugs used in diabetes	A10	66	(44.6)
Antiemetics and antinauseants	A04	58	(39.2)
Lipid-modifying agents	C10	58	(39.2)
Antibacterials for systemic use	J01	57	(38.5)
Drugs for acid-related disorders	A02	56	(37.8)
Diuretics	C03	46	(31.1)
β-Blocking agents	C07	39	(26.4)
Agents acting on the renin-angiotensin system	C09	37	(25.0)
Psycholeptics	N05	30	(20.3)
Drugs for obstructive airway diseases	R03	22	(14.9)
Cardiac therapy	C01	22	(14.9)
Vitamins	A11	22	(14.9)
Corticosteroids for systemic use	H02	21	(14.2)
Drugs for constipation	A06	20	(13.5)
Antiepileptics	N03	20	(13.5)
Antihypertensives	C02	14	(9.5)
Calcium-channel blockers	C08	13	(8.8)
Thyroid therapy	H03	13	(8.8)
Psychoanaleptics	N06	12	(8.1)
Antianemic preparations	B03	10	(6.8)
Other nervous system drugs	N07	10	(6.8)
Antihistamines for systemic use	R06	10	(6.8)
Blood substitutes and perfusion solutions	B05	6	(4.1)
Mineral supplements	A12	4	(2.7)
Urologicals	G04	3	(2.0)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	A07	3	(2.0)
Anthelmintics	P02	3	(2.0)
Antimycobacterials	J04	2	(1.4)
Antimycotics for systemic use	J02	2	(1.4)
Antiprotozoals	P01	2	(1.4)
All other therapeutic products	V03	2	(1.4)
Anti-parkinson drugs	N04	1	(0.7)
Antihemorrhagics	B02	1	(0.7)
Anti-inflammatory and antirheumatic products	M01	1	(0.7)
Muscle relaxants	M03	1	(0.7)
Antigout preparations	M04	1	(0.7)
Ophthalmologicals	S01	1	(0.7)

ATC = Anatomical Therapeutic Chemical classification.[16]

TABLE 3 (Part 1 of 2). Univariate and Multivariate Logistic Regression Models Estimating the Occurrence of ≥ 1 Pharmaceutical Intervention (PI) during Hospital Admission

Model No., Variable, and Category	No. (%) of Patients Without PI (*n* = 99)		With PI (*n* = 49)		OR (95% CI)		*p* Value
Univariate							
1: Sex							
Male	49	(49.5)	26	(53.1)	1.00	(reference)	
Female	50	(50.5)	23	(46.9)	0.87	(0.44–1.72)	0.68
2: Age (years)							
< 65	47	(47.5)	27	(55.1)	1.00	(reference)	
≥ 65	52	(52.5)	22	(44.9)	0.74	(0.37–1.46)	0.38
3: Charlson comorbidity index							
0–3	52	(52.5)	23	(46.9)	1.00	(reference)	
≥4	47	(47.5)	26	(53.1)	1.25	(0.63–2.48)	0.52
4: Renal failure							
No	73	(73.7)	35	(71.4)	1.00	(reference)	
Yes[a]	26	(26.3)	14	(28.6)	1.12	(0.52–2.41)	0.77
5: Electrolyte imbalance							
No	85	(85.9)	35	(71.4)	1.00	(reference)	
Yes[b]	14	(14.1)	14	(28.6)	2.43	(1.05–5.62)	0.038
6: Hemoglobin (*n* = 124)							
Within reference range[c]	51	(61.4)	20	(48.8)	1.00	(reference)	
Altered	32	(38.6)	21	(51.2)	1.67	(0.79–3.56)	0.18
7: Platelet count (*n* = 124)							
Within reference range[d]	63	(75.9)	31	(75.6)	1.00	(reference)	
Altered	20	(24.1)	10	(24.4)	1.02	(0.43–2.43)	0.97
8: Nasoenteric tube							
No	95	(96.0)	44	(89.8)	1.00	(reference)	
Yes	4	(4.0)	5	(10.2)	2.70	(0.69–10.54)	0.15
9: No. of medications							
< 5	18	(18.2)	1	(2.0)	1.00	(reference)	
5–8	41	(41.4)	21	(42.9)	9.22	(1.15–73.89)	0.036
≥ 9	40	(40.4)	27	(55.1)	12.15	(1.53–96.48)	0.018
10: ATC code B01							
Non-user	35	(35.4)	12	(24.5)	1.00	(reference)	
User	64	(64.6)	37	(75.5)	1.69	(0.78–3.64)	0.18
11: ATC code A03							
Non-user	44	(44.4)	26	(53.1)	1.00	(reference)	
User	55	(55.6)	23	(46.9)	0.71	(0.36–1.41)	0.32
12: ATC code A10							
Non-user	56	(56.6)	26	(53.1)	1.00	(reference)	
User	43	(43.4)	23	(46.9)	1.15	(0.58–2.29)	0.69
13: ATC code A04							
Non-user	63	(63.6)	27	(55.1)	1.00	(reference)	
User	36	(36.4)	22	(44.9)	1.43	(0.71–2.86)	0.32
14: ATC code C10							
Non-user	53	(53.5)	37	(75.5)	1.00	(reference)	
User	46	(46.5)	12	(24.5)	0.37	(0.17–0.80)	0.011

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TABLE 3 (Part 2 of 2). Univariate and Multivariate Logistic Regression Models Estimating the Occurrence of ≥ 1 Pharmaceutical Intervention (PI) during Hospital Admission

Model No., Variable, and Category	No. (%) of Patients Without PI (*n* = 99)		With PI (*n* = 49)		OR (95% CI)		*p* Value
15: ATC code J01							
Non-user	69	(69.7)	22	(44.9)	1.00	(reference)	
User	30	(30.3)	27	(55.1)	2.82	(1.39–5.73)	0.004
16: IV administration							
No	36	(36.4)	15	(30.6)	1.00	(reference)	
Yes	63	(63.6)	34	(69.4)	1.30	(0.62–2.70)	0.49
17: Multivariate[e]							
Electrolyte imbalance, yes†	NA		NA		2.68	(1.09–6.63)	0.033
No. of medications							
5-8	NA		NA		8.73	(1.07–71.36)	0.043
≥ 9	NA		NA		10.39	(1.28–84.05)	0.028
ATC code J01, user	NA		NA		2.76	(1.30–5.84)	0.008

CI = confidence interval, NA = not applicable, OR = odds ratio, B01 = antithrombotic agents, A03 = drugs for functional gastrointestinal disorders, A10 = drugs used in diabetes, A04 = antiemetics/antinauseants, C10 = lipid-modifying agents, J01 = antibacterials for systemic use.

[a]Creatinine clearance < 30 mL/min/1.73 m^2.

[b]Na^{2+} < 136 or > 145 mEq/L or K^+ < 3.5 or > 5.1 mEq/L.

[c]For men, 13.5–17.5 g/dL (135–175 g/L); for women, 12.0–16.0 g/dL (120–160 g/L).

[d]150 000–400 000/µL (150–400 × 10^9/L).

[e]Hosmer–Lemeshow $p = 0.425$; $R^2 = 0.191$ (Nagelkerke).

clinical pharmacy team could work preventively, instead of acting after a DRP occurs. Most of the current literature has used direct evidence of DRPs (e.g., documented adverse drug reaction) instead of indirect evidence such as pharmaceutical interventions, so the possibilities for comparison of our results with other studies were very limited.

The leading causes of pharmaceutical interventions in this study were related to prescribing errors, such as omission of essential prescribing information (e.g., route of administration) or prescribing of inappropriately high doses. In another study at a tertiary Brazilian hospital, the most common pharmaceutical interventions in the intermediate care unit were related to medication prescribed without indication (14.1%), prescription adjustment (14.1%), dose adjustment according to renal function (11.3%), use of potentially inappropriate medications for elderly patients (7.5%), dose adjustment when the initial dose was out of the therapeutic range (3.8%), and inadequate use of antimicrobial agents (1.9%).[18] Because higher doses are common prescribing errors and contribute to the occurrence of DRPs,[1,19,20] clinical pharmacists should pay special attention to the assessment of prescribed doses.

The medications most frequently prescribed in our study could reflect the high prevalence of cardiovascular and metabolic diseases among elderly patients.[21] Other possible reasons could be the frequent need to treat inpatients' pain and physicians' prescribing preferences. Supporting evidence comes from a Brazilian study conducted on 5 different wards of a teaching hospital, which showed that the overall prevalence of pain was 31.8% and that the analgesic most often prescribed to treat it was dipyrone (76.1%).[22] Similar to our results, the major classes of medications prescribed at a Nigerian tertiary hospital were vitamins (82.9%), antibiotics for systemic use (72.8%), and analgesics (60.0%).[23]

To the best of our knowledge, this is the first study in which electrolyte imbalance was significantly associated with the occurrence of pharmaceutical interventions. This finding reaffirms the need to correct serum electrolytes, especially given that such imbalances may be drug-related (e.g., diuretics, corticosteroids, laxatives, and angiotensin-converting enzyme inhibitors), to avoid negative clinical consequences such as muscle weakness, mental confusion, arrhythmias, ventricular fibrillation, and cardiac arrest.[24]

In this study, the prescription of 5 or more medications was significantly associated with the occurrence of pharmaceutical interventions. Given that hospital admission generally results in a significant increase in the number of drugs administered,[25] often because of the need for concurrent treatment of acute and chronic disorders,[26] inpatients are exposed to a greater risk of DRPs. That is why polypharmacy is frequently listed as a risk factor in DRP assessment tools that hospital pharmacists use to categorize the level of risk for inpatients and to prioritize patients for pharmaceutical care.[27] Nevertheless, the elderly population (the majority

of patients in our sample) frequently have many chronic conditions due to the aging process, so they are exposed to complex and long-term poly-pharmacotherapy.[28]

Similar to our results, data from 8713 admissions to a tertiary university hospital demonstrated that patients using systemic anti-infective agents had a 91% greater chance of experiencing a DRP.[3] This result may be related to the evidence that success of antibacterial treatment depends on several pharmacokinetic and pharmacodynamic parameters,[29] which can be altered as a result of the patients' clinical condition and age (e.g., impaired renal function, very low body weight, and previous use of an antibiotic). A French study involving 1408 adult inpatients categorized medications according to second-level ATC codes and showed that the only drugs associated with medication error were antithrombotic agents (B01), antibacterial agents for systemic use (J01), psycholeptics (N05), blood substitutes and perfusion solutions (B05), and analgesics (N02).[12]

One limitation of our study is that the pharmaceutical interventions included in the analysis occurred on any day of the hospital stay, and thus might not necessarily have been related to medications prescribed within 24 hours after admission. Furthermore, we did not investigate clinical conditions or classes of medications commonly identified as risk factors for ADEs (e.g., cognitive decline, antihypertensive agents, diuretics, and nonsteroidal anti-inflammatory drugs),[30] because of a lack of information in the patients' medical record or low prescription rates. The small sample size and the inclusion of patients from only 1 ward might have reduced the generalizability of the results. Another limitation is that non–patient-related factors were not evaluated. Clinical decision-making is a highly complex and dynamic process influenced by the knowledge, skills, attitudes, and context of the clinician.[31] Different pharmacists may make different decisions based on the same data and may have different thresholds for intervening. We also did not evaluate whether the pharmaceutical interventions led to any changes in clinical outcomes. However, in this ward, clinical pharmacists perform thorough follow-up of all inpatients, from admission to discharge, and were highly experienced in providing pharmaceutical care. We believe that the assumption that all pharmaceutical interventions performed were justified is likely true, because the pharmacists have developed their careers in the clinical setting, have obtained professional certifications of their knowledge, and had a standard of evidence-based thinking.

Although older age, female sex, and renal impairment are frequently cited as being associated with ADEs in adult inpatients,[30] we did not find them to be statistically associated with the occurrence of at least 1 pharmaceutical intervention. Interestingly, the ORs for older age and female sex revealed protection, not risk. We do not recommend that clinical pharmacists exclude the assessment of renal function from daily patient analysis, as this factor affects the pharmacodynamic and pharmacokinetic parameters of many drugs.[32]

We suggest future research with larger numbers of participants, longer periods of study, and more robust methods for finding the predictors of pharmaceutical interventions, with the purpose of exploring individual differences among pharmacists that may influence pharmaceutical interventions. There is a need to prioritize pharmacy services, which could be done through early identification of inpatients' characteristics at admission. Such identification could be related to pharmaceutical interventions and thus lead to the optimization of human and financial resources, as well as improved quality of care and patient safety.

CONCLUSION

In this study, 3 patient-level factors at the time of admission were associated with higher odds of a patient receiving at least 1 pharmaceutical intervention during the hospital stay: electrolyte imbalance, prescription of at least 5 medications, and prescription of at least 1 antibacterial for systemic use.

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Evaluation of Statin Use and Prescribing in Patients with Chronic Kidney Disease Not Receiving Treatment with Kidney Transplant or Dialysis

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ABSTRACT

Background: Chronic kidney disease (CKD) is a risk factor for cardiovascular disease. The Kidney Disease Improving Global Outcomes 2013 guidelines and the Canadian Cardiovascular Society 2016 guidelines recommend statins for primary prevention of cardiovascular disease in CKD patients aged 50 years or older who are not receiving treatment with kidney transplant or dialysis.

Objectives: To evaluate statin use for patients in the Vancouver General Hospital Kidney Care Clinic (VGH KCC) and to gain insight into the KCC nephrologists' practices and perspectives regarding the prescribing of statins for patients with CKD.

Methods: The study comprised 2 parts. Part 1 consisted of a cross-sectional study of all statin-eligible patients in the VGH KCC followed by a retrospective chart review. In the chart review, data were collected for 250 statin users and 250 non-users. Logistic regression analyses were performed to determine associations between demographic variables and statin use or non-use. Part 2 was an electronic survey of VGH KCC nephrologists.

Results: Of the 813 statin-eligible patients, 512 (63%) were taking a statin. Patients were approximately 5 times more likely to be receiving statin therapy when it was indicated for secondary versus primary prevention (adjusted odds ratio 4.64, 95% confidence interval 2.95–7.47). Eight of the 9 KCC nephrologists completed the survey, and 7 (87.5%) of these respondents indicated that they never or rarely prescribed statins themselves to KCC patients for primary prevention. However, the same number reported that they sometimes or often suggested statin initiation to family physicians. Three of the respondents indicated agreement with guideline recommendations, but many stated that the decision for statin initiation should be individualized to the patient. Strategies to improve statin prescribing rates that were endorsed by respondents included educating family physicians, creating preprinted orders and laboratory requisitions for statin initiation, providing educational materials about statins to patients, and implementing a protocol for KCC pharmacists to counsel patients about statins.

Conclusions: Many statin-eligible VGH KCC patients were not receiving statin therapy, and most of the KCC nephrologists considered statin prescribing as a role for family physicians. Within the KCC, future directions will be to develop a standardized approach to identify patients who would benefit from statin therapy, and to implement strategies to improve statin prescribing rates in appropriate patients.

Keywords: HMG-CoA reductase inhibitors, statins, chronic kidney insufficiency, cardiovascular disease, primary prevention

RÉSUMÉ

Contexte : L'insuffisance rénale chronique (IRC) est un facteur de risque de maladie cardiovasculaire. Les directives du Kidney Disease Improving Global Outcomes de 2013 et celles de la Société canadienne de cardiologie de 2016 recommandent l'utilisation de statines comme mode de prévention principal des maladies cardiovasculaires par les patients âgés d'au moins 50 ans et souffrant d'IRC, qui ne reçoivent pas de traitement par greffe rénale ou dialyse.

Objectifs : Évaluer l'utilisation des statines pour les patients résidant au Vancouver General Hospital Kidney Care Clinic (VGH KCC) et améliorer la compréhension des pratiques et points de vue des néphrologues de la KCC concernant la prescription de statines aux patients souffrant d'une IRC.

Méthodes : L'étude comportait deux parties. La première consistait en une étude transversale de tous les patients admis à recevoir des statines au VGH KCC, suivie d'un examen rétrospectif des dossiers. Les données destinées à cet examen ont été recueillies auprès de 250 utilisateurs de statines et de 250 non-utilisateurs. Les analyses de régression logistique ont permis de déterminer les associations entre les variables démographiques et l'utilisation (ou non) de statines. La deuxième partie consistait en une enquête menée électroniquement auprès des néphrologues du VGH KCC.

Résultats : Des 813 patients admissibles à l'utilisation de statines, 512 (63 %) en prenaient déjà. Les patients avaient environ cinq fois plus de chances de recevoir un traitement par statines, lorsque celles-ci étaient indiquées pour la prévention secondaire ou primaire (rapport de cote révisé 4,64, 95 % intervalle de confiance 2,95 - 7,47). Huit des neuf néphrologues de la KCC ont participé à l'enquête et sept (87,5 %) d'entre eux ont indiqué qu'ils n'avaient jamais, ou rarement, prescrit de statines aux patients du KCC dans le cadre d'une intervention primaire. Cependant, le même nombre de répondants a indiqué avoir parfois ou souvent proposé aux médecins de famille de commencer un traitement aux statines. Trois répondants ont indiqué être d'accord avec les recommandations préconisées dans les directives, mais bon nombre des néphrologues interrogés ont signalé que la décision d'entreprendre un tel traitement devait être individualisée. Les stratégies visant à améliorer les taux de prescription de statines approuvées par les répondants comprenaient la sensibilisation des médecins de famille, la création d'ordonnances et de demandes d'analyse en laboratoire préimprimées pour entreprendre un traitement aux statines, l'offre aux patients de matériel de formation sur le sujet et la mise en place d'un protocole pour les pharmaciens de la KCC leur permettant de conseiller les patients.

Conclusions : Beaucoup de patients admissibles à un traitement aux statines du VGH KCC ne le recevaient pas, et la plupart des néphrologues de la KCC considéraient que la prescription de ce type de traitement relevait des médecins de famille. Au sein de la KCC, les orientations futures consisteront à élaborer une approche standardisée pour identifier les patients qui tireraient profit d'une thérapie aux statines et à mettre en place des stratégies visant à améliorer les taux de prescription de statines aux patients concernés.

Mots-clés : inhibiteurs de l'HMG-CoA réductase, statines, insuffisance rénale chronique, maladie cardiovasculaire, prévention primaire

INTRODUCTION

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or laboratory markers of kidney damage that are present for at least 3 months.[1] Laboratory criteria meeting the definition of CKD include a urine albumin-to-creatinine ratio greater than 3.0 mg/mmol or an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 for at least 3 months.[1] CKD has been shown to be an independent risk factor for cardiovascular disease.[2]

In the population of patients with CKD who are not receiving renal replacement therapy with kidney transplant or dialysis, statins (HMG-CoA reductase inhibitors) have demonstrated benefit in reducing atherosclerotic events.[3] To date, the SHARP trial is the largest study to investigate the benefits of statin use specifically in patients with CKD.[4] This study, published in 2011, was a randomized double-blind trial that compared the combination of simvastatin 20 mg and ezetimibe 10 mg with placebo in 9270 patients with CKD and no history of myocardial infarction or coronary revascularization. Sixty-seven percent of the patients were not receiving dialysis, and the average age was 62 years in both groups. The combination of simvastatin and ezetimibe was associated with a statistically significant reduction in major atherosclerotic events relative to placebo (11.3% versus 13.4%; rate ratio 0.83, 95% confidence interval [CI] 0.74–0.94). These results were driven primarily by a reduction in ischemic strokes and arterial revascularization procedures. Among the 6247 patients who were not receiving dialysis at randomization, the combination of simvastatin and ezetimibe was not associated with any significant reduction in CKD progression.

On the basis of available evidence, the Kidney Disease Improving Global Outcomes (KDIGO) 2013 guidelines recommend initiation of statin therapy for primary prevention of cardiovascular disease in CKD patients who are 50 years of age or older and are not receiving treatment with kidney transplant or dialysis (grade 1A recommendation).[1] The Canadian Cardiovascular Society (CCS) 2016 guidelines also recognize CKD as a significant risk factor for cardiovascular disease, and CKD is listed as a statin-indicated condition in individuals 50 years and older.[5]

The Vancouver General Hospital Kidney Care Clinic (VGH KCC) enrolls CKD patients who are not receiving dialysis and have not undergone kidney transplant. Most of these patients are at least 50 years old and thus would be "statin-eligible" according to guideline recommendations. However, it has been observed that many KCC patients are currently not receiving statin therapy for primary prevention. In addition, the KCC nephrologists infrequently prescribe statins themselves, although they may suggest that a patient's family physician initiate a statin.

The primary objective of this study was to determine the proportion of statin-eligible patients enrolled in the VGH KCC who were receiving statin therapy. The secondary objectives were to gain insight into KCC nephrologists' practices and perspectives with regard to prescribing statins for CKD patients, to determine associations between demographic variables and statin use or non-use, and to estimate the odds of statin use when indicated for secondary versus primary prevention of cardiovascular disease.

METHODS

Study Setting

The VGH KCC provides care for approximately 1300 patients with CKD who have not received a kidney transplant and are not receiving dialysis. Patients are referred to the clinic after first being assessed by a VGH nephrologist. Nephrologists refer patients to the KCC if it is thought that they would benefit from a multidisciplinary approach to their renal care or if their renal function has declined to the point that they require education about kidney replacement therapy. Although some patients may be referred to the clinic immediately after the nephrologist's first assessment, a patient may be followed by their nephrologist for years before referral. The KCC health care team comprises pharmacists, nurses, dietitians, social workers, and nephrologists.

During the first KCC visit, each patient is seen by all members of the care team, with the exception of the nephrologist. At all subsequent visits, the patient is seen by their nephrologist and a clinic nurse; in addition, depending on their needs, the patient may also be seen by a pharmacist, dietitian, and/or social worker. The frequency of clinic visits is determined by the nephrologist according to the patient's clinical status and required level of care. The frequency generally ranges between monthly and yearly.

At each clinic visit, the patient's medications are reviewed by a pharmacist, nurse, or nephrologist, and the clinic nurse or pharmacist updates the patient's medication list in an electronic provincial database (PROMIS). The nephrologist completes a dictated note indicating the patient's past medical history and recent progress, as well as any medication recommendations to be considered by the patient's family physician. The dictation is subsequently uploaded to PROMIS and forwarded to the family physician.

Study Design and Population

This study comprised 2 parts that were conducted concurrently. It was approved by the University of British Columbia Clinical Research Ethics Board and by the Vancouver Coastal Health Research Institute. The need for informed consent was waived for part 1, and participants provided written consent in part 2.

Part 1 consisted of a single-centre cross-sectional study, followed by a retrospective chart review. VGH KCC patients were identified from PROMIS for study inclusion

if they were statin-eligible, based on the KDIGO 2013 and CCS 2016 guideline recommendations for patients with CKD. Thus, study inclusion criteria were enrolment in the VGH KCC; age 50 years or older; and a most recent eGFR less than 60 mL/min/1.73 m^2 and/or most recent albumin-to-creatinine ratio greater than 3.0 mg/mmol. Patients were excluded if they had a documented allergy to statin therapy or had attended fewer than 2 KCC appointments.

In the cross-sectional study component of part 1, data were collected from PROMIS on October 24, 2018, to determine the proportion of statin-eligible patients who were receiving statin therapy at the time. For the secondary analysis, all statin-eligible patients were separated into 2 groups according to whether they were statin users or non-users. A random number generator was then used to assign a number to each individual patient. Chart reviews were conducted for the patients who were assigned numbers 1 to 250 in each list. The total sample size of 500 patients for this analysis was determined with consideration of the time and resources available for data collection. Each chart review involved an assessment of the patient's most recent nephrologist dictation and demographic data available in PROMIS on or before October 24, 2018. Patients were then classified as having an indication for primary or secondary prevention of cardiovascular disease on the basis of documented comorbidities. Patients were considered to have an indication for secondary prevention if they had documented coronary artery disease, ischemic cerebrovascular disease, peripheral artery disease, and/or abdominal aortic aneurysm. The remaining patients were considered to have an indication for only primary prevention of cardiovascular disease.

In part 2 of the study, an electronic survey was developed to assess the perspectives on statin prescribing of the 9 VGH KCC nephrologists (Appendix 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/205). The survey was created using Qualtrics software, and the link to the survey was sent by email to the nephrologists on November 14, 2018. The survey remained open for 1 month. The responses were anonymous and were reviewed by the investigators after the survey had been closed.

Statistical Analysis

The proportion of statin-eligible patients who were receiving a statin was calculated as a percentage in part 1 of the study. The demographic characteristics of the 250 statin users and 250 non-users randomly selected for chart review were compared using the Student *t* test for quantitative variables and the χ^2 test for categorical variables.

Univariate logistic regression analyses were performed to determine unadjusted associations between demographic variables and statin use or non-use. Variables with associations having *p* values less than 0.1 were included in a multivariate logistic regression model to adjust for potential confounders. The *p* value threshold of 0.1 (instead of 0.05) was selected to increase sensitivity for detecting potentially relevant variables. Sex and ischemic cerebrovascular disease were also included in the model, as the study team deemed these to be clinically important variables. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. A second multivariate logistic regression analysis was performed specifically to compare the estimated odds of statin use when indicated for secondary versus primary prevention of cardiovascular disease.

All statistical tests were 2-tailed, and *p* values less than 0.05 were considered to be significant in the multivariate logistic regression models. Excel 2010 (Microsoft Corporation) and R 3.3.1 software were used for all statistical analyses.

In part 2 of the study, nephrologists' survey responses to multiple-choice questions were compiled and analyzed using descriptive statistics in Excel 2010 (Microsoft Corporation).

RESULTS

Cross-Sectional Study

Of the 982 patients who met the inclusion criteria, 169 patients were excluded, most because they had attended fewer than 2 KCC appointments (Figure 1). Of the 813 statin-eligible patients who met the study criteria, 512 (63%) were documented as receiving statin therapy.

Patient Characteristics in Retrospective Chart Review

The demographic characteristics of the 500 patients randomly selected for chart review are summarized in Table 1. The mean age was 76 years, and 291 (58%) were male. Most of the patients had both reduced eGFR (overall mean 25.5 mL/min/1.73 m^2) and elevated albumin-to-creatinine ratio (overall mean 97.7 mg/mmol). In addition to CKD, all of the patients had at least one other cardiovascular risk

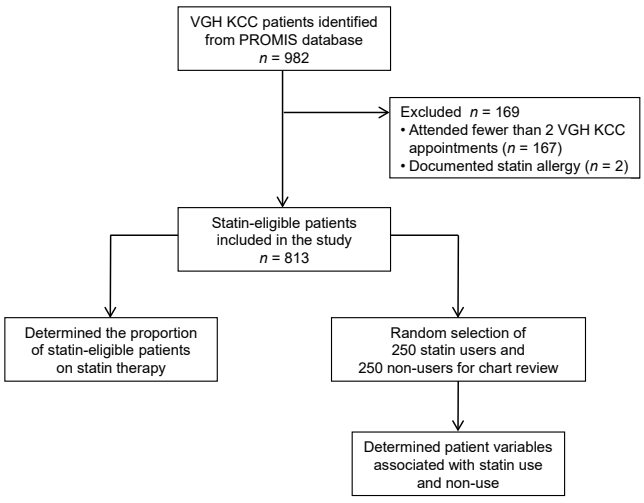

FIGURE 1. Study flow diagram for part 1 of the study. VGH KCC = Vancouver General Hospital Kidney Care Clinic.

TABLE 1. Characteristics of Patients

Characteristic	Study Group; No. (%) of Patients[a] Statin Users (n = 250)	Statin Non-users (n = 250)	p Value
Age (years) (mean ± SD)	77 ± 8	75 ± 10	0.048
Sex, male	155 (62)	136 (54)	0.10
eGFR (mL/min/1.73 m^2) (mean ± SD)	26 ± 10	25 ± 10	0.18
ACR (mg/mmol) (mean ± SD)	100.0 ± 133.0	95.2 ± 125.0	0.71
Laboratory criteria for CKD			0.17
Reduced eGFR only	45 (18)	58 (23)	
Albuminuria only	4 (2)	1 (<1)	
Reduced eGFR and albuminuria	201 (80)	191 (76)	
Body mass index (kg/m^2) (mean ± SD)	28.1 ± 6.2	26.5 ± 5.3	0.002
Ethnicity			0.004
White	109 (44)	146 (58)	
Asian	117 (47)	85 (34)	
Other	24 (10)	19 (8)	
Current smoker	7 (3)	10 (4)	0.62
Comorbidities			
Hypertension	233 (93)	213 (85)	0.006
Diabetes mellitus	159 (64)	71 (28)	< 0.001
Dyslipidemia	136 (54)	50 (20)	< 0.001
Coronary artery disease	87 (35)	16 (6)	< 0.001
Ischemic cerebrovascular disease	33 (13)	22 (9)	0.15
Peripheral artery disease	12 (5)	8 (3)	0.49
Abdominal aortic aneurysm	7 (3)	3 (1)	0.34
Indication for statin			< 0.001
Primary prevention of cardiovascular disease	138 (55)	208 (83)	
Secondary prevention of cardiovascular disease[b]	112 (45)	42 (17)	
Kidney replacement therapy plan			0.25
Conservative care	27 (11)	42 (17)	
Hemodialysis	25 (10)	27 (11)	
Peritoneal dialysis	20 (8)	18 (7)	
Undecided	178 (71)	163 (65)	

ACR = albumin-to-creatinine ratio, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, SD = standard deviation.
[a]Except where indicated otherwise.
[b]Indications for secondary prevention of cardiovascular disease were coronary artery disease, ischemic cerebrovascular disease, peripheral artery disease, and/or abdominal aortic aneurysm.

factor (i.e., hypertension, diabetes mellitus, dyslipidemia, and/or clinical atherosclerosis). The statin users were significantly older and had higher body mass index than the non-users. Ethnicity differed between the 2 groups as well: most statin users were of Asian background, whereas the majority of statin non-users were white. In addition, compared with statin non-users, higher proportions of statin users had documented diagnoses of hypertension, diabetes mellitus, dyslipidemia, and coronary artery disease. When comorbidities were categorized as indications for primary or secondary prevention of cardiovascular disease, a significantly greater proportion of statin users had at least 1 indication for secondary prevention, relative to non-users (45% versus 17%, $p < 0.001$).

Multivariate Logistic Regression Models for Statin Use and Non-use

In the first multivariate logistic regression model, which was used to determine associations between demographic variables and statin use or non-use, several factors were positively associated with statin use after adjustment for potential confounders (Table 2). These included older age, Asian ethnicity

TABLE 2. Multivariate Logistic Regression Model for Association between Patient Variables and Statin Use (n = 500)

Variable	Adjusted OR (95% CI)		p Value
Age, per 1-year increase	1.03	(1.00–1.06)	< 0.05
Male sex, relative to female sex	1.00	(0.64–1.56)	NSS
Kidney replacement therapy plan			
Conservative care	1.00	(reference)	–
Hemodialysis	2.75	(1.04–7.38)	< 0.05
Peritoneal dialysis	6.14	(2.12–18.35)	< 0.01
Undecided	3.61	(1.69–7.93)	< 0.01
Body mass index, per 1-unit increase	1.03	(0.99–1.08)	NSS
Ethnicity			
White	1.00	(reference)	–
Asian	1.68	(1.03–2.75)	< 0.05
Other	1.48	(0.67–3.31)	NSS
Comorbidity, relative to absence of the comorbidity			
Hypertension	1.10	(0.53–2.35)	NSS
Diabetes mellitus	2.75	(1.75–4.34)	< 0.01
Dyslipidemia	3.89	(2.47–6.20)	< 0.01
Coronary artery disease	8.60	(4.58–17.11)	< 0.01
Ischemic cerebrovascular disease	1.85	(0.88–3.94)	NSS

CI = confidence interval, NSS = not statistically significant, OR = odds ratio.

(relative to white ethnicity), and diagnoses of dyslipidemia, diabetes mellitus, or coronary artery disease. Patients with a plan for conservative care (i.e., no kidney replacement therapy in the event of end-stage renal disease) were less likely to be taking a statin than were patients with plans for dialysis. The patient factor having the largest association with statin use was coronary artery disease, with an adjusted OR of 8.60 (95% CI 4.58–17.11). However, no statistically significant association was found between statin use and ischemic cerebrovascular disease.

In the second multivariate logistic regression model, the estimated odds of statin use were compared when indicated for secondary versus primary prevention of cardiovascular disease. Patients were approximately 5 times more likely to be receiving statin therapy when it was indicated for secondary prevention, with an OR of 4.64 (95% CI 2.95–7.47) after adjustment for age, sex, ethnicity, body mass index, and kidney replacement therapy plan.

Survey of Nephrologists

Of the 9 KCC nephrologists, 8 completed the survey during the allotted time. The number of years of nephrology experience varied across respondents; one nephrologist had less than 5 years, 2 had 5–15 years, 4 had 16–25 years, and one had more than 25 years of experience.

For the purpose of this survey, "prescribing" referred to initiating therapy, as opposed to providing a prescription to continue existing therapy. The majority (6 [75%]) of the respondents believed it was appropriate for statins to be initiated by any of a CKD patient's regular physicians, including the patient's nephrologist. Nevertheless, all but 1 respondent (7 [87.5%]) stated that they never or rarely prescribed statins themselves for primary prevention of cardiovascular disease in KCC patients. Most (5 [62.5%]) also reported never or rarely prescribing statins for secondary prevention themselves. The remaining respondents indicated that they prescribed statins sometimes (1 [12.5%] and 3 [37.5%] for primary and secondary prevention, respectively). The frequency of suggesting statins was higher; in fact, 7 respondents (87.5%) indicated that they sometimes or often suggested statin initiation to the family physicians of KCC patients for both primary and secondary prevention. The nephrologists were asked to select potential obstacles to prescribing or suggesting statin therapy during KCC appointments, and time constraints were acknowledged by 4 respondents (50%).

Respondents identified various reasons for electing not to prescribe statins for primary prevention of cardiovascular disease: statin initiation not being a priority, need for monitoring, and drug interactions were each selected by 4 respondents (50%), and risk of adverse effects and increased pill burden were each selected by 5 respondents (62.5%). Only 2 respondents (25%) indicated that prescribing statins was outside their scope of practice.

Three (37.5%) of the respondents stated that "lack of evidence of benefit" was a potential reason for not initiating statin therapy for primary prevention. When the nephrologists were asked about their agreement with the KDIGO 2013 and CCS 2016 guideline recommendations, only 3 respondents (37.5%) indicated agreement. The remaining respondents stated that they disagreed (3 [37.5%]) or were undecided (2 [25%]), and these individuals were asked to provide their rationales. The most common responses were that the decision for statin initiation should be patient-specific, that the benefits of statin initiation may not be consistent across the entire spectrum of renal disorders, and that patients with limited life expectancy likely would not derive much benefit from statins.

Table 3 outlines respondents' perceptions about proposed strategies to increase statin prescribing rates for primary prevention of cardiovascular disease in KCC patients. Creating preprinted statin dosing orders, creating preprinted laboratory requisitions, providing educational materials about statins to patients, and implementing a protocol for KCC pharmacists to counsel patients about statins were each endorsed by 3 (37.5%) of the respondents. Providing education to family physicians about statins in CKD was the most preferred strategy: 5 respondents (62.5%) endorsed this approach.

TABLE 3. Nephrologists' Opinions on Proposed Strategies to Increase Statin Prescribing Rates for Primary Prevention of Cardiovascular Disease in Vancouver General Hospital KCC Patients

Proposed Strategy	No. of Nephrologists Believing Strategy Would Be Beneficial (n = 8)
Education for family physicians about statins in CKD	5
Preprinted order with statin options and dosing recommendations	3
Preprinted laboratory requisition for patients initiating statins	3
Protocol for KCC pharmacist to counsel patients initiating statins	3
Educational materials about statins for KCC patients	3
Increased duration of KCC appointments	1
Reminder on KCC patient assessment sheets	1
Education for nephrologists about statins in CKD	1
Education for KCC allied health staff about statins in CKD	1

CKD = chronic kidney disease, KCC = Kidney Care Clinic.

DISCUSSION

To our knowledge, this is the first study evaluating statin use in a multidisciplinary CKD clinic. We found that 512 (63%) of 813 statin-eligible patients in the KCC were receiving a statin. This rate of statin use is of concern because CKD is an established risk factor for cardiovascular disease, and most studies suggest that patients with CKD are 20 times more likely to die of cardiovascular disease than to develop end-stage renal disease.[6] Therefore, efforts should be made to reduce cardiovascular risk as much as possible. Although the KDIGO 2013 and CCS 2016 guidelines would both recommend statin therapy for every patient in this study, close to 40% of them were not receiving a statin. The results of the multivariate analyses revealed that the patients were much more likely to be taking a statin if they had an indication for secondary prevention of cardiovascular disease, especially coronary artery disease. This may reflect the well-established evidence for statins in patients with coronary artery disease,[7] as well as the fact that statins are included on preprinted orders for patients who are admitted for acute coronary syndromes in our province.

Our survey of nephrologists provided insights into possible reasons why statins are not more widely prescribed for primary prevention of cardiovascular disease in our KCC. Several nephrologists did not fully agree with the KDIGO 2013 and CCS 2016 recommendations because they believed that a patient-individualized approach was necessary to make decisions about statin initiation. Many of their concerns stemmed from potentially unfavourable risk–benefit ratios of statin use in certain populations, particularly elderly patients with limited life expectancy. This is perhaps the explanation for the lower odds of statin use among patients with plans for conservative care, as compared with patients for whom plans for dialysis were in place. Patients who have elected conservative care are typically older and frailer, and therefore less likely to derive long-term benefit from statin therapy. As a group, these KCC nephrologists appeared to initiate statins themselves more frequently for secondary prevention; 37.5% reported prescribing statins "sometimes" for secondary prevention, as compared to only 12.5% for primary prevention. This result is likely due to the perception that statin initiation is more important and has a more favourable risk–benefit ratio in the setting of clinical atherosclerosis.

The survey results also revealed potential areas for future study. A few nephrologists expressed uncertainty about the benefits of statin therapy across the spectrum of renal disorders. Although the SHARP trial[4] investigated the benefits of statin use for patients with CKD, the particular causes of CKD were not specified in that study, and it is therefore unclear whether its results are truly generalizable to all CKD patients. Future studies are warranted to elucidate this matter.

With respect to the VGH KCC nephrologists' prescribing practices, most of the survey respondents did not indicate that initiating statins was outside their scope of practice. In fact, a few respondents endorsed the creation of preprinted statin dosing orders and laboratory requisitions, which would serve to improve prescribing efficiency during KCC appointments. However, it appears that the respondents generally recommended statin initiation to family physicians more frequently than they prescribed statins themselves. In addition, providing education to family physicians was their most popular strategy to increase statin prescribing rates for primary prevention in KCC patients. These last 2 findings suggest that most of the nephrologists would prefer that family physicians be responsible for initiating statins. One reason for this preference may be the need for close monitoring when statin therapy is started, which was indicated as a barrier to prescribing statins by 50% of the respondents. Nephrologists may perceive family physicians as being better suited to initiate statins because they have more frequent follow-up with patients, which allows for closer monitoring for adverse events. Furthermore, among our KCC patients, it has been observed that family physicians often initiate statins and provide monitoring when recommended to do so by other specialists (e.g., cardiologists and neurologists).

The nephrologists' preference to defer statin initiation to alternate prescribers could also be an indication that they consider this intervention to be of low priority in their practices. Indeed, when the nephrologists were asked about prescribing statins for primary prevention, 50% expressed that it was not a priority. This response may be due to the lack of benefit seen with statin use, in terms of slowing CKD progression. Nephrologists likely place greater priority on renal-specific issues, such as interventions that delay CKD progression (e.g., hypertension and diabetes management, use of renin-angiotensin-aldosterone system inhibitors), management of anemia and mineral bone disorders, and plans for kidney replacement therapy.

The KCC nephrologists generally considered statin prescribing to be a role for family physicians, but nephrologists' practices may differ according to the particular CKD population and clinical setting. To date, this is the first study to evaluate nephrologists' opinions about statin therapy in CKD patients who are not receiving treatment with kidney transplant or dialysis. One previous multicentre study surveyed nephrologists about their attitudes toward statin use specifically in the population of patients receiving hemodialysis.[8] All of the 72 respondents indicated that they prescribed statins for hemodialysis patients, and 83% stated that they prescribed statins for secondary prevention of cardiovascular disease; prescribing practices for primary prevention were not described. These results may reflect the nephrologists' choice to continue statin therapy, given that the study definition of "prescribing" was not limited to therapy initiation. However, all of the respondents were able to list the parameters that they routinely monitored before and during statin initiation. Overall, compared with the nephrologists in our KCC, the nephrologists in this earlier study appeared to assume more responsibility for their patients' statin treatment. Possible reasons for this finding may be nephrologists' higher frequency of contact with patients in the hemodialysis versus KCC setting, as well as nephrologists' awareness that other physicians are often reluctant to prescribe medications to hemodialysis patients because of concerns about adverse effects and contraindications.

The rate of statin use in our clinic was found to be suboptimal; however, this presents an opportunity for the KCC pharmacists to play an important role in improving cardiovascular risk management for our patients. The KCC pharmacists are well positioned to help patients make informed decisions about statin initiation, to provide statin recommendations for appropriate patients, and to facilitate the communication of recommendations between nephrologists and family physicians.

This study had a number of limitations. First, it was conducted only in the VGH KCC, and the data on statin use and nephrologists' perspectives that we found may differ from those of other renal centres. In addition, patient classification of statin use or non-use was dependent on KCC pharmacists and nurses having updated medication lists in the PROMIS database. It is possible that some statin initiations and discontinuations were not entered in the system. Furthermore, given the cross-sectional design of part 1, it was not possible to determine the indication or indications for which the statins were originally prescribed (for those patients who were receiving statin therapy). Therefore, it could not be determined whether patients were originally initiated on statins for the purpose of primary or secondary prevention of cardiovascular disease. Another limitation was that the chart reviews conducted for the multivariate analyses were limited to nephrologist dictations, which may have contained inaccurate or incomplete data about patient comorbidities. Lastly, a sample size calculation was not done before conducting the chart reviews; instead, the sample size of 500 patients (250 statin users and 250 non-users) was selected according to the availability of time and resources. Nevertheless, several statistically significant associations were found between patient variables and statin use or non-use.

CONCLUSION

The majority of statin-eligible CKD patients in our KCC were receiving statin therapy. However, 37% of the patients were not receiving statin therapy despite having relevant indications, and these patients were therefore not receiving guideline-recommended care. Patients were much more likely to be receiving statin therapy if they had an indication for secondary prevention of cardiovascular disease, signalling that statin initiation for primary prevention may require greater emphasis in our clinic. Within the VGH KCC, future directions will be to further explore nephrologists' opinions about the guidelines for statin use and to develop a standardized approach to identify CKD patients for whom the benefits of statin therapy would outweigh the risks, based on individual patient factors. Nephrologist-preferred strategies will then be implemented to increase statin prescribing rates in appropriate patients, with a focus on providing education to family physicians. Ultimately, this may help to improve cardiovascular outcomes in our CKD patients.

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Stability of Compounded Clozapine 25 mg/mL and 50 mg/mL Suspensions in Plastic Bottles

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ABSTRACT

Background: Clozapine oral suspension is not commercially available in Canada but is required for administration to patients who cannot swallow intact tablets.

Objective: To evaluate the stability of 25 mg/mL and 50 mg/mL clozapine suspensions prepared in a 50:50 mixture of methylcellulose gel 1% and Oral Syrup (flavoured syrup vehicle, Medisca Pharmaceutique Inc) and stored in amber glycol-modified polyethylene terephthalate (PET-G) bottles over 120 days at 4°C and 25°C.

Methods: This study used a validated reverse-phase stability-indicating liquid chromatographic method capable of quantifying clozapine, 3 known degradation compounds, a known impurity, and an unknown compound. Three separate batches of 25 mg/mL and 50 mg/mL clozapine suspensions were prepared, divided into 100-mL aliquots, and stored in 120-mL PET-G bottles. Half of the bottles from each concentration were stored at room temperature (20°C to 25°C) and the other half were stored in the refrigerator (2°C to 8°C). On study days 0, 28, 60, 90, and 120, concentrations of clozapine, each of the 3 known clozapine degradation products, a known impurity, and an unknown compound were determined.

Results: When suspensions were stored in PET-G containers at room temperature or under refrigeration for 120 days, the concentration of clozapine remained above 95% of initial concentration, and the measured concentration of degradation products and impurities did not exceed the 0.5% limits set by regulatory authorities worldwide. The proportion of the initial concentration of clozapine remaining on day 120, based on fastest degradation rate with 95% confidence (1-sided), exceeded 92%, and the only degradation product found (clozapine lactam, 0.2%) and an unknown impurity (0.2%) also did not exceed allowable limits.

Conclusions: Compounded clozapine suspensions of 25 mg/mL and 50 mg/mL can be stored in amber PET-G containers for up to 120 days after preparation with storage at room temperature or under refrigeration.

Keywords: clozapine, stability, suspension

RÉSUMÉ

Contexte : La clozapine en suspension orale n'est pas disponible sur le marché canadien, mais elle est nécessaire pour les patients qui ne peuvent l'avaler sous forme de comprimé intact.

Objectif : Évaluer la stabilité des suspensions de clozapine de 25 mg/mL et de 50 mg/mL, préparées dans un mélange 50:50 de gel méthylcellulose à 1 % et de Sirop Oral (véhicule de sirop aromatisé, MEDISCA) et conservées dans des flacons ambrés en polytéréphtalate d'éthylène modifié au glycol (PET-G) pendant 120 jours à des températures de 4°C et 25°C.

Méthode : Cette étude a utilisé une méthode validée par chromatographie liquide indicatrice de stabilité en phase inverse pouvant quantifier la clozapine, trois composés de dégradation connus, une impureté connue et un composé inconnu. Trois lots séparés de suspensions de clozapine de 25 mg/mL et de 50 mg/mL ont été préparés, divisés dans des aliquotes de 100-mL et stockés dans des flacons en PET-G de 120-mL. La moitié des flacons de chaque concentration a été conservée à température ambiante (de 20°C à 25°C), et l'autre moitié au réfrigérateur (de 2°C à 8°C). Aux jours 0, 28, 60, 90 et 120 de l'étude, on a déterminé les concentrations de clozapine, celles de chacun des trois produits de dégradation de la clozapine, celles d'une impureté connue et d'un complexe inconnu.

Résultats : Lorsque les suspensions étaient stockées dans des contenants en PET-G à température ambiante et réfrigérées pendant 120 jours, la concentration de clozapine demeurait au-dessus de 95 % de la concentration initiale; la concentration mesurée des produits de dégradation et des impuretés ne dépassait pas la limite de 0,5 % fixée par les autorités de règlementation mondiales. La proportion de concentration initiale de clozapine restante au 120^{e} jour, sur la base du taux de dégradation le plus rapide avec un intervalle de confiance de 95 % (unilatéral), dépassait 92 %, et le seul produit de dégradation trouvé (clozapine lactam, 0,2 %) ainsi qu'une impureté inconnue (0,2 %) ne dépassaient pas non plus les limites autorisées.

Conclusions : Les suspensions de clozapine composées de 25 mg/mL et de 50 mg/mL peuvent être conservées dans des contenants ambrés PET-G jusqu'à 120 jours après leur préparation, soit à température ambiante, soit dans un réfrigérateur.

Mots-clés : clozapine, stabilité, suspension

INTRODUCTION

Clozapine suspension is not commercially available in Canada, yet there is a need for this suspension to be available for patients who may have dysphagia or require dose administration under observation. To date, only 1 study concerning the stability of clozapine suspensions has been published.[1] In that study, 20 mg/mL suspensions of clozapine were prepared in 6 different suspending vehicles (Ora-Sweet and Ora-Plus suspending vehicles, a 1:1 mixture of Ora-Sweet and Ora-Plus, the suspending vehicle used by the Hospital for Sick Children [Toronto, Ontario], simple syrup, and a noncommercial vehicle known as Guy's pediatric mixture), and their stability was evaluated. Each suspension was stored in amber plastic containers at 23°C and retained more than 95% of the initial concentration during 63 days of storage, regardless of the suspending vehicle.[1] However, with commonly used maintenance doses of 300 to 600 but not exceeding 900 mg/day,[2,3] and an average dosage of 200 mg bid, suspensions with concentration of 25 mg/mL or 50 mg/mL have been judged as more convenient. Furthermore, since prescriptions can be written for up to a 3-month supply, we wished to test the stability of such suspensions over a period of at least 3 months. However, no data exist at either concentration or for this storage period, and the formulations of suspending agents may have changed since the original study was published in 2005.

In pharmacy practice, the end points used to judge stability of a drug have changed over the past 50 years. In the 1970s, the last study day on which the observed concentration was greater than 90% of the initial concentration was deemed to be the expiry date. This criterion works where analytical error is exceptionally low or zero. However, because analytical variability always exists, the trend for the concentration to decline to a concentration of 90%, established by linear regression, came to be considered a more robust end point than the last day on which more than 90% remained.[4] Although this end point is statistically stronger, on the day that linear regression indicates 90% will remain, there is a 50% chance that the proportion remaining is actually less than 90% of the initial concentration. Calculation of confidence intervals can reduce this uncertainty and may have been first proposed in 1991 by Chow and Shao,[5] was supported by Carstensen and others[6] in 1992, and was restated by Shao and Chow[7] in 1994. Confidence intervals have been used in pharmacy practice stability studies only in the past 20 years. The lower 95% confidence limit constructed about the slope of the drug product of interest represents the fastest degradation rate. The intersection of this lower limit of the 95% confidence interval and 90% remaining is generally accepted as the beyond-use date (BUD). A 1-sided (lower-bound) 95% confidence interval increases the confidence that a pharmacist can have in compounded products, reducing to just 5% the chance that less than 90% will remain.

Degradation products of various medications have been identified and noted to be sensitive indicators of stability[8]; however, such degradation products are generally not commercially available, so pharmacy practitioners have not developed or used criteria based on degradation products to determine the BUD. In contrast, regulatory authorities, which do not regulate pharmacist-compounded products, define shelf life on the basis of degradation product limits and approve drugs on the basis of safety and efficacy. As part of their evaluation of safety, regulatory authorities worldwide, through the International Council on Harmonisation (ICH), have agreed to limit the amount or proportion of degradation products and impurities in pharmaceutical dosage forms.[9,10] Lower thresholds may be set if the degradation product is unusually toxic. Manufacturers determine the shelf life and release each lot of product according to analysis demonstrating that degradation products and impurities do not exceed these limits. For clozapine, the measured amount of any 1 of 3 known degradation compounds (clozapine lactam, a bis-compound, and a desmethyl compound) or of a known impurity (*N*-methyl piperazine, also known as aminopiperazide) cannot exceed 0.5%. Furthermore, if the amount of an individual unknown impurity exceeds 0.2%, or the total amount of all degradation products, the known impurity, and the unknown compound exceeds 1%, the shelf life is deemed to have been reached.[9,10] This approach can be followed only if practitioners have access to reference standards of the degradation products and an analytical method capable of separating and measuring each degradation product specifically. Since the identity of and reference standards for degradation products are generally not available to pharmacists early in a product's life cycle, pharmacy practitioners have not routinely measured, reported, or evaluated BUDs using degradation products. Nevertheless, the concentrations of degradation products have been included in the current evaluation of clozapine stability as an additional measure of the potency, purity, and quality of the formulation.

To our knowledge, this is the first study in which a product compounded by pharmacy has been evaluated with the degradation testing methodology defined by regulatory bodies such as Health Canada and the US Food and Drug Administration, in addition to confidence interval analysis of the active pharmaceutical ingredient (clozapine). Although regulatory agencies have limited authority over compounding, concentrations of degradation products have been included as a measure of product purity, to provide compounding pharmacists with confidence in the stability of the formulation and the recommended BUD.

The objective of this study was to evaluate the stability of 25 mg/mL and 50 mg/mL oral suspensions of clozapine stored for up to 120 days in amber glycol-modified polyethylene terephthalate (PET-G) bottles at 4°C (2°C to 8°C)

and room temperature (20°C to 25°C; described hereafter as 25°C) through measurement of concentrations of clozapine, known degradation products, and impurities. During the 120-day study period, suspensions were visually inspected for appearance, colour, the ability to be resuspended or caking, odour, and measured pH.

In the evaluation of stability, the intersection of the lower limit of the 95% confidence interval constructed about the clozapine concentration was used to estimate a BUD. As an assurance of safety, the 0.5% limit on each of 3 known clozapine degradation products and a known impurity was also used in establishing a safe storage period.

METHODS

Formulations Studied

Before the stability study, physical studies were undertaken to determine the suitability of the suspension in various suspending vehicles, including mixtures of vehicles at various ratios. These studies evaluated commercially available methylcellulose gel 1% (product no. 3060, Medisca Pharmaceutique Inc), Oral Syrup flavoured syrup vehicle (product no. 2511, Medisca Pharmaceutique Inc), and a 50:50 mixture of these 2 products. These suspending vehicles were screened for their ability to form a well-dispersed suspension and maintain the initial pH (between 5.5 and 6.2), with limited foaming, particle aggregation, and caking. Samples were examined for changes in colour, any clumping, ease of resuspension, and pH (digital pH meter, Beckman) over 120 days storage at 25°C and 4°C.

The most acceptable suspending agent was the 50:50 mixture of methylcellulose gel 1% and the flavoured syrup vehicle, Oral Syrup. This mixture of suspending agents was used to compound the suspensions used in our evaluation of clozapine stability.

Development and Validation of Stability-Indicating Assay

Liquid Chromatography

Reverse-phase stability-indicating liquid chromatographic methods with ultraviolet (UV) detection, either at 230 nm using a 31.5% acetonitrile and 68.5% phosphate buffer mobile phase[1] or at 254 nm using a 40% acetonitrile and 60% water mobile phase,[11] have been described previously. The previous investigators observed but did not identify degradation products.[1,11] Skibiński and others[12] forced the degradation of clozapine, identified 6 degradation products, determined their respective masses, and obtained fragmentation spectra by tandem mass spectrometry, which allowed structural identification. Two of the degradation products were observed following forced UV photodegradation, although they were not observed under typical photolysis conditions or during storage. The remaining 4 degradation products are now commercially available as individual standards or as a mixture,[13] which can be useful for assessing the stability-indicating nature of a particular method.

The analytical method used for the current study was similar to the previously published methods, although here the degradation products were identified, separated, and quantified, which did not occur in the previous studies.[1,11] This method is used by the manufacturer for product release in Canada and is stability-indicating. The reverse-phase liquid chromatographic method used a phosphate buffer and acetonitrile (80:20 v/v) solvent system to elute clozapine and its degradation products from the formulation. Clozapine eluted at 5.7 minutes, well separated from the 4 degradation products and an impurity, when the mobile phase was pumped at 1.0 mL/min through a 4.6 cm × 50 mm reverse-phase 3-µm LC-18 column (ACME Canadian Life Science; product no. ACMC 18-3-05046). Samples of 5 µL were introduced into the liquid chromatographic system using an auto injector (automatic liquid sampler, Hewlett-Packard). The column effluent was monitored with a photodiode array (diode array detector, Agilent) at 226 nm. A signal from the detector was integrated and recorded with a chromatography data system (OpenLAB, version A.01.05, Agilent).

Stability-Indicating Methodology

The acceptance criteria of the validated analytical method require that the within-day residual standard deviation (RSD%) for triplicate injections of each standard be not more than 2%, the between-days RSD% not exceed 5%, and recovery (accuracy) not exceed an absolute deviation of 2%. This method was capable of separating clozapine from the 3 known clozapine degradation products (clozapine lactam, a bis-compound, desmethyl clozapine), the known impurity (aminopiperazide), and an unknown compound.

The separation and quantification of these compounds indicates that the method is stability-indicating and that it meets or exceeds published and accepted standards.[14-16]

Samples of the suspending vehicle mixture, with and without clozapine, were assayed to ensure that the vehicle did not interfere with the assay.

Validation of Assay

Once assurance of the specificity of the analytical method had been completed, the validation phase followed, during which accuracy and reproducibility of the standard curves were evaluated over a 5-day period, and system suitability criteria (theoretical plates, tailing, and retention time) were developed to ensure consistent chromatographic performance on each study day.[17] On each validation day, 10 mg of clozapine (USP reference standard) was accurately weighed and dissolved in water to prepare standards. Then, 5-µL samples of each standard and a blank were chromatographed in duplicate to create the standard curve. The range

of the calibration curve encompassed the diluted test concentration of clozapine samples.

Within-day and between-day errors were assessed by the coefficients of variation of the peak areas of standards.

Stability Study

Clozapine suspensions (25 mg/mL and 50 mg/mL) were prepared with 100-mg clozapine tablets (Clozaril, HLS Therapeutics Inc, Etobicoke, Ontario) in a 50:50 mixture of methylcellulose gel 1% and Oral Syrup to prepare 3 separate 1-L batches of each concentration of suspension. The suspensions were prepared with 2 different lots of 100-mg clozapine tablets (HLS Therapeutics Inc; lot 18027, expiry August 2021, and lot 19050, expiry April 2022). The suspending vehicle was prepared with 2 different lots of methylcellulose gel 1% (Medisca Pharmaceutique Inc; lot 627663, expiry May 2020, and lot 628337, expiry July 2020) and 2 lots of flavoured Oral Syrup (Medisca Pharmaceutique Inc; lot 622919, expiry September 2021, and lot 622919A, expiry September 2021). The procedure for making the 25 mg/mL suspension is presented in Appendix 1. The suspensions were all well suspended, not thick or viscous, and were easy to pour.

Two 100-mL aliquots of each batch were poured into 120-mL amber coloured PET-G plastic graduated bottles (product no. 7293, Medisca Pharmaceutique Inc), for a total of 6 bottles for each concentration. One bottle from each of the 3 batches of each concentration was placed in a refrigerator at 4°C (2°C to 8°C). The other bottle from each of the 3 batches of each concentration was stored at 25°C (i.e., 20°C to 25°C).

Each test container was manually shaken, and 5 mL was withdrawn from each separate bottle (using a pipette) following initial compounding on day 0 and then subsequently on days 28, 60, 90, and 120; the concentration of clozapine and degradation products was determined in these samples. From each of the well-mixed 25 mg/mL suspensions, a 5-mL sample (taken individually from each of the 3 separate containers at each temperature) was diluted to 100 mL with a 50:50 mixture of methanol and water diluent. The mixture was then vortexed and a 10-mL aliquot was further diluted to 100 mL with a 50:50 mixture of methanol and water. The solution was then filtered through a 0.7-µm glass fibre filter, and 5 µL of the supernatant was injected into the high-performance liquid chromatography system. A similar method of preparation was followed for the 50 mg/mL suspension, although the first dilution in equal parts of methanol and water was completed with 200 mL of solvent. Chromatographic analysis was completed using the validated liquid chromatographic system described above, with UV detection at 226 nm. The area under the clozapine peak at 226 nm was subjected to least-squares linear regression, and the actual clozapine concentration in each sample was determined by interpolation from the standard curve and correction by the dilution factor. The percent of declared content (25 mg/mL or 50 mg/mL) was reported in summary tables.

Statistical Analysis

Within-day and between-day analytical error was assessed by replicate analysis of standards. After determining the coefficient of variation of the analytical method, a power calculation indicated that duplicate injection could distinguish between concentrations that differed by at least 10% within each individual container.[18,19] During the study, analytical error was assessed by replicate analysis of study samples. The mean and coefficient of variation were calculated for duplicate analyses from each of the 3 different bottles on each study day. These results are reported in summary tables.

The percent remaining was analyzed by linear regression, and a 95% confidence interval (1-sided, lower-bound) was constructed around the slope of percent remaining versus study day. The lower limit of this confidence interval represents the fastest degradation rate with 95% confidence (1-sided), and the time to achieve 90% remaining using this fastest degradation rate was calculated. Concentrations were considered within acceptable limits if the following 2 conditions were met: first, the measured clozapine concentration on that study day was greater than 90% of the initial (day zero) concentration, and second, the concentration on that day, estimated using the fastest degradation rate with 95% confidence, also exceeded 90% of the initial (day zero) concentration.

As an additional evaluation of suspension stability and purity, the measured amount of any 1 of 3 known degradation compounds (clozapine lactam, a bis-compound, and a desmethyl compound) or of a known impurity (*N*-methyl piperazine, known as aminopiperazide) cannot exceed 0.5%. Furthermore, if the amount of an unknown compound exceeds 0.2%, or the total amount of all degradation products, the known impurity, and the unknown compound exceeds 1%, the shelf life would be judged to have been reached.[9,10] A 2003 Health Canada guidance document[10] recommended application of a 1-sided 95% confidence limit; however, given that clozapine was commercially available more than 20 years before adoption of this guidance, the stability and lot acceptance criteria used by the pharmaceutical industry have not changed and do not use the confidence interval method. To replicate current pharmaceutical standards, the current study applied the "not-more-than" limits for each degradation product (0.5%), impurities (0.2%), and total degradation and impurities (1%), rather than limits based on a confidence interval. Although regulatory agencies have no authority in compounding, the inclusion of degradation compounds when evaluating the stability of these formulations provides additional confidence in product purity, as well as confidence in the recommended BUD.

RESULTS

Physical Study

The physical study of clozapine suspensions demonstrated that both concentrations of the suspension in a 50:50 mixture of methylcellulose gel 1% and flavoured Oral Syrup remained an opaque, yellow, milky suspension for the 120-day storage period at both temperatures. During the 120-day physical study period, some separation did occur, but no caking or clumping was visually evident, and all suspensions were easily redispersed with shaking. The pH of the suspensions stored at both 4°C and 25°C in suspending vehicle ranged between 5.60 and 5.97 for the 25 mg/mL preparations and between 5.79 and 6.05 for the 50 mg/mL suspensions for the duration of the 120-day study period.

Stability-Indicating Assay

The separation and detection of clozapine in the presence of degradation compounds and impurities must be demonstrated before the method can be considered stability-indicating. Clozapine eluted at 5.7 minutes, and the degradation products did not interfere with clozapine quantification (Figure 1). Furthermore, each of the degradation products was well separated from clozapine and the other degradation products, and each could be measured specifically. The suspending vehicle did not interfere with measurement of clozapine or any of the degradation products.

As a result of the chromatographic separation of the degradation products from clozapine and the lack of interference of the suspending agent with clozapine and the degradation products, it was concluded that this analytical method was stability-indicating.

Assay Error during the Study Period

During the study period, within-day analytical variability of the study samples averaged 2.13%, and between-day analytical reproducibility (as measured by the standard deviation of regression, *Sy.x*) averaged 2.05%.

Chemical Stability and Statistics

The percent remaining of the initial clozapine concentration as observed on each day during the study period is presented in Table 1. The concentration of clozapine in the suspending vehicle in all study samples (both concentrations) remained at or above 95.1% of the initial concentration when stored in amber PET-G bottles at both storage temperatures for 120 days. The 1-sided 95% confidence limits showed that the lowest percent remaining of clozapine exceeded 92% on study day 120 for all combinations of concentration and storage temperature. Analysis of variance detected no differences in percent remaining in the clozapine suspensions due to study day ($p = 0.26$), temperature ($p = 0.16$), or concentration ($p = 0.08$). Multiple linear regression also detected no differences in percent remaining due to study day ($p = 0.34$), temperature ($p = 0.17$), or concentration ($p = 0.09$).

Two of the known clozapine degradation products (a bis-compound and the desmethyl clozapine), as well as the known impurity (aminopiperazide), were not detected in any sample during the 120-day study period. The other known degradation product, clozapine lactam, was detected in some samples (Table 2); however, the limit of 0.5% was not reached after 120 days of storage at either temperature or concentration. The unknown compound was also detected in some samples (Table 3); the observed maximum of 0.2% was reached on days 90 and 120 in the 25 mg/mL suspension stored at room temperature. Table 4 presents combined data for impurities and degradation products. None of the degradation products or impurities were detected at concentrations exceeding their specific limits during the 120-day study period.

DISCUSSION

This study has demonstrated the physical and chemical stability of 25 mg/mL and 50 mg/mL clozapine suspensions

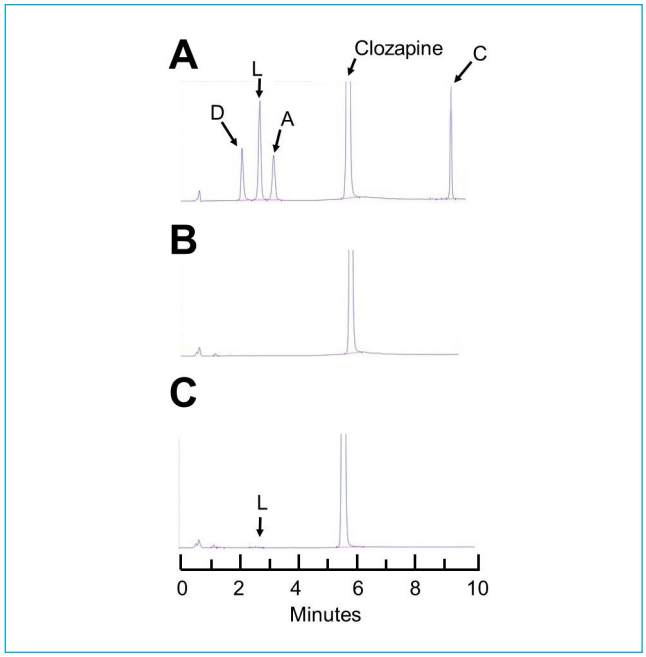

FIGURE 1. Chromatograms of clozapine. Panel A represents desmethyl clozapine at concentration 12.5 µg/mL (labelled "D" and eluting at 2.1 minutes), clozapine lactam (labelled "L" and eluting at 2.7 minutes), the aminopiperazide (labelled "A" and eluting at 3.2 minutes), and an unknown compound (labelled "C" and eluting at 9.2 minutes), with 50 mg/mL clozapine (eluting at 5.7 minutes) in the suspending vehicle. Panel B represents the 50 mg/mL clozapine suspension on day 0, when no degradation products are present. Panel C represents the same 50 mg/mL suspension after 120 days storage at room temperature. Small amounts of clozapine lactam (labelled "L") were detected at 2.7 minutes, representing concentrations of about 0.1%.

TABLE 1. Percent of Clozapine Remaining on Each Study Day and Calculation of Time to Achieve 90% Remaining (T_{90}) with 95% Confidence

	Nominal Concentration and Storage Temperature[a]; % Remaining (Mean ± SD)			
	25 mg/mL		50 mg/mL	
Study Day	RT	4°C	RT	4°C
0	95.10±1.49	97.97±1.12	100.67±3.93	100.80±2.25
28	95.73±4.13	97.47±1.13	101.47±0.35	100.20±0.89
60	96.93±0.66	102.77±3.01	97.80±2.83	100.27±1.80
90	97.13±1.71	105.03±2.57	103.47±3.46	102.27±1.70
120	99.37±1.96	97.97±2.45	99.87±0.70	98.33±4.53
Slope (as degradation rate, %/day)	0.0329	0.0255	0.0011	-0.0094
Standard deviation of regression ($S_{y.x}$)[b]	0.532	3.718	2.403	1.545
Point estimate of % remaining on day 120	103.95	103.06	100.14	98.87
Lowest estimate of % remaining on day 120 (with 95% confidence)[c]	102.38	92.07	93.03	94.30

RT = room temperature, SD = standard deviation.
[a]For RT storage, the temperature ranged from 20°C to 25°C; for refrigerated storage (shown as "4°C" in the table), the temperature actually ranged from 2°C to 8°C.
[b]The standard deviation of the regression is approximately equivalent to the coefficient of variation.
[c]Confidence intervals are based on 95% one-sided confidence limits. Only the lower limit is provided here.

TABLE 2. Clozapine Lactam[a] Observed, by Study Day

	Nominal Concentration and Storage Temperature[b]; % Clozapine Lactam Observed			
	25 mg/mL		50 mg/mL	
Study Day	RT	4°C	RT	4°C
0	0.033	0.00	0.00	0.00
28	0.100	0.00	0.00	0.00
60	0.100	0.00	0.10	0.00
90	0.133	0.00	0.10	0.00
120	0.200	0.00	0.10	0.00

RT = room temperature.
[a]Allowable limit for clozapine lactam was 0.5%.
[b]For RT storage, the temperature ranged from 20°C to 25°C; for refrigerated storage (shown as "4°C" in the table), the temperature actually ranged from 2°C to 8°C.

TABLE 3. Unknown Clozapine Impurity[a] Observed, by Study Day

	Nominal Concentration and Storage Temperature[b]; % Unknown Impurity Observed			
	25 mg/mL		50 mg/mL	
Study Day	RT	4°C	RT	4°C
0	0.000	0.00	0.00	0.00
28	0.000	0.00	0.00	0.00
60	0.067	0.00	0.00	0.00
90	0.200	0.10	0.05	0.00
120	0.200	0.10	0.10	0.10

RT = room temperature.
[a]Allowable limit for unknown individual clozapine impurity was 0.2%.
[b]For RT storage, the temperature ranged from 20°C to 25°C; for refrigerated storage (shown as "4°C" in the table), the temperature actually ranged from 2°C to 8°C.

stored in amber PET-G bottles for 120 days. The measured concentration of clozapine remained greater than 95% for the entire 120-day study period, and no degradation product or impurity was measured above its allowable limit. Regression analysis also demonstrated that the concentration of clozapine was likely to remain above 92.1% (with 95% confidence) for the 120-day study period. This analysis supports a BUD of 120 days for both concentrations at both temperatures. While it is recognized that regulatory agencies have limited authority over compounding, the inclusion of pharmaceutical regulatory standards for the concentration of degradation products provide an assurance of product purity and should increase compounding pharmacists' confidence in the recommended BUD.

The clozapine results obtained in this study are very similar to the results reported by Walker and others,[1] although the previous publication did not measure or report concentrations of degradation products, and the longer duration of this study allowed a longer BUD to be reported. Re-analysis of the data of Walker and others[1] by a method similar to the one used in the current study estimated that the amount remaining on day 61 ranged from 91.9% to 97.9%, for concentrations of 20 mg/mL in a variety

TABLE 4. Total Degradation Products and Impurities[a] Observed, by Study Day

	Nominal Concentration and Storage Temperature[b]; % Total Degradation Products and Impurities Observed			
	25 mg/mL		50 mg/mL	
Study Day	RT	4°C	RT	4°C
0	0.033	0.00	0.00	0.00
28	0.100	0.00	0.00	0.00
60	0.167	0.00	0.10	0.00
90	0.333	0.10	0.15	0.00
120	0.400	0.10	0.20	0.10

RT = room temperature.
[a]Allowable limit for total impurities and degradation products was 1%.
[b]For RT storage, the temperature ranged from 20°C to 25°C; for refrigerated storage (shown as "4°C" in the table), the temperature actually ranged from 2°C to 8°C.

of suspending agents stored in amber polyethylene bottles. Comparable values in the current study on day 61 ranged from 95.97% to 101.21%. Both studies used the Clozaril brand of clozapine tablets.

In the evaluation of methods for determining stability, assessment based solely on the observed concentration or percent remaining at the end of the study period does not take into account analytical variability and error, whereas the confidence interval approach[5-7,20] does account for this variability and presents a conclusion that more conservatively estimates the time to reach 90% remaining. For example, although the measured concentration of clozapine remained greater than 95% for the entire 120-day study period of the current study, confidence interval analysis predicts a less than 5% chance that the concentration of clozapine will be below 92% on the 120th day of storage. Stability studies are conducted in completely controlled environments, yet in real life, suspensions will be removed from the fridge on a daily basis and may be exposed to temperatures above 25°C. The use of confidence intervals yields a more conservative conclusion, reducing the possibility that a product with lower-than-desired potency is administered to patients.

A power calculation using the mean square error from the analysis of variance indicated that this study had the ability to detect a difference in concentration of more than 6%. Given that all of the observed differences due to temperature or container were less than 2%, none of these differences were statistically significant.

Assurance of the specificity of the analytical method is also very important. The separation and detection of intact drug in the presence of degradation compounds must be demonstrated before the method can be considered stability-indicating. Since all known degradation products and impurities were measured specifically and their concentrations estimated, the method was judged to be stability-indicating. Furthermore, the accuracy and reproducibility of the analytical method on each study day during the stability study provides the required confidence in the assay methodology.

Limitations

The stability observed with these suspensions cannot be extrapolated to other suspending vehicles or formulations compounded with other clozapine tablet formulations. This report and the previous publication[1] both used the same brand of clozapine product, Clozaril. Therefore, although we have no evidence that any differences in excipients that might exist between formulations would or would not affect the stability of suspensions, we cannot extrapolate these data to other clozapine tablet formulations.

CONCLUSION

Clozapine, as 25 mg/mL and 50 mg/mL suspensions, stored in amber PET-G bottles at 4°C or 25°C for 120 days retained more than 95% of the measured initial concentration, and no degradation product or impurity exceeded the allowable limit during the entire storage period. This study also estimated a less than 5% chance that the clozapine concentration would be below 92% of the initial concentration after 120 days of storage at either temperature. Clozapine suspensions of 25 mg/mL and 50 mg/mL can therefore be stored for up to 120 days after preparation, maintaining the desired potency and purity.

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APPENDIX 1: Compounding instructions to prepare 1 L of clozapine suspension 25 mg/mL

1.	Count out required clozapine 100-mg tablets (250 tablets).
2.	Crush and triturate tablets to form a fine, homogeneous powder.
3.	Levigate powder with less than 200 mL of MCG 1% to form a homogeneous liquid-like dispersion.
4.	Add mixture to about 200 mL MCG 1% in a 1000-mL beaker and mix continuously using high-shear mixing techniques.
5.	Wash mortar and pestle with remaining MCG 1%, transfer to beaker, and mix.
6.	Add about 400-mL Oral Syrup and continue mixing the suspension until homogeneous.
7.	Add remaining Oral Syrup to prepare a total volume of 1000 mL of suspension. Mix well.
8.	Transfer the suspension to an amber 120-mL PET-G bottle.
9.	Label and assign a BUD of 120 days, room temperature (or refrigeration).

BUD = beyond-use date, MCG = methylcellulose gel, PET-G = polyethylene terephthalate.

Prescription Modification by Pharmacists in a Hospital Setting: Are Ontario Pharmacists Ready?

Vincent Vuong, Ramola Bhojwani, Anjana Sengar, and Allan Mills

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ABSTRACT

Background: Under Ontario's *Public Hospitals Act*, the scope of professional practice of hospital pharmacists is approved by each hospital's medical advisory committee. Some Ontario hospitals have adopted policies or medical directives related to prescription modification, allowing pharmacists to broadly adapt, discontinue, hold, or renew prescriptions as part of their clinical scope of practice.

Objectives: The primary objective of this study was to describe Ontario hospital pharmacists' perception of their readiness to independently modify prescriptions. The secondary objectives of this study were to gather opinions on the perceived benefits, drawbacks, facilitators, and barriers to prescription modification by pharmacists and to determine how various factors affect perceived readiness.

Methods: A confidential web-based survey with Likert-type quantitative questions and qualitative open-ended questions was distributed to 936 hospital pharmacists in Ontario between May and July 2019. Mean scores were calculated for the following constructs affecting prescription modification: self-efficacy, support from the practice environment, and support from interprofessional relationships. Independent *t* tests were conducted to compare responses between subgroups of interest. The answers to open-ended questions were analyzed thematically.

Results: The survey had a 29% response rate ($n = 271$). The mean self-efficacy score was 5.2 out of 7 (standard deviation [SD] 1.0, Cronbach $\alpha = 0.88$), equivalent to "quite sure". The mean score for support from the practice environment was 3.3 out of 5 (SD 0.4, Cronbach $\alpha = 0.75$), equivalent to "not a factor". The mean score for support from interprofessional relationships was 4.2 out of 5 (SD 0.1, Cronbach $\alpha = 0.80$), equivalent to "weak support". Improved efficiency of care, timelier interventions to improve medication safety and efficacy, and improved interprofessional collaboration were cited as benefits of prescription modification by pharmacists. Potential for inappropriate decision-making and miscommunication were cited as concerns. Respondents in hospitals who were already performing prescription modification reported higher self-efficacy to modify prescriptions in clinical areas of both familiarity and unfamiliarity and greater support from prescribers.

Conclusions: A large proportion of respondents to a survey of Ontario hospital pharmacists expressed an encouraging level of readiness to independently modify prescriptions. Responses to open-ended questions in this study provided valuable insights to inform widespread adoption of this practice change.

Keywords: pharmacy, hospital, Ontario, prescription, modification, adaptation

RÉSUMÉ

Contexte : En vertu de la *Loi sur les hôpitaux publics* de l'Ontario, le comité consultatif de chaque hôpital approuve l'élargissement de la pratique professionnelle des pharmaciens d'hôpitaux. Certains hôpitaux de l'Ontario ont adopté des politiques ou des directives médicales concernant la modification de la prescription. Celles-ci autorisent les pharmaciens à adapter, cesser, suspendre ou renouveler largement les prescriptions dans le cadre de leur champ de pratique.

Objectifs : L'objectif principal de cette étude visait à décrire la perception des pharmaciens d'hôpitaux de l'Ontario de leur degré de préparation à modifier des prescriptions de manière indépendante. Les objectifs secondaires consistaient à recueillir les opinions sur les avantages, les inconvénients, les éléments de facilitation et les obstacles perçus par les pharmaciens au sujet de la modification de la prescription et de définir comment divers facteurs influençaient la perception de leur degré de préparation.

Méthodes : Entre mai et juillet 2019, 936 pharmaciens d'hôpitaux en Ontario ont reçu une enquête confidentielle menée sur Internet comportant des questions quantitatives de type Likert et des questions ouvertes qualitatives. Les scores médians ont été calculés pour les concepts suivants liés à la modification de la prescription : l'autoefficacité, le soutien de l'environnement de pratique et le soutien des relations interprofessionnelles. Des tests *t* indépendants ont été menés pour comparer les réponses entre les sous-groupes sous-groupes qui intéressaient les auteurs. Les réponses aux questions ouvertes ont été analysées par thème.

Résultats : Le taux de réponses à l'enquête se montait à 29 % ($n = 271$). Le score moyen pour le thème « Autoefficacité » était de 5,2 sur 7 (écart type [ET] 1, Cronbach $\alpha = 0,88$), ce qui équivaut à la réponse « Assez certain ». Le score moyen pour le thème « Soutien de l'environnement de pratique » était de 3,3 sur 5 (ET 0,4, Cronbach $\alpha = 0,75$), ce qui équivaut à la réponse « N'est pas un facteur ». Le score moyen pour le thème « Relations interprofessionnelles » était de 4,2 sur 5 (ET 0,1, Cronbach $\alpha = 0,80$), ce qui équivaut à la réponse « Soutien faible ». Les pharmaciens ont cité l'amélioration de l'efficacité des soins, les interventions en temps opportun visant à améliorer l'innocuité et l'efficacité des médicaments ainsi que l'amélioration de la collaboration interprofessionnelle comme étant des avantages de la modification indépendante des prescriptions. Ils ont aussi indiqué que le risque de prise de décision inappropriée ainsi que la mauvaise communication constituaient pour eux un sujet de préoccupation. Les répondants qui pratiquaient déjà la modification de la prescription en milieu hospitalier ont indiqué un gain d'autoefficacité de la modification des prescriptions dans des domaines cliniques qui leur sont familiers ou non, ainsi qu'un plus grand soutien de la part des prescripteurs.

Conclusions : Une grande partie des répondants à une enquête menée auprès de pharmaciens d'hôpitaux de l'Ontario ont jugé que leur degré de préparation à la modification indépendante des ordonnances était prometteur. Les réponses aux questions ouvertes de cette étude fournissent des éclaircissements précieux sur l'adoption généralisée de ce changement de pratique.

Mots-clés : pharmacie, hôpital, Ontario, prescription, modification, adaptation

INTRODUCTION

To improve the quality, accessibility, and sustainability of the Canadian health care system, pharmacists working in collaborative professional environments should practise to the full extent of their knowledge and expertise.[1] Within the health care team, pharmacists possess a unique skill set and knowledge base related to the use of medications. In a large database study, hospital pharmacist activities such as formulary development, prescriber education, drug order review, and participation in patient care rounds were shown to reduce mortality rates.[2] Randomized studies have demonstrated reductions in hospital visits, drug-related readmissions, length of hospital stay, and health care costs in association with interventions by hospital pharmacists.[3,4] Pharmacists possess, at a minimum, a Bachelor of Pharmacy or Doctor of Pharmacy degree, and many pharmacists have undertaken postgraduate clinical training. Hospital pharmacists in Canada are trained to have the knowledge, skills, and judgment to make independent decisions related to drug therapy optimization, in collaboration with the patient and the care team.

While reviewing prescriptions, pharmacists regularly identify drug therapy problems, such as the wrong dose for a given indication or organ dysfunction, the wrong dosage form, the wrong drug regimen, or the wrong route of administration (Table 1). In addition, pharmacists often identify situations where discontinuing, holding, or renewing medications would be beneficial, such as duplication of therapy or medications with an inappropriate stop date. For a majority of hospitals in Ontario, current inpatient pharmacy practice involves the pharmacist contacting the prescriber to suggest a drug therapy change and documentation of any resulting telephone or verbal prescription in the patient's chart. This process can interrupt the workflow of both the pharmacist and the prescriber and could potentially lead to delay in optimal therapy for the patient.

In Ontario, with the passing of Bill 179,[5,6] pharmacists are now permitted to adapt and renew prescriptions while adhering to the standards of practice of the National Association of Pharmacy Regulatory Authorities[7] and the Ontario College of Pharmacists (OCP) Code of Ethics.[8] However, under Ontario's *Public Hospitals Act*, the professional practice scope of hospital pharmacists, including prescription adaptation and renewal, must be approved by each hospital's medical advisory committee. A minority of Ontario hospitals currently have policies or medical directives that allow for general adaptation, discontinuation, holding, or renewal of medication orders by pharmacists,

TABLE 1. Examples of Prescription Modification by Pharmacists

Identified Drug-Related Problem	Current Order	Medication Order Written by the Pharmacist
Renal impairment dosing recommendations	Enoxaparin 40 mg SC daily for DVT prophylaxis (estimated creatinine clearance 25 mL/min)	Change enoxaparin to 30 mg SC daily for DVT prophylaxis
Patient has difficulty swallowing	Levofloxacin 750 mg PO daily × 5 days for pneumonia	Change levofloxacin to 750 mg IV daily × 5 days for pneumonia
	Phenytoin 300 mg PO daily	Phenytoin 150 mg NG bid
	Diltiazem CD 120 mg PO daily	Diltiazem immediate-release 30 mg NG qid
Product strength not available	Ciprofloxacin 400 mg PO bid × 3 days for UTI	Change ciprofloxacin to 500 mg PO bid × 3 days for UTI
Strength not specified	Flovent 1 puff bid	Flovent 250 mcg 1 puff bid
Incorrect directions	Risedronate 150 mg PO daily	Risedronate 150 mg PO monthly
Dosage form alternative	Betamethasone 0.1% lotion	Betamethasone 0.1% cream
Discontinue duplicate therapy	Patient has an order for enoxaparin, and new order for apixaban is received	Discontinue enoxaparin
Discontinue vaccine upon clarification of vaccine history	Prescriber ordered PNEUMOVAX 23, despite patient already having received a recent dose in the community	Discontinue PNEUMOVAX 23 (once confirmed with community prescriber that vaccine was previously administered)
Hold order	Olanzapine 25 mg PO daily (pharmacist completed BPMH and determines dose to be 2.5 mg PO daily)	Hold olanzapine 25 mg PO daily (RPh reviews with MD)
Renew chronic [long-term] medication	Eye drops for glaucoma discovered on completing the BPMH, but not ordered	latanoprost 0.005% one drop in right eye daily at bedtime

BPMH = best possible medication history, CD = controlled delivery, DVT = deep vein thrombosis, MD = physician, NG = nasogastric tube, RPh = registered pharmacist, UTI = urinary tract infection.

without the approval and/or signature of the authorized prescriber, and that are not limited to specific drugs, drug classes, or indications. See Box 1 (glossary of terms) for the definition of prescription adaptation, as well as other terms used in this article.

Outside of Ontario, several Canadian provinces have already legislated independent pharmacist prescribing, including Alberta, where pharmacists with "additional prescribing authority" can prescribe medications within their level of professional competence.[10] A literature search of MEDLINE, Embase, Scopus, and IPA databases identified numerous barriers preventing prescription modification by pharmacists from becoming routine practice in Ontario hospitals, including fear of liability, lack of confidence, stress, lack of employer support, and lack of physician acceptance.[11-15] To date, an assessment of the readiness of Ontario hospital pharmacists to modify prescriptions in a hospital setting has not been conducted.

The primary objective of this study was to determine, by means of a provincial survey, the perception of readiness of hospital pharmacists in Ontario to independently modify prescriptions, from individual and organizational perspectives. For the purposes of this study, prescription modification by pharmacists includes adaptation, discontinuation, holding, or renewal of medication orders. Narcotics, controlled drugs, and targeted substances were excluded, because pharmacists in Ontario do not have the authority to modify prescriptions for these medications. A secondary objective of this study was to gather opinions about the perceived benefits, drawbacks, facilitators, and barriers to pharmacists performing prescription modification, to inform the creation or adoption of tools, training materials, technology, or changes in workflow to help improve uptake. Another secondary objective was to determine how various factors, such as years of practice, location of pharmacy education, highest pharmacy degree obtained, postgraduate residency training, or hospital size, affected pharmacists' perceived readiness to modify prescriptions in a hospital setting.

METHODS

Study Design and Setting

A confidential, self-administered web-based survey was made available for completion by hospital pharmacists in Ontario, Canada. The survey sample was based on a list of pharmacists, provided by the OCP, who reported practising in an accredited Ontario hospital pharmacy workplace and consented to sharing their contact information for research purposes. An email invitation to participate in the study, with a link to the online survey (using the SurveyMonkey platform), was sent to all pharmacists on this list. The initial study invitation was sent at the beginning of May 2019, with reminder emails sent at the 2-, 6-, and 10-week time points. The overall survey period was from May to July 2019. To encourage response to the survey, participants were given the opportunity to win one of two $50 gift cards. From a total of 2550 hospital pharmacists practising in Ontario at the time of this study (according to OCP data), a sample size of 334 participants was calculated to be representative for purposes of a descriptive survey, with a confidence level of 95% and a margin of error of 5%.[16]

Survey eligibility was limited to pharmacists in Part A of the Public Register maintained by the OCP, that is, pharmacists who were licensed in Ontario and currently practising at an accredited Ontario hospital pharmacy.[9] Pharmacy interns and pharmacy students were excluded, because the study aimed to gather thoughts and experiences from practising pharmacists. Part B pharmacists were also excluded, because prescription modification would not be applicable to their practice settings.[9] Additionally, the 4 authors of this manuscript were excluded from participation.

The study was approved by the Trillium Health Partners Research Ethics Board. All participants in this study provided written informed consent via the online survey tool.

BOX 1: Glossary of Terms

Prescription adaptation: Prescription adaptation involves altering the dose, dosage form, regimen, or route of administration (e.g., to address a patient's unique needs and circumstances). Adapting a prescription does not include therapeutic substitution, which involves changing a pre-existing prescription to a chemically different product that is considered to be therapeutically equivalent.[5,6]
Prescription renewal: Prescription renewal involves providing a patient with a prescription that repeats a prescription previously provided to that patient (e.g., for the purpose of continuity of care).[5,6]
Prescription modification: Prescription modification is an umbrella term encompassing prescription adaptation, as well as discontinuation, holding, or renewal of a prescription.
Part A pharmacist[a]: Pharmacists registered in Part A in Ontario are those who provide patient care and have worked a minimum of 600 hours in patient care over the previous 3 years. Patient care includes providing pharmacy services to the public, such as compounding, dispensing, providing drug information and education, and monitoring and managing medication therapy.[9]
Part B pharmacist[a]: Pharmacists registered in Part B in Ontario are those who do not, and have declared that they will not, provide patient care.[9]

[a]The educational and practice requirements for Part A and Part B of the Public Register (as maintained by the Ontario College of Pharmacists [OCP]) are specified by the OCP's Quality Assurance Committee.

Survey Questions

To assess the readiness of Ontario hospital pharmacists to modify prescriptions, an ad hoc survey tool was designed with a mixture of quantitative Likert-type questions and qualitative open-ended questions. Existing instruments to assess readiness for change in a health care setting were either too narrow or too broad in scope, were not well suited to a health care context, or lacked reliability and validity testing.[17] In their perspective article, Holt and others[18] conceptualized readiness for change in health care practice as consisting of various psychological and structural factors at both individual and organizational levels. Psychological readiness describes the extent to which an individual or organization is cognitively and emotionally inclined to accept, embrace, and implement a change, whereas structural readiness describes the extent to which the circumstances surrounding an individual or organization enhance or inhibit the acceptance and implementation of change. Our survey tool aimed to measure several of these factors in relation to the adoption of prescription modification by pharmacists.

An existing survey instrument with evidence for reliability and validity was developed by Guirguis and others[19] for the purpose of measuring factors that influence pharmacists' adoption of prescribing in Alberta, Canada. We contacted the authors of that survey instrument and obtained permission to adapt their survey instrument to address our primary objective. For our Likert-type questions, we adapted 3 of the 8 scales with strong evidence for reliability and validity from the survey instrument by Guirguis and others,[19] including questions about self-efficacy, support from the practice environment, and support from interprofessional relationships (for the complete survey, see Appendix 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/205). We included additional qualitative open-ended questions to address one of our secondary objectives.

Pilot Test

Before the survey was launched, a pilot survey was conducted with 25 hospital pharmacists at Trillium Health Partners in Ontario, Canada, to test for face validity, comprehensibility, completeness, layout, and participant burden of the survey tool. Completion of the pilot survey did not preclude participation in the provincial survey. Median time to complete the pilot survey was 18 minutes. To reduce respondent burden, nonessential demographic questions were removed, and open-ended questions were made optional. The wording of ambiguous questions was simplified, and the order of questions was modified to facilitate survey completion. Because of issues in interpreting questions in the "support from practice environment" scale, the questions were modified to inquire about factors more specific to prescription modification, such as amount of pharmacy staffing, current workload, technology, physical environment, and employer's expectations. All changes to the survey were approved by the Trillium Health Partners Research Ethics Board before launch of the provincial survey.

Data Analysis

The response rate was calculated by dividing the number of survey respondents by the number of eligible participants. Survey respondents had to complete all mandatory questions to be included in the study. Demographic and practice information about survey respondents was summarized and compared with similar information for the total population of Ontario hospital pharmacists, to indicate representativeness.

Each response to a quantitative Likert-type question was converted to a numeric value. Responses were plotted and examined for normal distributions. Descriptive statistics, including means, medians, and standard deviations, were reported as appropriate for each quantitative question. We calculated means from the Likert-type scale data, as it is reasonable to do so if the data follow a normal distribution,[20] and we could still draw inferences from the data because the values on our scales were reasonably distributed.[21] Our revised tool was not previously tested in Ontario for the purposes of our research question, so the internal consistency of each of the 3 constructs (self-efficacy, support from the practice environment, and support from interprofessional relationships) was recalculated using the Cronbach α coefficient, a measure of how closely correlated a set of questions are within a construct. An α value greater than 0.70 was considered to indicate adequate reliability. Assuming internal consistency, overall construct mean score and standard deviation were determined by pooling the mean scores and their standard deviations for all questions within each construct. Exploratory subgroup analyses were conducted by performing independent *t* tests between subgroups on the mean scores of each quantitative question, with *p* values less than 0.05 being considered statistically significant.

For qualitative open-ended questions, thematic analysis was performed using NVivo 12 (QSR International) and Excel (Microsoft Corporation). All individual responses for each question were reviewed and coded into major themes and subthemes. Irrelevant responses to each question were removed. Each question response was reviewed numerous times, and major themes and subthemes were refined and quantified as patterns emerged. Selected quotes were highlighted.

RESULTS

From a list of 947 pharmacists provided by the OCP, 11 pharmacists were deemed ineligible to participate, which left a total of 936 eligible participants (Figure 1). Of the 936 eligible participants, 271 (29.0%) completed the survey. These 271 respondents represented 10.6% of the 2550 hospital

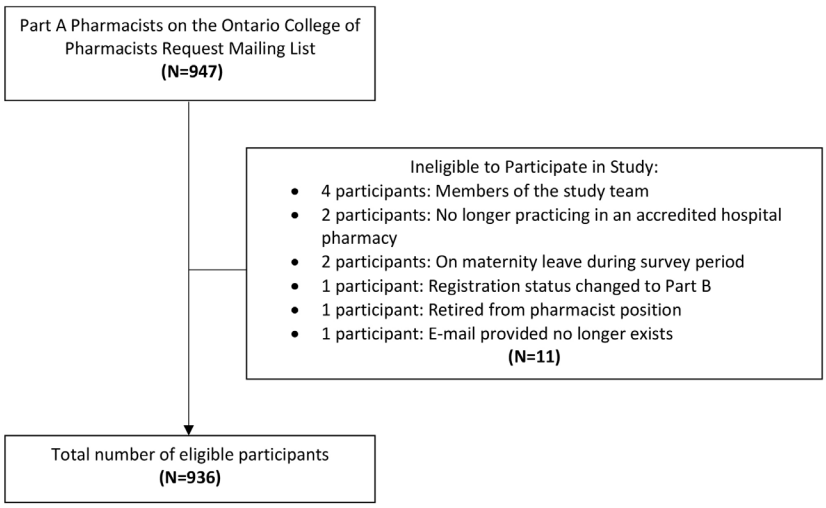

FIGURE 1. Flow chart of eligibility to participate in the survey.

pharmacists in Ontario. Relative to all hospital pharmacists in Ontario, the survey respondents were similar in distribution of gender, location of pharmacy education, and years of practice, with the caveat that the OCP Public Register reports data only for years licensed in Ontario and does not account for years of practice outside Ontario (Table 2). Of the 271 survey respondents, 56 (20.7%) reported that their hospital workplace had an existing policy or medical directive to broadly modify prescriptions, whereas 215 respondents (79.3%) reported that their workplaces did not have such policies or directives.

Among the 271 survey respondents, the mean score across the 7 questions for the self-efficacy scale was 5.2/7 (standard deviation [SD] 1.0, Cronbach α = 0.88), indicating that respondents were "quite sure" that they could perform various aspects of prescription modification, including patient assessment, modification within clinical areas of both familiarity and nonfamiliarity, modification of both pre-existing and newly started therapies, documentation, and acceptance of responsibility for medication management (Table 3). The mean score across the 5 questions in the "support from practice environment" scale was 3.3/5 (SD 0.4, Cronbach α = 0.75), indicating that factors such as amount of pharmacy staffing, current patient load and/or other workload, technology, the physical practice environment, and the employer's expectations were "not a factor" in facilitating or hindering respondents' ability to modify orders. The mean score across the 2 questions in the "support from interprofessional relationships" scale was 4.2/5 (SD 0.1, Cronbach α = 0.80), indicating that respondents felt that their relationships with prescribers, nurses, and other allied health professionals provided "weak support" in facilitating their ability to modify orders.

Subgroup analyses are reported in Appendix 2, Supplementary Tables S1–S7 (available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/205). Respondents working in hospitals with an existing prescription modification policy or medical directive (relative to those in hospitals without such policies) reported higher self-efficacy to perform patient assessments (6.0/7 versus 5.4/7, $p < 0.001$), to modify orders in clinical areas of unfamiliarity (3.6/7 versus 3.1/7, $p = 0.039$), and to accept responsibility for medication management (6.0/7 versus. 5.6/7, $p = 0.019$). Respondents at these hospitals also reported greater support from employers (4.2/5 versus 3.6/5, $p < 0.001$), prescribers (4.6/5 versus 4.0/5, $p < 0.001$), and nursing and allied health professionals (4.6/5 versus 4.3/5, $p = 0.007$). Male respondents reported higher self-efficacy than female respondents to modify orders in clinical areas of unfamiliarity (3.6/7 versus 3.1/7, $p = 0.036$). Respondents with 10 years or more of practice experience (relative to those with less than 10 years of practice experience) reported amount of pharmacy staffing (2.8/5 versus 3.4/5, $p = 0.001$) and current patient load and/or workload (2.5/5 versus 2.9/5, $p = 0.025$) as greater barriers to modifying prescriptions. Respondents with pharmacy residency training (relative to those without residency training) reported greater support from employers (4.0/5 versus 3.5/5, $p = 0.001$), prescribers (4.4/5 versus 4.0/5, $p < 0.001$), and nursing and allied health professionals (4.5/5 versus 4.3/5, $p = 0.037$). Respondents working at hospitals with more than 500 beds (relative to those from hospitals with up to 500 beds) reported greater support from prescribers (4.4/5 versus 4.1/5, $p = 0.007$) but less support from pharmacy staffing (2.7/5 versus 3.2/5, $p = 0.012$).

Major themes and subthemes generated from the qualitative questions are summarized in Table 4. Clear benefits of prescription modification by pharmacists to pharmacy practice as a whole include reducing workload, streamlining the distribution process, resolving drug therapy problems in a timelier manner, and increasing interprofessional collaboration. Nearly 1 in 10 responses linked the ability to independently modify prescriptions with

increased job satisfaction, autonomy, and engagement. One respondent noted, "[Pharmacist prescription modification] helps me develop a stronger relationship with the patient care team as I can truly be the medication expert [who] can fix the patients' drug related problems." Listed benefits to patients included improving medication efficacy and safety through proactive pharmacist interventions, improving patient-centred care, and providing more opportunities for patient–pharmacist interaction.

Regarding potential problems, over a third of open-ended responses cited inappropriate decision-making because of factors such as improper or insufficient data collection or patient assessment; pharmacist limitations, such as gaps in therapeutic knowledge, lack of time, or lack of confidence; and pharmacy department limitations, such as inadequate staffing and logistical issues. One respondent expressed, "Pharmacists are not trained to assess patients and therefore I don't believe we should have the ability to largely modify prescriptions." Another third of responses cited miscommunication within the care team as a potential concern, including poor documentation of the care plan by the prescriber, poor communication of the change by the pharmacist to the care team, and confusion about responsibilities. A quarter of responses cited the potential for conflict among members of the care team or with the hospital organization. As one respondent noted, "Physicians think pharmacists will get too much power. In my hospital this has been an issue—they view us as a threat." Regarding personal limitations, less than 10% of responses reported personal barriers such as underdeveloped relationships with prescribers at their institution or personality traits such as avoidance of conflict or shyness. Regarding

TABLE 2. Characteristics of Survey Respondents and Hospital Pharmacists in Ontario

Characteristic	No. (%) of Respondents (*n* = 271)		No. (%) of Hospital Pharmacists in Ontario[a] (*n* = 2550)	
Gender				
Female	203	(74.9)	1961	(76.9)
Male	67	(24.7)	589	(23.1)
Other	1	(0.4)	0	
Location of pharmacy education				
Ontario	197	(72.7)	1776	(69.6)
Elsewhere in Canada	40	(14.8)	389	(15.3)
United States	15	(5.5)	170	(6.7)
International, outside United States	19	(7.0)	215	(8.4)
Years of practice[b]				
0–4	64	(23.6)	504	(19.8)
5–9	39	(14.4)	528	(20.7)
10–14	31	(11.4)	425	(16.7)
≥ 15	137	(50.6)	1093	(42.9)
Highest pharmacy degree obtained			Data not available	
BScPharm	146	(53.9)		
PharmD, entry-level	54	(19.9)		
PharmD, postgraduate	53	(19.6)		
Other	18	(6.6)		
Postgraduate training			Data not available	
Hospital pharmacy residency	91	(33.6)		
No hospital pharmacy residency	180	(66.4)		
Hospital size, by number of beds			Data not available	
< 50	9	(3.3)		
50–200	57	(21.0)		
201–500	146	(53.9)		
> 500	59	(21.8)		
Existing prescription modification policy or medical directive			Data not available	
Policy	46	(17.0)		
Medical directive	10	(3.7)		
None	215	(79.3)		

[a]Data provided by the Ontario College of Pharmacists.
[b]For survey respondents, these data refer to years of practice in a hospital setting; for Ontario pharmacists, these data refer to years licensed to practice in Ontario.

the consequences of clinical errors, respondents were most worried about harming the patient, followed by losing the trust of other health care professionals or patients, litigation, regulatory board consequences (e.g., licence revocation or suspension), and employment consequences such as loss of employment. Despite these potential consequences, roughly 15% of responses did not indicate any concerns with prescription modification by pharmacists, including the following statements from respondents: "[As pharmacists], we are professionals and need to be accountable for our decisions" and "If we are to expand our therapeutic involvement, we would naturally need to expand our liability."

Regarding needs for additional training, two-thirds of responses cited clinical training in specialty areas such as pediatrics, intensive care, or antimicrobial stewardship, as well as other broad topics including therapeutic drug monitoring, interpreting laboratory results and diagnostic tests/imaging, approach to diagnosis and differentials, and basic

TABLE 3. Overall Survey Responses (n = 271)

	Data by Question			Data for Construct		
Survey Section and Questions[a]	**Mean**	**Median**	**SD**	**Mean**	**SD**	**Cronbach α**
Self-efficacy — How sure are you that you could:				5.2 out of 7 *Quite sure*	1.0	0.88
Question 1: Perform a patient assessment to modify any medication order?	5.5 out of 7 *Very sure*	6.0 out of 7 *Very sure*	1.3			
Question 2: Modify any medication order in a clinical area that you are familiar with?	5.8 out of 7 *Very sure*	6.0 out of 7 *Very sure*	1.1			
Question 3: Modify any medication order in a clinical area that you are not familiar with?	3.2 out of 7 *Somewhat sure*	3.0 out of 7 *Somewhat sure*	1.6			
Question 4: Modify any medication order for patients starting a new therapy in hospital?	4.5 out of 7 *Quite sure*	5.0 out of 7 *Quite sure*	1.6			
Question 5: Modify any medication order for patients continuing a pre-existing therapy from home?	5.3 out of 7 *Quite sure*	6.0 out of 7 *Very sure*	1.4			
Question 6: Perform appropriate documentation for the rationale of modifying a medication order?	6.0 out of 7 *Very sure*	6.0 out of 7 *Very sure*	1.1			
Question 7: Accept responsibility for medication management?	5.7 out of 7 *Very sure*	6.0 out of 7 *Very sure*	1.3			
Support from practice environment — To what extent would the following factors in your current practice location affect your ability to modify any medication order?				3.3 out of 5 *Not a factor*	0.4	0.75
Question 1: Amount of pharmacy staffing?	3.0 out of 5 *Not a factor*	3.0 out of 5 *Not a factor*	1.4			
Question 2: Current patient load and/or other workload?	2.7 out of 5 *Not a factor*	2.0 out of 5 *Weak barrier*	1.4			
Question 3: Technology?	3.6 out of 5 *Weak support*	4.0 out of 5 *Weak support*	1.3			
Question 4: Physical practice environment?	3.4 out of 5 *Not a factor*	3.0 out of 5 *Not a factor*	1.2			
Question 5: Employer's expectations?	3.7 out of 5 *Weak support*	4.0 out of 5 *Weak support*	1.2			
Support from interprofessional relationships — To what extent would the following factors affect your ability to modify any medication order?				4.2 out of 5 *Weak support*	0.1	0.80
Question 1: Relationship with prescribers?	4.2 out of 5 *Weak support*	4.0 out of 5 *Weak support*	1.4			
Question 2: Relationship with nursing and allied health professionals?	4.3 out of 5 *Weak support*	5.0 out of 5 *Weak support*	1.4			

SD = standard deviation.

[a]Complete details for each question are provided in Appendix 1 (available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/205).

physical assessments. One-third of responses to the same question supported having training to clearly outline the scope, restrictions, and expectations of any policy or medical directive, guidance on medical-legal implications, and appropriate documentation and monitoring procedures. Respondents felt that it was important to engage other health care professionals: "I think in a roll-out situation, communication to all stakeholders would be essential". For technology, over 80% of responses cited technological improvements that would facilitate access to all necessary patient information, including computerized physician order entry, electronic medical records, e-documentation, electronic medication administration records, and access to community data. For department-wide changes, nearly half of responses suggested active support and training from leadership, including ongoing continuous quality improvement and educational procedures, such as regular auditing or competency reassessment processes. A quarter of responses suggested optimization of pharmacy staff roles, including ensuring consistent pharmacist clinical coverage on consecutive days, minimizing technical responsibilities for pharmacists, and optimizing the scope of practice of pharmacy technicians. Suggested tools included creating case-based examples of different types of prescription modifications, having standardized templates for clinical assessment and documentation, and creating hospital-specific dosing guidelines.

DISCUSSION

Responses to the survey's quantitative questions provided valuable insights that Ontario hospital pharmacists feel they are individually ready to take on the practice change of prescription modification and do not feel that organizational factors such as their practice environment or interprofessional relationships present any barriers to performing this task. With the final sample size of 271 respondents, the quantitative results of our descriptive survey study were adequately representative of the population of hospital pharmacists in Ontario, with a confidence level of 95% and a margin of error of 6%.[22]

Although our subgroup analyses were exploratory in nature, we can still draw inferences from the data, because parametric methods such as the *t* test are robust enough to account for violations of assumptions.[21] Higher scores for self-efficacy and support from interprofessional relationships for respondents working at institutions with existing

TABLE 4 (part 1 of 4). Emergent Themes from Qualitative Open-Ended Questions

Open-Ended Question	Major Themes No. (% Frequency)	Subthemes
A) How could pharmacist prescription modification benefit my practice? *594 responses*	A1. Improve efficiency 316 (53.2%)	A1.1. Reduce workload, wastages, and cost A1.2. Provide faster medication turnaround and streamlined distribution process A1.3. Resolve drug therapy problems in a more timely manner A1.4. Facilitate continuity of care
	A2. Improve my ability to provide better patient care 148 (24.9%)	A2.1. Improve medication efficacy and safety A2.2. Provide patient-centred care A2.3. Improve patient–pharmacist relationship
	A3. Promote full utilization of pharmacists' scope of practice 86 (14.5%)	A3.1. Improve job satisfaction, engagement, and autonomy A3.2. Increase ability to reinforce medication expertise A3.3. Provide more opportunities for self-learning and professional advancement
	A4. Increase interprofessional collaboration 44 (7.4%)	A4.1. Improve interprofessional relationships A4.2. Share accountability and responsibility for patient care A4.3. Provide opportunities for interprofessional teaching
B) How could pharmacist prescription modification benefit patients? *485 responses*	B1. Improve patient outcomes 447 (92.2%)	B1.1. Improve medication efficacy and safety B1.2. Reduce delay to appropriate drug therapy B1.3. Facilitate continuity of care B1.4. Provide patient-centred care B1.5. Reduce length of hospital stay B1.6. Increase access to care B1.7. Improve patient satisfaction and hospital experience B1.8. Improve medication adherence
	B2. Increase interaction with pharmacists 30 (6.2%)	B2.1. Increase opportunities for discussion with pharmacist and development of a patient–pharmacist relationship B2.2. Improve understanding of the hospital pharmacist's role
	B3. Financial savings 8 (1.6%)	B3.1. Pharmacist review of drug coverage options B3.2. Pharmacist-initiated change to formulary alternative

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TABLE 4 (part 2 of 4). Emergent Themes from Qualitative Open-Ended Questions

Open-Ended Question	Major Themes No. (% Frequency)	Subthemes
C) What are some problems that could arise from pharmacist prescription modification? *461 responses*	C1. Inappropriate prescription modification by pharmacist 161 (34.9%)	C1.1. Incomplete or inaccurate data collection and/or patient assessment C1.2. Pharmacist limitations C1.3. Pharmacy department limitations C1.4. Lack of a double-check for pharmacists C1.5. Conflict of interest
	C2. Miscommunication within care team 137 (29.7%)	C2.1. Poor prescriber documentation of original rationale, care plan, and/or diagnosis C2.2. Poor pharmacist communication of change to the care team C2.3. Confusion with regard to responsibilities, accountability, and liability C2.4. Prescriber's failure to note changes C2.5. Confusion regarding discharge medications C2.6. Logistical/technology errors
	C3. Potential conflict with members of the care team or hospital leadership 118 (25.6%)	C3.1. Prescriber–pharmacist disagreement, conflict, or loss of trust after modification C3.2. Disapproval of full pharmacist scope by prescribers or hospital leadership C3.3. Conflict with nursing or other allied health
	C4. Potential for less verbal discussion with prescriber 17 (3.7%)	C4.1. Missed opportunities to educate prescribers C4.2. Less opportunity to establish rapport, consensus
	C5. Poor patient acceptance 15 (3.3%)	C5.1. Lack of patient–pharmacist communication regarding change C5.2. Lack of trust in pharmacists
	C6. Increase in pharmacist workload and responsibilities 7 (1.5%)	C6.1 Increase in pharmacist workload
	C7. Increase in wastage 6 (1.3%)	C7.1. Duplication of work C7.2. Excessive ordering of lab tests
D) What consequences from clinical errors due to pharmacist prescription modification am I concerned about? *219 responses*	D1. Patient harm or medication error 67 (30.6%)	D1.1. Adverse drug reaction, toxicity, or death D1.2. Deterioration of current condition
	D2. Loss of support, trust, or confidence from others 42 (19.2%)	D2.1. From other health care professionals D2.2. From patients or the general public D2.3. From the hospital organization
	D3. Litigation 40 (18.3%)	D3.1. To individual pharmacist D3.2. To hospital organization
	D4. No concerns 28 (12.8%)	D4.1. Pharmacists should practise at their own comfort level/competence D4.2. Pharmacists should recognize when a discussion with the prescriber is warranted D4.3. Pharmacists should perform appropriate assessment, documentation, and follow-up D4.4. Pharmacists must stay within the scope of the policy/medical directive
	D5. Regulatory board consequences 18 (8.2%)	D5.1. Licence revocation/suspension D5.2. Fine D5.3. Patient filing a concern with regulatory college
	D6. Liability insurance 11 (5.0%)	D6.1. Uncertainty of insurance coverage for prescription modification activities D6.2. Increased insurance premiums
	D7. Employment consequences 9 (4.1%)	D7.1. Loss of employment D7.2. Patient/family complaint to hospital employer D7.3. Employer reprimand
	D8. Personal stress 4 (1.8%)	D8.1. Loss of self-confidence D8.2. Mental stress over decisions made

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TABLE 4 (part 3 of 4). Emergent Themes from Qualitative Open-Ended Questions

Open-Ended Question	Major Themes No. (% Frequency)	Subthemes
E) What types of additional training would be beneficial to support my ability to modify orders? *224 responses*	E1. Additional clinical training 146 (65.2%)	E1.1. Specialty clinical areas or medication-related topics E1.2. Interpreting diagnostic imaging, tests, and lab values E1.3. Diagnosis and differentials E1.4. Physical assessment E1.5. Continuing education E1.6. Residency training
	E2. Training specific to pharmacist prescription modification 78 (34.8%)	E2.1. Scope, restrictions, and expectations of policy/medical directive E2.2. Appropriate documentation E2.3. Pharmacotherapy work-up process and clinical judgment E2.4. Effective communication strategies E2.5. Medical-legal implications E2.6. Practice cases E2.7. Policy dissemination to other health care professionals E2.8. Appropriate monitoring/follow-up E2.9. Pharmacist peer mentorship E2.10. Feedback from other stakeholder groups E2.11. Certification/recertification processes
F) What are personal limitations in my ability to perform prescription modification? *186 responses*	F1. Lack of knowledge, experience, or training 97 (52.2%)	F1.1. Lack of knowledge in particular therapeutic areas or medications F1.2. Missing information for patient data gathering F1.3. Lack of experience/training with clinical assessment and/or decision-making F1.4. Lack of training in diagnosis and differentials F1.5. Not keeping up with new evidence and guidelines F1.6. Lack of retail and outpatient pharmacy experience
	F2. Lack of time 46 (24.7%)	F2.1. Competing priorities and workload F2.2. Inefficiencies in practice
	F3. Fear 13 (7.0%)	F3.1. Fear of making an incomplete or inaccurate assessment F3.2. Fear of liability F3.3. Fear of damage to relationships or loss of trust
	F4. Lack of confidence/comfort 12 (6.5%)	F4.1. Lack of confidence with clinical decision-making F4.2. Lack of comfort in areas outside of my expertise
	F5. Underdeveloped relationship with interprofessional team 12 (6.5%)	F5.1. Lack of relationship with prescribers F5.2. Lack of relationship with nursing and allied health
	F6. Personality traits or personal beliefs 4 (2.2%)	F6.1. Avoidance of conflict F6.2. Shyness F6.3. Disagreement with pharmacists' clinical scope of practice
	F7. Ability to receive feedback 1 (0.5%)	F7.1. Difficulty with handling complaints
	F8. Physical barriers 1 (0.5%)	F8.1. Limited by dispensary role; unable to physically review paper chart or interview patient

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TABLE 4 (part 4 of 4). Emergent Themes from Qualitative Open-Ended Questions

Open-Ended Question	Major Themes No. (% Frequency)	Subthemes
G) What is some technology that could improve my ability to perform prescription adaptation? *135 responses*	G1. Improvements to the hospital information system 95 (70.4%)	G1.1. Electronic medical records, charting, medication administration records, and bedside data G1.2. Computerized physician order entry G1.3. Electronic pharmacist documentation G1.4. Integration of separate software programs G1.5. Electronic generation of clinical lists, reports, and drug queries G1.6. Off-site access G1.7. Electronic medication reconciliation
	G2. Access to health information in the community 18 (13.3%)	G2.1. Community labs, diagnostic imaging, or tests G2.2. Community pharmacy data (e.g., filled prescriptions, insurance coverage) G2.3. Provincial/national centralized EMR system
	G3. Access to computers 11 (8.1%)	G3.1. Personal laptop/tablet computer G3.2. Additional workstations/workspace
	G4. Access to particular clinical resources (e.g., UpToDate, Dynamed, Lexicomp, Micromedex, Sanford Guide) 8 (5.9%)	G4.1. On-site access G4.2. Mobile applications
	G5. Improvements in peer-to-peer communication 3 (2.2%)	G5.1. Improved methods to reach physicians
H) What are some department-wide changes that could better prepare my pharmacy department to perform prescription adaptation? *196 responses*	H1. Provide support and continuing education 91 (46.4%)	H1.1. Development of a standardized policy/medical directive H1.2. Involvement of interprofessional staff H1.3. Pharmacist training sessions H1.4. Support from pharmacy management and hospital leadership H1.5. Continuous quality improvement H1.6. Pharmacist peer education and mentorship H1.7. Improve onboarding for new hires
	H2. Increase efficiency of pharmacist clinical roles 31 (15.8%)	H2.1. Allocate more time to clinical activities H2.2. Optimize scope of pharmacy technicians H2.3. Standardize documentation processes H2.4. Consistency of clinical coverage for consecutive days H2.5. More program-focus instead of dispensary-focus
	H3. Optimize pharmacist staffing 22 (11.2%)	H3.1. Increase pharmacy staffing H3.2. Rational scheduling/cross-coverage H3.3. Preference for hiring experienced staff
	H4. Develop support tools 21 (10.7%)	H4.1. Case-based examples or guidelines on different types of prescription modifications H4.2. Documentation templates H4.3. Clinical guidelines (e.g., renal dosing, antibiotic dosing) H4.4. Clinical assessment/care plan templates
	H5. Increase technology investment 15 (7.7%)	See subthemes for question G
	H6. Reduce pharmacist dispensary roles 8 (4.1%)	H6.1. Minimize or remove order entry or other technical responsibilities H6.2. Dedicated dispensary versus clinical pharmacists, rather than a mixed clinical and dispensary role
	H7. Develop prerequisite or alternative policies/medical directives 4 (2.0%)	H7.1. Prescription modification limited to particular drugs or drug classes (e.g., vancomycin or aminoglycosides) H7.2. Pharmacist prescribing (e.g., for minor ailments, nicotine replacement therapy) H7.3. Harmonization of existing policies/medical directives
	H8. Increase physical workspace 4 (2.0%)	H8.1. Additional workspace within dispensary or on floors

EMR = electronic medical records.

prescription modification policies or medical directives suggests a positive reception for this practice change. The fact that respondents with 10 years or more of experience reported pharmacy staffing and patient load as greater barriers than did newer pharmacists may reflect the increasing clinical responsibilities of hospital pharmacists and the increasing strain of patient volumes on the Canadian health care system. Higher scores from residency-trained respondents regarding support from employers and other health care professionals could be due to factors ranging from greater comfort with working alongside the interprofessional team to feeling more valued and supported by their employers as a result of their specialized training, as well as differences in the collaborative practice environment of respondents. Compared with smaller hospitals, facilities with more than 500 beds can be subject to higher patient loads, but may have higher numbers of medical learners and residency-trained pharmacists, who could foster interprofessional collaboration.

The qualitative responses from our survey highlighted many benefits of prescription modification and identified potential limitations that pharmacists might experience. Word clouds, based on word frequency within the responses, were created to form snapshots of these perceived benefits and limitations (Figures 2 and 3). To minimize potential problems with this practice change, it is imperative that pharmacists always practise within their own comfort level and competence, putting the patient's best interests at the core of each intervention. Pharmacists can prevent miscommunication by ensuring that appropriate verbal communication is provided to care team members within a reasonable time frame after interventions are performed. When applicable, written standardized documentation should always be provided. If pharmacists are unsure of the patient's status and/or the prescriber's intent, the prescriber should be contacted for clarification. If hospital pharmacy departments wish to pursue prescription modification by pharmacists, a methodical process to gather input from the pharmacy team, physician leaders, and other interprofessional staff is highly recommended. The roll-out plan should include communication and dissemination to all affected stakeholders. Offering training sessions catered to the needs and concerns of the pharmacist group and putting structures in place to maintain continuous quality improvement of the practice change are suggested.

A major limitation of this study was its reliance on self-reported data to provide insights into pharmacists' perceptions of their own readiness and how other health care professionals and stakeholders may view them. Future studies could gather input from nonpharmacy stakeholders. such as prescribers, nurses, other allied health professionals, and hospital administrators. There was a risk of sampling bias and nonresponse bias, as pharmacists who volunteered to be on the OCP mailing list and completed the survey might differ significantly from those who did not complete the survey. We attempted to minimize bias by inviting a large population (over one-third of all Ontario hospital pharmacists) and matching our survey sample to the overall population of Ontario hospital pharmacists on factors such as gender, location of pharmacy education, and years of practice. Finally, this study focused on pharmacy legislation in Ontario, and its results may not be applicable outside this province. Despite differences in pharmacy

FIGURE 2. Word cloud representing the benefits of prescription modification by pharmacists, as perceived by survey respondents.

FIGURE 3. Word cloud representing limitations related to prescription modification by pharmacists, as perceived by survey respondents.

practice from one province to another, it is hoped that the insights gathered from this study will be useful for preparing hospital pharmacy departments for future implementation or continuous quality improvement of similar changes in pharmacists' scope of practice.

CONCLUSION

A large proportion of Ontario hospital pharmacists expressed an encouraging level of readiness to perform prescription modification. Future directions include conducting prospective studies to characterize the impact of this practice change on measurable outcomes and to continue the pursuit of full pharmacist scope of practice across Canada and abroad.

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Evaluating a Pharmacist-Led Opioid Stewardship Initiative at an Urban Teaching Hospital

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ABSTRACT

Background: Deaths due to overdose from illicit drugs have risen in Canada, despite various community-led harm reduction programs. There have been limited pharmacist-led inpatient initiatives aimed at reducing opioid harm. The authors' group recently developed and implemented the Medication and Risk Factor Review, Optimize, Refer at Risk Patients, Educate and Plan (MORE) tool, a systematic checklist designed to help pharmacists follow and enhance the safety of in-hospital opioid prescribing.

Objectives: To evaluate the impact of a pharmacist-led opioid stewardship program utilizing the MORE tool in the care of patients at one tertiary teaching hospital.

Methods: This study involved a review of health care records for patients admitted to general surgery and internal medicine clinical teaching units at a tertiary hospital between September 10 and December 31, 2018, for whom opioids were prescribed during the hospital stay. A descriptive data analysis was performed for patients who underwent assessment with the MORE tool.

Results: Of the 210 patients who met the initial eligibility criteria, including in-hospital opioid therapy for at least 3 days, 50 were assessed by a pharmacist using the MORE tool. For 40 (80%) of these patients, the pharmacist recommended an intervention, and 35 (87.5%) of these interventions were accepted by the prescriber. Among all 50 patients, the most common pharmacist interventions were adding or optimizing non-opioid pain medications (23 patients [46%]), decreasing opioid dose or frequency (15 patients [30%]), and adding a bowel regimen (9 patients [18%]).

Conclusions: Most patients who underwent assessment by a pharmacist had risk factors for adverse events from opioid prescriptions and/or suboptimal orders and drug combinations. The MORE tool provided a guided approach for pharmacists to make targeted interventions aimed at improving opioid safety. A dedicated opioid stewardship pharmacist might be able to provide additional benefit.

Keywords: opioid-related disorders, pharmacists, stewardship, health care

RÉSUMÉ

Contexte : Les décès provoqués par les surdoses de drogues illégales ont augmenté au Canada, malgré les divers programmes communautaires axés sur la réduction des risques. Le nombre d'initiatives menées par les pharmaciens auprès des patients hospitalisés visant à réduire les dommages causés par les opioïdes est limité. Le groupe d'auteurs de cette étude a récemment élaboré et mis en place l'outil Medication and Risk Factor Review, Optimize, Refer at Risk Patients, Educate and Plan (MORE) : une liste de contrôle systématique conçue pour aider les pharmaciens à respecter et à renforcer la sécurité de la prescription d'opioïdes en milieu hospitalier.

Objectifs : Évaluer l'impact d'un programme de gestion des opioïdes dirigé par des pharmaciens à l'aide de l'outil MORE pour les soins des patients résidant dans un hôpital d'enseignement tertiaire.

Méthodes : Cette étude impliquait l'examen des dossiers de santé des patients admis dans les unités d'enseignement clinique de chirurgie générale et de médecine interne d'un hôpital tertiaire entre le 10 septembre et le 31 décembre 2018. Des opioïdes ont été prescrits à ces patients lors de leur séjour hospitalier. Une analyse descriptive des données a été menée auprès des patients ayant fait l'objet d'une évaluation à l'aide de l'outil MORE.

Résultats : Sur les 210 patients qui répondaient aux critères d'admissibilité initiaux, notamment à celui d'un traitement aux opioïdes à l'hôpital pendant au moins trois jours, 50 ont fait l'objet d'une évaluation à l'aide de l'outil MORE. Le pharmacien a recommandé une intervention auprès de 40 de ces patients (80 %), et le prescripteur a accepté 35 de ces interventions (87,5 %). Les interventions des pharmaciens les plus répandues réalisées auprès des 50 patients consistaient en l'ajout ou en l'optimisation des analgésiques sans opioïdes (23 patients [46 %]); en la diminution de la dose d'opioïdes ou de leur fréquence (15 patients [30 %]); et en l'ajout d'un régime d'hygiène intestinale (9 patients [18 %]).

Conclusions : La plupart des patients ayant fait l'objet d'une évaluation menée par un pharmacien présentaient des facteurs de risque d'effets indésirables découlant des prescriptions d'opioïdes et/ou d'ordonnances et de combinaisons médicamenteuses sous-optimales. L'outil MORE a permis aux pharmaciens d'adopter une approche guidée pour qu'ils puissent effectuer des interventions ciblées visant à améliorer l'innocuité des opioïdes. Un pharmacien affecté spécifiquement à la gestion des opioïdes pourrait offrir des avantages supplémentaires.

Mots-clés : troubles liés aux opioïdes, pharmaciens, gestion, soins de santé

INTRODUCTION

Deaths due to illicit drug overdose have steadily increased in Canada in the past few years.[1] In British Columbia, 1550 people died from a preventable overdose in 2018, 985 in 2019, and an additional 1723 in 2020.[2] The tragic number of deaths and overdoses due to opioid use led to the declaration of a public health emergency in April 2016.[3] Various measures have been implemented to address this public health emergency, but few interventions have addressed the role of prescription opioids. Research indicates that individuals who experienced an overdose were more likely to have had an opioid prescription for pain and were more likely to have used prescription opioids on a long-term basis (typically for more than 3 months) over the previous 5 years, relative to people who did not experience an overdose.[4] In addition, chronic opioid use at 1 year after hospital discharge is more common among opioid-naive patients for whom an opioid was prescribed at discharge than among patients who did not receive opioids in the hospital.[5] These results suggest a potential need for in-hospital pharmacist interventions, such as opioid stewardship, to address prescribing patterns that affect this public health emergency.

Opioid stewardship is defined as the implementation of coordinated interventions to improve, monitor, and evaluate the use of opioids to support and protect the people using these drugs.[6] The goal of an opioid stewardship program is to ensure optimal analgesic prescribing, using opioid and non-opioid alternatives, to reduce the risk of adverse events and to avoid the development of opioid use disorder in patients and/or their family and acquaintances. Opioid stewardship should not be considered an attempt to stop necessary and appropriate opioid therapy for patients for whom other options have been tried without success, or those with indications for which opioids have proven benefit. Rather, opioid stewardship attempts to ensure that opioids are used in a safe and rational manner.

Recent research regarding opioid stewardship programs has included an assessment of a pharmacist-led pain service in a community hospital setting, which showed a reduction in opioid use, an increase in use of co-analgesic medications, such as acetaminophen and nonsteroidal anti-inflammatory drugs, and an overall increase in patient satisfaction.[7] Another pharmacist-led opioid stewardship program implemented in a Canadian primary care centre showed an increase in opioid tapering and a decrease in overall opioid doses.[8]

We conducted this study at St Paul's Hospital, a 430-bed tertiary teaching hospital located in a community of Vancouver, British Columbia, that is heavily affected by the opioid crisis. At this hospital, the Addictions Medicine Consult Team, the Acute Pain Service, and the Chronic Pain Service oversee opioid therapy for specific subsets of patients by consultation. Opioid use by the rest of the hospital's patient population receives less focused attention. In an effort to target opioid prescribing in the broader hospital population, our team developed the MORE tool. The MORE Clinical Pharmacist Opioid Review and Optimization Tool gets its name from an acronym based on the following concepts: Medication and Risk Factor Review, Optimize, Refer at Risk Patients, Educate and Plan. It was created in response to the need for a pharmacist-led opioid stewardship initiative based on best practices from the literature and feedback from local pharmacist focus groups.[9] This clinical tool provides a systematic checklist for pharmacists to follow to enhance the safety of opioid prescribing while ensuring effective pain management.[9] The latest version of the tool is available in Appendix 1 (see https://www.cjhp-online.ca/index.php/cjhp/issue/view/205.) Details about the development of this tool were published previously.[9]

The MORE tool was implemented for use by hospital pharmacists working on general medical and surgical units at the study hospital in August 2018. As specified in the tool itself, the MORE tool was intended for use in the assessment of patients with noncancer pain. For initial implementation, as evaluated here, the tool was not applied in the emergency department, critical care units, or other specialty units. If the initial roll-out is deemed successful, expansion to other areas of the hospital will be considered. For further details on how pharmacists can use the MORE tool, please refer to our previous work.[9]

The aim of the current study was to evaluate the impact of our hospital's pharmacist-led opioid stewardship program utilizing the MORE tool.

METHODS

Design

This study involved a retrospective review of health care records for patients admitted to general surgery and internal medicine clinical teaching units at the tertiary hospital between September 10 and December 31, 2018, for whom opioids were prescribed during the hospital stay. The pharmacist-driven MORE tool had been implemented in August 2018, before the current study began.

Patient Population

The baseline population was identified using the pharmacy computer system, which listed all adult patients (≥ 19 years of age) admitted to an internal medicine clinical teaching unit or general surgery ward at the tertiary hospital who received at least 1 prescription for either regularly scheduled or "as-needed" opioid therapy for a duration of 3 days or longer. Patients who were being actively followed by the Addictions Medicine Consult Team or one of the pain services before the MORE tool became available were excluded from the baseline population. In addition, patients were excluded if their only opioid prescription was for opioid

agonist treatment for opioid use disorder (e.g., methadone or buprenorphine–naloxone). The opioid stewardship cohort consisted of patients in the baseline population who underwent assessment with the MORE tool. Completed and partially completed MORE assessments were routinely collected, along with other pharmacy documentation materials, when patients were discharged.

Sample Size

A convenience sample was chosen that included all patients who were admitted during the 4-month study period and who met the inclusion criteria. From this group, detailed chart review was conducted for patients for whom a MORE assessment was completed. It was felt that this time frame would be adequate to indicate the impact of the tool in guiding pharmacist-led opioid stewardship during the early implementation phase.

Outcomes

The primary outcome measures were the proportion of patients in the baseline population who were assessed by a clinical pharmacist using the MORE tool (thus forming the opioid stewardship cohort) and the proportion of patients in the opioid stewardship cohort for whom an opioid stewardship intervention suggested by a pharmacist was documented in the MORE tool.

The secondary outcome measures included mean numbers (per patient) of suboptimal orders, risk factors for opioid-related adverse events, and opioid stewardship interventions (actions) among medical patients relative to surgical patients. Other secondary outcome measures included the proportions of pharmacist-recommended interventions that were accepted or implemented, pharmacist-recommended interventions that were documented in the health record, and patients who experienced any chart-documented, opioid-related adverse event.

Data Collection

For the baseline population, data collection was limited to the elements needed to determine whether the patient met the inclusion criteria. For the opioid stewardship cohort, the following demographic and baseline clinical characteristics were collected from the patient chart: age, sex, ward of admission, reason for admission, comorbidities, opioid medications before admission, substance use history as documented in the patient history, and in-hospital medications, specifically opioids ordered (regimen and total daily dose, as morphine milligram equivalents [MME] per day), concurrent non-opioid analgesics (dose and regimen), and documentation of any changes in the opioid regimen. Documentation of pain management and opioid prescribing interventions, either suggested by the pharmacist or implemented by other health care providers, was also recorded.

Comorbidities were extracted from the past medical history in the electronic chart. Regular opioid use before admission and median daily MME used in hospital were gathered from the MORE assessment and confirmed via review of the patient chart.

Statistical Analysis

Descriptive statistics were used to analyze the data, and the results are reported using means, medians, and proportions.

The research protocol was submitted to the Providence Health Research Ethics Board and approved before the commencement of data collection.

RESULTS

Assessment with the MORE tool was completed for a total of 50 patients admitted during the defined study period, 30 on medicine units and 20 on surgery units; A total of 5 pharmacists performed these assessments, all of them residency trained, with a range of 1 to 10 years of experience.

The baseline characteristics of patients in the opioid stewardship cohort are reported in Table 1. Patients assessed by clinical pharmacists with the MORE tool tended to be elderly (mean age 69.1 years), and 33 (66%) were female. A third of patients had prescriptions for regularly scheduled opioids before admission, and a similar proportion had a comorbid psychiatric diagnosis such as anxiety or depression. In hospital, hydromorphone was the most commonly prescribed opioid, representing 85% of all opioid orders.

Primary Outcome Measures

A study flow diagram of patients in the baseline population and the opioid stewardship cohort is presented in Figure 1. The clinical pharmacists used the MORE tool to assess 24% (50/210) of eligible patients receiving opioids (baseline population) who were admitted during the study period.

Of the 50 patients assessed with the MORE tool (the opioid stewardship cohort), pharmacists suggested interventions for 40 (80%).

Secondary Outcome Measures

Among the 50 patients in the opioid stewardship cohort, there were 52 suboptimal medication orders or medication combinations, yielding a mean of 1.04 suboptimal orders per patient. The most frequent problems with suboptimal orders were suboptimal dose, route, or frequency of opioids; lack of optimized non-opioid pain medications; and duplicate opioid orders. The breakdown of the various suboptimal orders is presented in Table 2.

A total of 79 risk factors for adverse events were found in the opioid stewardship cohort, for a mean of 1.58 per patient. The most common risk factors were age older than 75 years, kidney or liver impairment, and a history of substance use disorder. The breakdown of these risk factors is presented in Table 3.

TABLE 1. Patient Characteristics

Characteristic	Service; No. (%) of Patients[a]		
	Medicine (*n* = 30)	Surgery (*n* = 20)	All Patients (*n* = 50)
Mean age (years)	71.6	65.5	69.1
Sex, female	21 (70)	12 (60)	33 (66)
Comorbidities			
Atrial fibrillation	4 (13)	3 (15)	7 (14)
Coronary artery disease	5 (17)	3 (15)	8 (16)
Chronic pain	5 (17)	0 (0)	5 (10)
Chronic obstructive pulmonary disease	7 (23)	1 (5)	8 (16)
Depression	7 (23)	1 (5)	8 (16)
Diabetes	7 (23)	3 (15)	10 (20)
Dyslipidemia	6 (20)	4 (20)	10 (20)
Hypertension	16 (53)	10 (50)	26 (52)
Hypothyroidism	3 (10)	3 (15)	6 (12)
Osteoarthritis	5 (17)	2 (10)	7 (14)
Osteoporosis	6 (20)	0 (0)	6 (12)
Smoking history	3 (10)	2 (10)	5 (10)
History of substance use disorder[b]	5 (17)	4 (20)	9 (18)
Psychiatric diagnosis	9 (30)	8 (40)	17 (34)
Receiving regularly scheduled opioids before admission	11 (37)	5 (25)	16 (32)
Opioids on medication administration record on day of discharge	24 (80)	15 (75)	39 (78)
Proportion of hospital stay (measured in days) with opioid therapy			
Mean % of hospital stay with as-needed opioid therapy	85.7	86.6	86.1
Mean % of hospital stay with scheduled opioid therapy	61.7	41.2	54.2
Median daily MME[c] received			
Total (as needed and/or regular)	20	27.5	20
Regular	35.3	20	30

[a]Except where indicated otherwise.
[b]Substance use disorder includes alcohol use disorder and polysubstance abuse.
[c]Morphine milligram equivalents, based on opioids ordered and used, as reported in the pharmacy system.

The pharmacists suggested a total of 62 optimization interventions. The most common interventions were adjusting the dose or frequency of opioids and optimizing or adding non-opioid pain medications (such as acetaminophen). The mean number of optimization interventions per patient was 1.24. The mean number of optimization interventions per medicine patient was 1.47, whereas the mean per surgical patient was 0.9. Of the 40 patients with an intervention suggested by the pharmacist, 35 (87.5%) had the interventions accepted by the care team. Among all 50 patients in the opioid stewardship cohort, 17 (34%) had a note related to their opioids or pain management in the progress notes section of the patient chart. The breakdown of the various pharmacist interventions is presented in Table 4.

The pharmacists suggested a total of 6 referrals to other services, specifically the Addictions Medicine Consult Team, the Acute Pain Service, the Chronic Pain Service, and the palliative care team.

A total of 55 education or planning interventions were suggested (mean 1.1 interventions per patient). These interventions involved 22 of the 50 patients in the opioid stewardship cohort, which indicates that patients with education or planning interventions typically had multiple interventions of this type. The mean numbers of education interventions by service type were 1.23 per patient in the medicine units and 0.9 per patient in the surgical units. The most common educational interventions were discussion of pain goals (14 patients [28%]), counselling about non-opioid options (13 patients [26%]), and recommendation to taper or discontinue opioids (12 patients [24%]). The breakdown of the various education and planning interventions is shown in Table 5.

Five (10%) of the patients in the opioid stewardship cohort had a chart-documented adverse event, 2 with sedation and 3 with "other" adverse events (hallucinations and dizziness, nausea, or opioid withdrawal).

DISCUSSION

In this study, clinical pharmacists selected the patients who would undergo assessment using the MORE tool as a guide. It is likely that the pharmacists used their clinical judgment to preferentially select patients with readily apparent risk factors or suboptimal analgesic orders. Overall, the patients selected for assessment were older and more predominately female, and many had medical comorbidities such as hypertension, diabetes, or psychiatric comorbidities. Interestingly, this population contrasts with literature reports of those most at risk for opioid use disorder, specifically men aged 50 years or older.[10] It is possible that the more typical at-risk population described in the literature is preferentially assessed and followed by specialty addiction or pain services at the study hospital. As such, the group targeted by pharmacists in the current study may represent an under-recognized at-risk population.

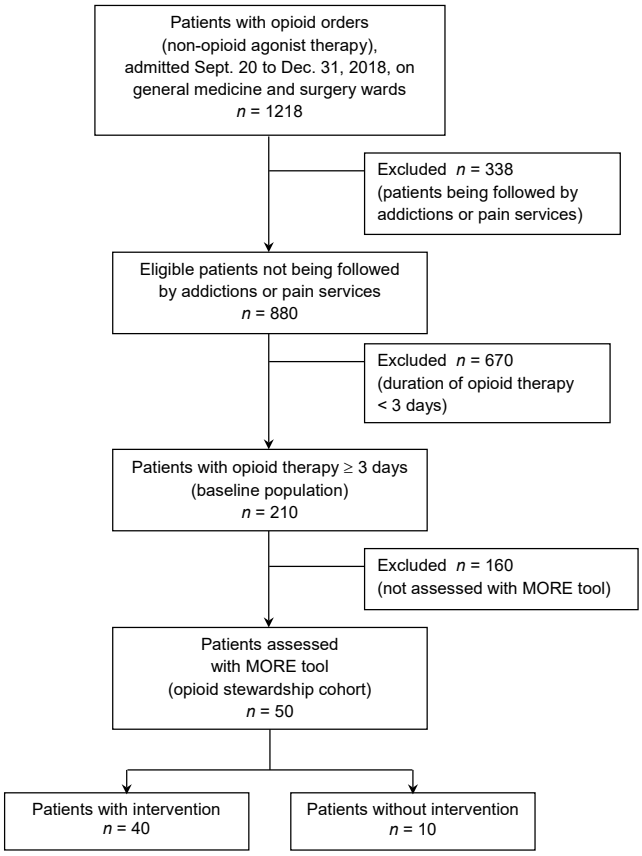

FIGURE 1. Study flow diagram.

The pharmacists were able to apply the tool in 24% of the patients for whom in-hospital use of opioids was prescribed for more than 3 days. Although this proportion may seem low, it is important to highlight that these patients were not concurrently under the care of physicians with specialized training in pain or addiction management. Instead, they represent the larger population of hospitalized patients who receive opioids without review by medical experts in pain or addiction. Also, the clinical pharmacists added assessment using the MORE tool to their existing workload and were not given additional dedicated time for this activity. Assessment of this under-recognized population by the pharmacy team, despite limited resources for doing so, suggests that clinical pharmacists can have an important role in opioid stewardship. It also suggests that there may be value in having a dedicated opioid stewardship team, similar to the antimicrobial stewardship model, since there remains a substantial proportion of patients who are receiving opioids but are not being formally assessed for risk. The activities of a dedicated opioid stewardship team could

TABLE 2. Suboptimal Medication Orders and Drug Combinations

	Service; No. (%) of Patients		
Suboptimal Order	**Medicine (*n* = 30)**	**Surgery (*n* = 20)**	**All Patients (*n* = 50)**
IV or subcutaneous route ordered when oral route was feasible	4 (13)	6 (30)	10 (20)
Excessively frequent regular dosing (< q4h)	4 (13)	3 (15)	7 (14)
Order > 10 MME/dose for opioid-naïve patient	4 (13)	2 (10)	6 (12)
Regular opioid use for a patient with as-needed opioid order	3 (10)	5 (25)	8 (16)
Long-acting opioids started for acute pain within first 5 days of hospital stay	0 (0)	1 (5)	1 (2)
Benzodiazepines and opioids ordered together	2 (7)	4 (20)	6 (12)
Combinations of different opioids for acute pain	4 (13)	0 (0)	4 (8)
Multiple opioid orders for as-needed use (with same route of administration)	2 (7)	1 (5)	3 (6)
No adjunctive acetaminophen or nonsteroidal anti-inflammatory drug	1 (3)	1 (5)	2 (4)
No other adjunctive pain medications ordered (e.g., for neuropathic pain)	5 (17)	0 (0)	5 (10)

MME = morphine milligram equivalents.

include conducting in-depth patient interviews, reviewing past and current pain therapies, identifying non-opioid analgesic combinations to be added to current therapy, and educating other health care professionals about updated guidelines and evidence for use of opioids.

At the time of our study, there was limited published information on pharmacist-led opioid stewardship interventions; however, since our study was completed, several reports describing pharmacist-led opioid stewardship programs have been published. One report described implementation of a pharmacy-directed pain management service.[7] This pharmacy consult–based pain management service aimed to achieve optimal pain management, reduce adverse events associated with pain medications, and reduce the use of higher-risk pain medications.[7] The authors showed decreased use of high-risk opioid medications, such as parenteral hydromorphone and fentanyl, and increased use of co-analgesics, including acetaminophen and non-steroidal anti-inflammatory drugs such as ibuprofen and naproxen.[7] That study differed from ours, in that it was a consult-based service with dedicated clinical pharmacists. In another study, conducted in a primary care setting, the pharmacist at the intervention primary care clinic reviewed patient charts for opioid prescribing, communicated with clinic physicians, and offered suggestions for opioid tapering.[8] In that study, there was a reduction in mean daily

TABLE 3. Risk Factors for Adverse Events due to Opioids

Risk Factor	Service; No. (%) of Patients					
	Medicine (*n* = 30)		Surgery (*n* = 20)		All Patients (*n* = 50)	
Age > 75 years	13	(43)	3	(15)	16	(32)
Family history of substance use disorder	0	(0)	1	(5)	1	(2)
Any history of substance use disorder	5	(17)	4	(20)	9	(18)
Kidney or liver impairment	5	(17)	5	(25)	10	(20)
Low body mass index	5	(17)	3	(15)	8	(16)
Multiple overlapping fills of opioids documented in PharmaNet prescription database	2	(7)	0	(0)	2	(4)
Multiple prescribers for opioids documented in PharmaNet prescription database	1	(3)	0	(0)	1	(2)
Opioid dose rapidly increased in recent days or weeks	1	(3)	4	(20)	5	(10)
Psychiatric diagnosis	9	(30)	8	(40)	17	(34)
Receiving > 50 MME of opioid daily (but < 100 MME)[a]	3	(10)	1	(5)	4	(8)
Receiving > 100 MME of opioid daily[a]	5	(17)	1	(5)	6	(12)

[a]MME = morphine milligram equivalents, based on opioids received according to medication administration records in hospital.

TABLE 4. Pharmacist Optimization Interventions

Intervention	Service; No. (%) of Patients					
	Medicine (*n* = 30)		Surgery (*n* = 20)		All Patients (*n* = 50)	
Add bowel regimen	9	(30)	0	(0)	9	(18)
Add non-opioid pain medication[a]	7	(23)	4	(20)	11	(22)
Optimize non-opioid pain medication	10	(33)	2	(10)	12	(24)
Decrease opioid dose or frequency	9	(30)	6	(30)	15	(30)
Change intravenous or subcutaneous to oral route	3	(10)	3	(15)	6	(12)
Deprescribe as-needed opioid	3	(10)	0	(0)	3	(6)
Deprescribe regularly scheduled opioid	1	(3)	2	(10)	3	(6)
Switch to different opioid	2	(7)	1	(5)	3	(6)

[a]Acetaminophen, gabapentin, and/or nonsteroidal anti-inflammatory drug.

TABLE 5. Pharmacist Education and Planning Interventions

Intervention	Service; No. (%) of Patients		
	Medicine (*n* = 30)	Surgery (*n* = 20)	All Patients (*n* = 50)
Chart documentation about education or planning intervention	1 (3)	4 (20)	5 (10)
Counsel on non-opioid options	9 (30)	4 (20)	13 (26)
Counsel on proper use and disposal of excess supply	2 (7)	2 (10)	4 (8)
Discuss pain goals	8 (27)	6 (30)	14 (28)
Pain/opioid plan communicated to community health care providers	1 (3)	0 (0)	1 (2)
Recommend appropriate duration/quantity	6 (20)	0 (0)	6 (12)
Recommend opioid taper or discontinuation	10 (33)	2 (10)	12 (24)

opioid doses over a 4-month period.[8] The pharmacist in that study added review of patients' electronic charts for opioid prescribing to their existing workload (similar to what was required of the pharmacists in our study), rather than having a consult-based analgesic review. The main difference between this second study and ours was the setting: our study took place in a tertiary hospital, where the caseload of each pharmacist and patients' acuity may differ from those in a primary care centre.

The current study also demonstrates that risk factors for opioid-related adverse events, such as advanced age, impaired organ function, and prior psychiatric history or substance use history, are common in the general medical and general surgical populations. Most of the patients assessed in this study had at least 1 suboptimal opioid or co-analgesic order. One-third of the patients were receiving opioids before admission, despite having risk factors for adverse effects or development of an opioid use disorder. It is also concerning that on the day of discharge, most of the medical patients (80%) still had opioids on their medication administration record, despite only 37% of them having had opioid prescriptions before hospital admission. This can likely be explained by the fact that for many patients, opioids are prescribed on an as-needed (PRN) basis during their hospital stay and although they may not need any doses, the orders remain on their medication profile until discharge. In our study, patients had orders for as-needed administration of opioids for 86.1% of their hospital stay, with orders for regularly scheduled opioids for only 54.2% of their stay. It was not clear how many patients still required PRN doses on the day of discharge; however, given the link between prescribing opioids at the time of hospital discharge and the increased risk of prolonged opioid use, earlier or more frequent reassessment of the need for ongoing opioid therapy (including PRN orders) is warranted. In addition, if the patient continues to have high opioid requirements at the time of discharge, there is a need to address the risk of opioid withdrawal symptoms on discharge and the potential need for opioid tapering.

The pharmacists suggested various interventions to optimize opioid prescribing and mitigate the risk of adverse events. One of the most common interventions was a simple one: adding a non-opioid co-analgesic. The pharmacists often added regularly scheduled non-opioid medications, even when they did not initially mark this option within the suboptimal orders section of the MORE tool. The pharmacists suggested more interventions for medicine patients than for surgical patients. Some experts have proposed that opioid stewardship interventions should be focused on surgical patients[10]; however, our study suggests that the risk for opioid-related adverse effects is at least as high, if not higher, for medical patients as it is for surgical patients, which resulted in a greater number of pharmacist interventions for this group (means 1.47 and 0.9 per patient, respectively, in the opioid stewardship cohort). Despite the relatively high frequency of suggested interventions, the number of chart notes documenting pharmacist interventions was low. We assumed that most pharmacist interventions in this study resulted in collaborative discussion with the care teams instead of a chart note.

In interpreting the results of this study, it is important to note that professional judgment was involved in the selection of the opioid stewardship cohort. As a result, the frequency of risk factors and the need for interventions might have been higher in the opioid stewardship cohort than in the general hospital population. Because we did not review the charts of patients who were not assessed by pharmacists using the MORE tool, we cannot draw conclusions about the frequency of risk factors in that population. The types of interventions might have been influenced by individual pharmacists and their comfort level in intervening in opioid prescribing. Furthermore, we did not assess the clinical validity of the interventions or whether potentially beneficial interventions were omitted. Initial implementation

of the tool was limited to general medical and surgical patients needing treatment for noncancer pain, and the results of this study cannot be extrapolated to other patient populations, such as those receiving critical care or in the emergency department.

Anecdotally, the pharmacists' use of the MORE tool declined after initial implementation. The pharmacists reported that they found the tool useful but time-consuming, and we suspect that this added workload was the reason for decline in its utilization over time. Nonetheless, we found that with the aid of the MORE tool, clinical pharmacists were able to provide opioid stewardship to 50 of 210 patients, with 40 of these receiving pharmacist interventions and recommendations. The results of this study may be generalized to other hospital pharmacy departments, where a formalized checklist may help to guide opioid stewardship within pharmacists' day-to-day routine.

CONCLUSION

This study demonstrated the existence of many hospitalized patients who are not formally assessed for opioid stewardship interventions but who could benefit from such interventions. Most patients assessed by pharmacists in this study had risk factors for overdose and/or suboptimal orders and drug combinations. With the aid of a clinical tool, pharmacists were able to identify and address a variety of issues, such as suboptimal medication orders, drug combinations, and risk factors for adverse reactions, and were able to optimize therapy and provide patient education. Despite these positive interventions, it may be difficult for clinical pharmacists to add comprehensive opioid stewardship activities to their current activities. For this reason, a dedicated opioid stewardship pharmacist or team might be a worthwhile addition to clinical care.

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Pharmacy Distribution, Clinical, and Management Services: A Survey of Small Hospitals in Canada Supported by Telepharmacy Services

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ABSTRACT

Background: The Canadian Society of Hospital Pharmacists' *Hospital Pharmacy in Canada Report* presents data from pharmacy departments that service hospitals with at least 50 acute care beds. This report provides valuable data on pharmacy distribution, clinical, and management services in relation to hospital size, type, and geographic region. Pharmacy and hospital leadership use these extensive data in identifying baseline, benchmarking current, and planning enhanced pharmacy services. However, for most of Canada's small hospitals, such data remain unknown, and leadership remains uninformed.

Objective: To gather and analyze data about current pharmacy distribution, clinical, and management services in hospitals with fewer than 50 acute care beds receiving third-party remote pharmacy (telepharmacy) services.

Methods: In April 2019, pharmacy administrators of hospitals in Ontario, Quebec, and Saskatchewan that had fewer than 50 acute care beds and were using third-party telepharmacy services were invited to complete a comprehensive survey addressing concepts similar to those in the Hospital Pharmacy in Canada Survey. The following data on clinical pharmacy practice were collected: models of care, assignments to patient care programs, pharmacists' activities, performance indicators, and professional evaluation. The description of pharmacy distribution services comprised type of system, technology, location, hours of operation, method of medication order entry and verification, and medication administration records. Details on facilities' parenteral admixture infrastructure, policy for and provision of sterile compounding, and pharmacy department human resources, including composition and staffing ratios, were also collected.

Results: Of the 27 hospitals in Ontario, Quebec, and Saskatchewan that were invited to participate, 24 (89%) completed the survey. The median facility size was 19 acute care beds.

Conclusions: Previously unavailable in Canada, these quantitative data from small hospitals supported by telepharmacy services provide facts about pharmacy distribution, clinical, and management services to inform hospital and pharmacy leaders. Creation of a survey unique to small hospitals, whether or not they use telepharmacy services, could provide a valuable resource to assist in the benchmarking, planning, and enhancement of pharmacy services in remote and rural communities.

Keywords: small hospital, telepharmacy, pharmacy practice, remote, rural, survey

RÉSUMÉ

Contexte : Le *Rapport sur les pharmacies hospitalières canadiennes* de la Société canadienne des pharmaciens d'hôpitaux expose les données provenant des services de pharmacie qui appuient les hôpitaux comptant au moins 50 lits de soins aigus. Il offre de précieuses données sur les services de distribution des médicaments, les services cliniques et de gestion en relation avec la taille, le type et la région géographique des hôpitaux. Les équipes de direction des pharmacies et des hôpitaux utilisent ces données exhaustives pour déterminer une base de référence, évaluer les services de pharmacie actuels et planifier l'amélioration des services. Cependant, la plupart des petits hôpitaux du Canada ne disposent pas de ce type de données, et les équipes de direction n'en sont pas informées.

Objectif : Réunir et analyser des données sur la distribution de médicaments, les services cliniques et la gestion des services pharmaceutiques actuels dans les hôpitaux comptant moins de 50 lits de soins aigus, qui reçoivent des services de pharmacie à distance (services de télépharmacie) fournis par des tiers.

Méthode : En avril 2019, les administrateurs de pharmacie d'hôpitaux en Ontario, au Québec et en Saskatchewan remplissant ces critères ont été invités à répondre à une enquête exhaustive abordant des concepts similaires à ceux de Sondage sur les pharmacies hospitalières canadiennes. Les données suivantes sur la pratique de la pharmacie clinique ont été recueillies : modèles de soins, affectation des pharmaciens à des programmes particuliers de soins des patients, activités des pharmaciens, indicateurs de performance et évaluation professionnelle. La description des systèmes de distribution des médicaments par les pharmacies comprenait : le type de système, la technologie, le lieu, les heures de service, le mode de saisie et de vérification des ordonnances de médicaments ainsi que les dossiers d'administration. Les détails concernant l'infrastructure pour l'administration de solutions parentérales, la politique relative aux composés stériles et à leur distribution ainsi que les ressources humaines des services de pharmacie, y compris la composition et les ratios en personnel, ont également été recueillis.

Résultats : Sur les 27 hôpitaux en Ontario, au Québec et en Saskatchewan invités à participer à l'enquête, 24 (89 %) y ont répondu. La taille moyenne des installations était de 19 lits de soins aigus.

Conclusions : Autrefois indisponibles au Canada, ces données quantitatives provenant de petits hôpitaux soutenus par des services de télépharmacie livrent des faits concernant le système de distribution des médicaments au sein des pharmacies, les services cliniques et de gestion, qui permettent de guider les cadres des hôpitaux et de la pharmacie. La création d'une enquête unique destinée aux petits hôpitaux, utilisant ou non des services de télépharmacie, pourrait constituer une précieuse ressource pour aider à évaluer, à planifier et à améliorer les services pharmaceutiques dans les communautés rurales et éloignées.

Mots-clés : petit hôpital, télépharmacie, pratique de la pharmacie, éloigné, rural, enquête

INTRODUCTION

The health care delivery system in Canada continually aims to improve in response to community needs. The provision of high-quality, cost-effective health care is of paramount importance for every clinical service in the country. Pharmacists play a significant role in patient care, contributing to treatment goals by addressing medication- and disease-related issues, optimizing medication management, providing education to patients and other health care providers, and addressing gaps in patient care. Pharmacy practice in Canada is guided by legislation, codes of ethics, and professional regulatory authorities such as Accreditation Canada, which govern minimum standards.[1] In addition, several organizations encourage and promote excellence in hospital pharmacy, including the Canadian Society of Hospital Pharmacists (CSHP), the International Pharmaceutical Federation, and the Canadian Pharmacists Association. The CSHP's vision is to lead and inspire excellent pharmacy practice integral to patient-centred care in hospitals and other collaborative health care settings, and it continuously assesses the progress of pharmacy services in Canadian hospitals in achieving such excellence. The *Hospital Pharmacy in Canada Report* (referred to hereafter as "the Report"), based on a nationwide survey, has been published every 3 to 4 years since 1986.[2] With the 2016/17 (21st) edition, the survey and resulting publication were, for the first time, conducted under the auspices of the CSHP Hospital Pharmacy in Canada Survey Board, which now operates as an affiliated board of the CSHP. The Report is the culmination of an extensive analysis of data gathered via an online survey of leadership of pharmacy departments across Canada. It has been of substantial value to Canadian hospital pharmacy leadership for sharing information on distribution, clinical, and management services and practices within their health care facilities. The most recent Hospital Pharmacy in Canada Survey, conducted in spring 2017, had a high response rate: 180 (83%) of eligible hospitals, with eligibility based on the criterion of 50 or more acute care beds, participated.[3,4] Quantitative data sought included information about pharmacy distribution, clinical, and management services, hospital programs and services, pharmacy human resources, and technology in relation to hospital size, type, and geographic region. Today, pharmacy and hospital leaders use these data to identify baseline values, to benchmark current pharmacy services, workload, and resources, and to assist leaders in the planning and expansion of pharmacy services, with the overall goals of improving patient care, optimizing health outcomes, and reducing health care costs. The American Society of Health-System Pharmacists (ASHP) conducts national surveys of pharmacy services in hospital settings in the United States, to describe practices and technologies used to manage and improve medication systems. The ASHP survey is open to all hospitals, including those with fewer than 50 acute care beds.[5-7]

The Canadian Institute for Health Information reported that Canada had 591 hospitals (acute to long-term care) in 2017/18.[8] However, up to 62% of Canadian institutions, including small hospitals (fewer than 50 acute care beds) are not represented in the *Hospital Pharmacy in Canada Report*. As the role of pharmacists in direct patient care continues to increase, we believe that assessing the current state of pharmacy services and the resources available to small hospitals is necessary to deliver best pharmacy practices and equitable care for all Canadians, regardless of the location and size of their hospital; such assessments form a cornerstone of Canada's universal health care policies. Although pharmacy services in small hospitals have been assessed in the United States, to date the data required to provide the highest-quality cost-effective pharmacy services for patients receiving care in small Canadian health care institutions, often located in remote and rural communities, remain unknown. Given that the majority of institutions in Canada are small hospitals that may require a unique approach to assessment, an initial exploration of a subset of such hospitals may be appropriate. As the only third-party hospital telepharmacy provider in Canada, Northwest Telepharmacy Solutions uses a shared distribution, clinical, and management model to provide services to a broad range of Canadian hospitals that vary in size and extent of services, with and without on-site pharmacists. These factors and the ongoing relationship between small hospitals and the telepharmacy services offered by this company (the authors' employer) presented an opportunity for the current study.

The aim of this study was to bridge the gap in the availability of comprehensive quantitative data on hospital pharmacy services supported in whole or in part by telepharmacy in small hospitals in Canada.

METHODS

Study Design

A comprehensive structured survey was developed to describe distribution, clinical, and management services and practices within small hospitals (< 50 acute care beds) in Canada and allow comparison with larger hospitals (≥ 50 acute care beds). This survey was based on the well-respected and well-utilized CSHP *Hospital Pharmacy in Canada Report*,[3] with survey questions covering the same domains. This cross-sectional survey targeted leaders of pharmacy departments that service hospitals with fewer than 50 acute care beds supported, either fully or in part, by third-party telepharmacy services, in remote and rural communities representing certain provinces of Canada, with or without on-site pharmacists. Before the survey was distributed,

contact information for pharmacy leadership was pre-established through the telepharmacy provider.

The criteria for inclusion were pharmacy departments providing services for hospitals (single-site or multiple-site) with fewer than 50 acute care beds in total, with pharmacy services supported, in whole or in part, by a telepharmacy provider. There were no exclusion criteria.

The survey was made available in the following formats: Microsoft Word, Adobe PDF, and online through a link to the SurveyMonkey platform. Before distribution, the survey was pretested, in all formats, by 2 pharmacists (P.N., S.D.) for accuracy, clarity, and functionality. The estimated time for completion of all sections (where applicable) was 45 minutes. The survey was available for 90 days.

In April 2019, eligible hospital pharmacy administrators were invited to participate in the survey via secure email. The survey introduction letter included an electronic copy of the most recent CSHP *Hospital Pharmacy in Canada Report* and a copy of the study survey in Microsoft Word and Adobe PDF formats, as well as an online link to the SurveyMonkey platform. Instructions detailing survey completion, deadlines, and contacts for support were also included. The complete survey content and instructions are available upon request to the corresponding author. For the minority of institutions that did not complete the survey by the requested deadline, an email reminder was sent 2 weeks after the first deadline to establish whether the site wished to participate. If an email response or survey was still not completed, a telephone call was made 2 weeks later. Telephone support for survey completion (i.e., data entry) was offered, primarily to reduce the time commitment required of pharmacist leaders responsible for managing more than one pharmacy department. No incentive was offered to participants, and participation was voluntary. Because the study did not involve living human participants or human biological materials, ethics approval was not sought.

Data Analysis

The survey responses were aggregated and coded into a spreadsheet (Excel 2016 for Windows, Microsoft Corporation). Two researchers (P.N., O.P.), working independently, manually reviewed the survey responses for completeness before the analyses were performed. Descriptive statistics were used to analyze the prevalence of respondents' choices, to characterize the scope of clinical pharmacy practice, pharmacy human resources, drug distribution systems, and technology. For analysis of each survey question, all submitted responses were used, and denominators were adjusted according to the number of respondents or the number of responses as appropriate. The Shapiro-Wilk normality test was performed for each applicable set of variables. The test rejected the normality assumption, and medians are therefore reported.

Staffing ratios per acute or total (acute and non-acute) patient-days were calculated. The numerator in these ratios is the number of hours of staff time that a pharmacy department was operating during a year (budgeted hours). The denominator was the number of acute or total patient-days, respectively. For purposes of staffing ratios, 1.0 full-time equivalent (FTE) was defined as 2080 hours per year.

RESULTS

Facility Characteristics

Twenty-seven eligible facilities from Ontario, Quebec, and Saskatchewan were invited to participate in the survey, and there was an 89% (24/27) response rate (Figure 1). The baseline characteristics of participating hospitals are summarized in Table 1. Participating facilities had medians of 19 acute care beds and 14 non–acute care beds. For fiscal year 2018/19, the median occupancy rate was 77.1%, with median length of stay 6.2 days and a median of 8823 patient-days. Standard operating hours for the hospital pharmacies averaged 41.5 (standard deviation 12.7) hours per week. None of the study pharmacy departments was open for 168 hours/week (i.e., "24/7").

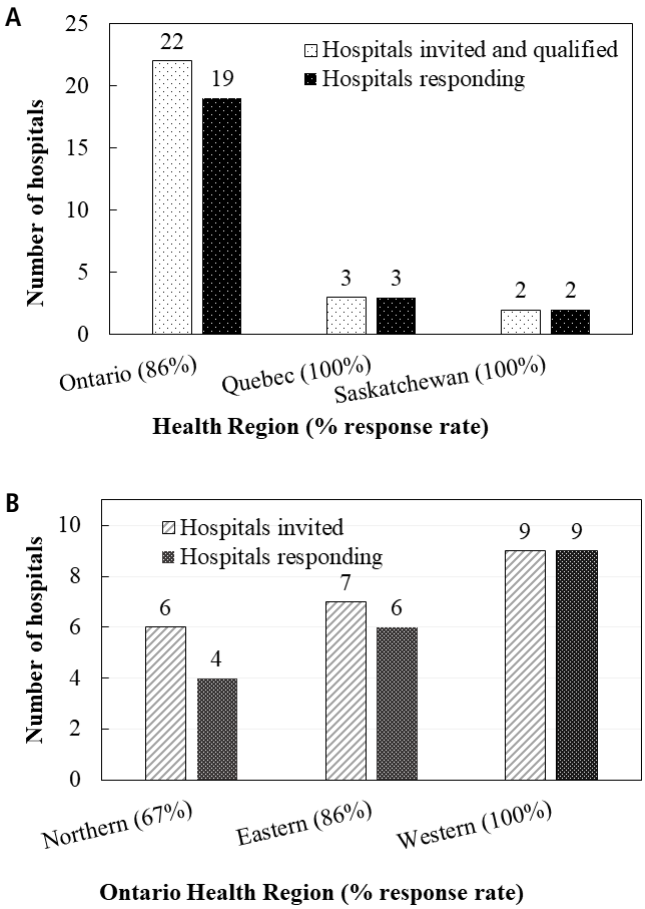

FIGURE 1. Response to the survey by province (A) and by Ontario health region (B).

TABLE 1. Characteristics of Participating Hospitals

Characteristic	Province or Region; No. of Beds[a]						
		Ontario					
	Overall	Western	Eastern	Northern	All ON	SK	QC
No. of hospitals	24	9	6	4	19	2	3
Total no. of beds							
Acute care	481	176	139	50	365	21	95
Non-acute care	1550	1170	67	51	1288	5	257
Median no. of beds							
Acute care	19	22	25	13	21	11	39
Non-acute care	14	20	14	13	14	3	97
Occupancy rate, %	77.1 (n = 18)	85.0	83.0	32.3	80.2	51.2	NA
Median length of inpatient stay (days)	6.2 (n = 17)	6.1	8.7	5.8	6.2	4.6	NA
Patient-days/year							
No. of respondents	16	7	6	3	16	0	0
Median patient-days/year	8823	9603	8415	4251	8823	NA	NA
Mean time that pharmacy was open (h/week)	41.5	46.2	39.9	40.0	42.9	30.0	40.0

ON = Ontario, NA = not available, QC = Quebec, SK = Saskatchewan.
[a]Except where indicated otherwise.

Clinical Pharmacy Practice

Of the formal hospital inpatient care programs listed in the survey, respondents reported a facility median of 4. Most hospitals reported the availability of a general medicine program (92%, 22/24), nearly half had a pain or palliative care program (46%, 11/24), and 33% (8/24) had a general surgery program (Table 2). Overall, 71% of respondents indicated that their facility had an assigned pharmacist (at least 0.2 FTE) for at least 1 inpatient practice area. All facilities with inpatient programs for infectious disease/AIDS/antimicrobial stewardship (n = 7), mental health (n = 3), neurology and/or stroke (n = 2), hematology and anticoagulation (n = 2), and hematology-oncology (n = 1) had a pharmacist assigned to these programs. Other programs having a high rate of clinical involvement by pharmacists included rehabilitation (83%, 5/6), general surgery (75%, 6/8), critical care (75%, 3/4), general medicine (73%, 16/22), and geriatrics (71%, 5/7).

Seventy-nine percent (19/24) of facilities declared that they had at least 1 of the 17 outpatient programs listed in the survey, with a median of 1 outpatient program per facility. Forty-three percent (10/23) of respondents reported assignment of a designated pharmacist to at least 1 outpatient practice area. Emergency was the most common outpatient service, and 38% of facilities (5/13) reported pharmacist involvement. Hospitals reporting the following outpatient programs all had a pharmacist assignment: hematology (n = 1), diabetes (n = 1), general surgery (n = 1), and rehabilitation (n = 1) (Table 3). Although an outpatient geriatrics program was present in 6 facilities, none of these had a pharmacist assigned.

Pharmacy Practice, Clinical Activities, and Evaluation

In 63% (15/24) of the hospitals surveyed, the pharmacy practice model was described as a "clinical generalist model with limited differentiation of roles" (i.e., nearly all pharmacists had both distribution and clinical responsibilities), with one-third of the remaining hospitals (33%, 3/9) having a practice model that was "mostly distributive pharmacists with limited clinical services".[3] The range of pharmacists' clinical activities was vast, despite the small size of participating hospitals (Table 4). Clinical pharmacist activities reported for at least 50% of areas included review or approval of medication order sets, dosing adjustments, medication order review before administration of the first dose, prioritization of drug therapy management according to patient complexity, reporting of adverse drug reactions, clinical documentation, and medication-related continuity of care for discharged patients. Clinical pharmacist activities reported as existing in less than 50% of areas (some or none) were development of patient care plans, monitoring of responses to medication therapy, daily review of medication profiles, and writing of medication orders as part of their scope of practice. Medication reconciliation was not often completed by pharmacists in these facilities.

Survey responses revealed that the collection of data concerning clinical pharmacy key performance indicators (cpKPIs) was primarily aimed at medication reconciliation, on admission (for 76%–100% of patients) reported by 58% (14/24) of respondents and on discharge (for 76%–100% of patients) reported by 45% (9/20) of respondents (Table 5). For individual cpKPIs not currently collected, 30% to 47%

TABLE 2. Profile of Pharmacist Assignment to Inpatient Programs[a]

Inpatient Service	No. of Respondents Reporting that Program Exists	No. (%) of Respondents Reporting Pharmacist Assigned to Program[b]	
Adult critical care	4	3	(75)
Asthma and/or allergy	3	1	(33)
Cardiovascular and/or lipid	1	0	(0)
Diabetes	7	2	(29)
General medicine	22	16	(73)
General surgery	8	6	(75)
Geriatrics	7	5	(71)
Gynecology and/or obstetrics	6	3	(50)
Hematology-anticoagulation	2	2	(100)
Hematology-oncology	1	1	(100)
Infectious diseases, AIDS, antimicrobial stewardship	7	7	(100)
Mental health	3	3	(100)
Neurology and/or stroke	2	2	(100)
Pain and/or palliative care	11	7	(64)
Pediatric critical care	2	0	(0)
Rehabilitation	6	5	(83)
Renal dialysis	0	0	(0)
Transplantation	0	0	(0)
Total no. of programs	92	63	(68)

[a]Base: 24 respondents.
[b]Percentages calculated in relation to the number of respondents reporting that the particular program exists (previous column).

TABLE 3. Profile of Pharmacist Assignment to Outpatient Programs[a]

Outpatient Service	No. of Respondents Reporting that Program Exists	No. (%) of Respondents Reporting Pharmacist Assigned to Program[b]	
Asthma and/or allergy	1	0	(0)
Cardiovascular and/or lipid	2	0	(0)
Diabetes	1	1	(100)
Emergency	13	5	(38)
General medicine	4	0	(0)
General surgery	1	1	(100)
Geriatrics	6	0	(0)
Gynecology and/or obstetrics	3	0	(0)
Hematology	1	1	(100)
Hematology and/or anticoagulation	0	0	(0)
Infectious diseases, AIDS, antimicrobial stewardship	2	1	(50)
Mental health	1	0	(0)
Neurology and/or stroke	2	0	(0)
Pain and/or palliative care	3	0	(0)
Rehabilitation	1	1	(100)
Renal dialysis	2	0	(0)
Transplantation	0	0	(0)
Total no. of programs	43	10	(23)

[a]Base: 18 respondents.
[b]Percentages calculated in relation to the number of respondents reporting that the particular program exists (previous column).

of the participating small hospitals planned to do so in the next year.

There was an equal distribution of approaches to evaluating clinical pharmacy services, ranging from a structured approach to defining and prioritizing pharmacists' activities to currently determining a means to evaluate pharmacists' direct patient care services (Table 6). Sixty-seven percent (8/12) of respondents used self-evaluation methods to assess the provision of direct patient care by pharmacists, and 33% (4/12) reported peer-review evaluation. In facilities where direct patient care pharmacy services were evaluated, 70% (7/10) assessed conformity of documentation with clinical practice and 50% (5/10) considered answers to drug information questions. Only 1 facility (4%) reported the presence of established mechanisms to measure medication-related outcomes.

Pharmacy Distribution Systems

Facilities reported differences between acute and non-acute care beds in terms of the types of pharmacy drug distribution systems employed (Figure 2). Centralized unit-dose distribution (67%, 16/24) was the most common drug distribution system for acute care beds, with decentralized distribution from automatic dispensing cabinets (ADCs) for 63% (15/24) of respondents, and decentralized distribution from pharmacy satellites for 4% (1/24). Older drug distribution systems, specifically total wardstock (33%, 8/24) and traditional (13%, 3/24), remained in use for acute care beds. Non-acute care beds were serviced primarily by decentralized unit-dose ADCs (72%, 13/18), followed by a centralized unit-dose system (39%, 7/18). Eighteen facilities were using decentralized unit-dose ADCs, with 17 (94%) having them in the emergency department, 15 (83%) in general adult

TABLE 4. Profile of Clinical Pharmacy Activities[a]

Clinical Pharmacy Activity	No. of Respondents	Level of Implementation[b]; No. (%) of Respondents							
		Exists in All Areas		Exists in Most Areas		Exists in Some Areas		Does Not Exist	
Pharmacists are involved in identifying, developing, reviewing, or approving new medication order sets	23	7	(30)	12	(52)	3	(13)	1	(4)
Pharmacy department has identified drug therapy management as a service that should be provided consistently by all pharmacists	24	14	(58)	6	(25)	2	(8)	2	(8)
Pharmacists adjust dosing of medications on the basis of patient's response or pharmacokinetic characteristics	24	6	(25)	8	(33)	5	(21)	5	(21)
Pharmacists review medication orders before the first dose is administered	24	0	(0)	15	(63)	8	(33)	1	(4)
Drug therapy management services are prioritized for inpatients according to the complexity of patients' medication therapy	24	4	(17)	10	(42)	4	(17)	6	(25)
Pharmacists are involved in monitoring and reporting potential and actual ADEs	24	5	(21)	13	(54)	5	(21)	1	(4)
Pharmacists routinely document recommendations and assess progress and achievement of therapeutic goals in patients' medical records	23	5	(22)	8	(35)	10	(43)	0	(0)
Pharmacists facilitate medication-related continuity of care when patients experience transitions of care	23	1	(4)	6	(26)	12	(52)	4	(17)
Pharmacists monitor patients' responses to medication therapy	23	5	(22)	6	(26)	12	(52)	0	(0)
Medication profiles of all patients are reviewed for appropriateness at least once daily by a pharmacist	22	1	(5)	9	(41)	7	(32)	5	(23)
The facility has processes to ensure medication-related continuity of care for discharged patients	23	10	(43)	3	(13)	8	(35)	2	(9)
Inpatient pharmacists are authorized by policy or protocol to write medication orders as part of their scope of practice	22	6	(27)	2	(9)	3	(14)	11	(50)
Drug therapy management services are prioritized for outpatients according to the complexity of patients' medication therapy	21	2	(10)	3	(14)	1	(5)	15	(71)
Outpatient pharmacists are authorized by policy or protocol to write medication orders and/or prescriptions as part of their scope of practice	21	0	(0)	3	(14)	0	(0)	18	(86)
Pharmacists provide discharge education to patients at the facility	23	0	(0)	0	(0)	10	(43)	13	(57)
When a patient's genetic characteristics are known, pharmacists have a role in adjusting dosing or changing therapy for select medications	21	0	(0)	1	(5)	3	(14)	17	(81)
Pharmacists participate in the facility's cardiopulmonary resuscitation teams	24	0	(0)	0	(0)	4	(17)	20	(83)
Pharmacists participate in the facility's rapid response teams	22	0	(0)	0	(0)	1	(5)	21	(95)
Medication reconciliation is performed by pharmacy staff at the facility	24	4	(17)	3	(13)	5	(21)	12	(50)
Pharmacists are involved in developing patient care plans	24	4	(17)	5	(21)	11	(46)	4	(17)

ADE = adverse drug event.
[a]Base: All respondents.
[b]Numeric definitions of levels of implementation: "exists in all areas" = 100%; "exists in most areas" = 50%–99%; "exists in some areas" = 1%–49%; "does not exist" = 0%.

TABLE 5. Clinical Pharmacy Key Performance Indicators (cpKPIs)[a]

cpKPI	No. of Respondents	Extent of Implementation[b]; No. (%) of Respondents: For 76%–100% of Patients	For 51%–75% of Patients	For 26%–50% of Patients	For 1%–25% of Patients	Plan to Collect in Next Year
Provision of documented medication reconciliation at admission	24	14 (58)	0 (0)	0 (0)	2 (8)	8 (33)
Pharmacist participation in interprofessional patient care rounds	20	2 (10)	3 (15)	3 (15)	6 (30)	6 (30)
Provision of documented medication reconciliation on discharge	20	9 (45)	1 (5)	1 (5)	3 (15)	6 (30)
Provision of comprehensive direct patient care from a pharmacist	20	1 (5)	2 (10)	1 (5)	9 (45)	7 (35)
Resolution of DTPs by a pharmacist	20	1 (5)	4 (20)	2 (10)	6 (30)	7 (35)
Provision of education by a pharmacist about disease(s) and medication(s)	19	0 (0)	1 (5)	1 (5)	8 (42)	9 (47)
Development of a pharmaceutical care plan by a pharmacist	19	0 (0)	2 (11)	1 (5)	7 (37)	9 (47)
Provision of medication education by a pharmacist at discharge	19	0 (0)	0 (0)	1 (5)	9 (47)	9 (47)

DTP = drug therapy problem.
[a]Basis for data collection: respondents who answered question about cpKPIs in terms of extent of implementation, where extent of implementation refers to the proportion of patients at each facility who received care associated with each particular cpKPI.
[b]Basis for extent of implementation: facilities with data collection.

TABLE 6. Evaluation of Clinical Pharmacy Services

Criterion	No. (%) of Respondents
General[a]	*n* = 17
A structured approach is used to define and prioritize pharmacist activities	7 (41)
Other clinical pharmacy performance indicators (not cpKPIs) are being collected	7 (41)
The provision of direct patient care pharmacy services is being evaluated	6 (35)
Methods used to evaluate provision of direct patient care by pharmacy services[b]	*n* = 12
Self-evaluation by the pharmacist	8 (67)
Retrospective chart review	2 (17)
Direct observation	1 (8)
Peer-review evaluation	4 (33)
Knowledge and competence testing	0 (0)
Other	6 (50)
Aspects of clinical practice evaluated[b]	*n* = 10
Conformity of documentation with clinical practice	7 (70)
Development of an individualized pharmaceutical care plan	0 (0)
Medication counselling and evaluation of adherence	2 (20)
Answers to drug information questions	5 (50)
Mechanisms established to measure patients' medication-related outcomes[c]	*n* = 23 1 (4)
Patients' medication-related outcomes are used to evaluate the performance of pharmacists	*n* = 21 0 (0)

cpKPI = clinical pharmacy key performance indicator.
[a]Basis for data collection: respondents who answered question about outpatient services.
[b]Basis for analysis: facilities where provision of direct patient care pharmacy services was evaluated (multiple mentions permitted).
[c]Basis for analysis: all respondents.

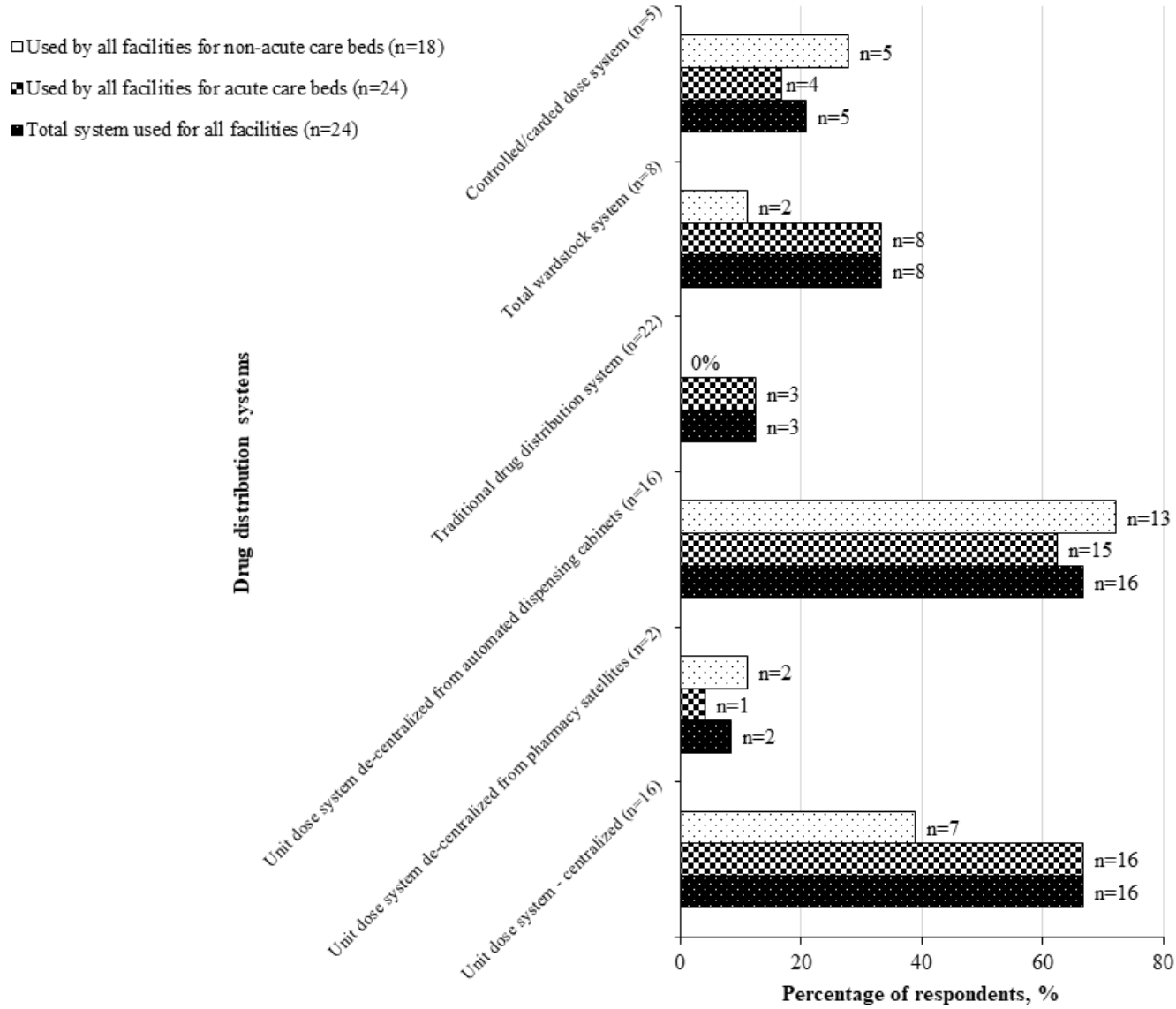

FIGURE 2. Percentage of respondents using various drug distribution systems for patient care areas with inpatient beds. The base for calculating percentages was the number of respondents with complete answers to questions about drug distribution systems. Individual respondents could provide multiple responses.

medical/surgical units, 6 (33%) in operating rooms, and 4 (22%) in recovery rooms (Table 7).

Medication Order Entry and Verification

The task of order entry was performed by technicians at 71% (17/24) of the hospitals, by pharmacists at 42% (10/24), by others (e.g., nurses) at 21% (5/24), and by physicians at 17% (4/24) (Table 8). If order entry verification was required, pharmacists were most often responsible for this task. In 57% (4/7) of the facilities, pharmacist order entry did not require verification, compared with 33% (3/9) of facilities where physician order entry did not require verification.

With regard to pharmacist review of at least 95% of all orders for appropriateness before medications were accessed at times when the hospital pharmacy department was closed, the responses varied: this occurred for 12% (2/17) of facilities with access to a night cupboard or similar after-hours medication supply system, for 18% (3/17) of those with ADC access, and for 24% (4/17) of respondents before medication orders appeared on the medication administration record (MAR). By comparison, when the pharmacy was open, pharmacist review of at least 95% of routine medication orders before medications were dispensed from the central or satellite pharmacy was reported by 45% (9/20) of respondents, before medications were dispensed from ADCs by 60% (12/20), and before appearance of the order on the MAR by 40% (8/20). For all respondents, the mean total weekly time that pharmacists spent on order verification was 66.4 hours, including weekdays and weekends.

The majority of hospital MARs (75%, 18/24) were generated in hard copy using the pharmacy information system, with manual documentation of the doses administered. In more advanced facilities, 21% (5/24) of MARs were derived electronically from databases aligned with the pharmacy information system, with electronic documentation of administered doses.

TABLE 7. Automated Dispensing Cabinets[a]

Location of ADC	No. (%) of Facilities (n = 18)	
General adult medical and surgical units	15	(83)
General pediatric medical and surgical units	1	(6)
Adult critical care units	1	(6)
Pediatric critical care units	0	(0)
Operating rooms	6	(33)
Recovery rooms	4	(22)
Labour and delivery units	2	(11)
Antepartum and postpartum units	1	(6)
Mental health units	2	(11)
Emergency departments	17	(94)

[a]Basis for analysis: all facilities with automated dispensing cabinets (n = 18).

Infrastructure for Parenteral Admixtures and Policy Provision of Sterile Compounding

In most facilities (61%, 14/23), pharmacy departments did not offer sterile compounding services for nonhazardous medications. Where the pharmacy department did offer sterile compounding services for nonhazardous medications, the medications were supplied by external providers for 26% (6/23), with the remainder supplied by the pharmacy department (13%, 3/23). Hence, most facilities (80%, 16/20) reported no physical space requirements for sterile compounding services of nonhazardous medications, such that 83% (15/18) of facilities had not adopted the standard operating procedures outlined in the USP General Chapter <797> standards.[9]

Similarly, more than half of the facilities reported that compounding services for nonhazardous medications were not required for their patient population, and where such services were required, 30% (7/23) of respondents reported that

TABLE 8. Medication Order Entry and Verification[a]

Activity	No. of Responses	Staff Group Performing Activity; No. (%) of Respondents				
		All	Pharmacist Only	Pharmacy Technician Only	Either Pharmacist or Pharmacy Technician	Verification Not Required
Order entry is done by prescribing physicians, entering their own orders	24	4 (17)	NA	NA	NA	NA
Verification of order entry by prescribing physicians is done by …	24	9 (38)	6 (67)	0 (0)	0 (0)	3 (33)
Order entry is done by prescribing pharmacists, entering their own orders	20	2 (10)	NA	NA	NA	NA
Verification of order entry by prescribing pharmacists is done by …	20	7 (35)	3 (43)	0 (0)	0 (0)	4 (57)
Order entry is done by pharmacists, entering prescribers' orders	24	10 (42)	10 (100)	NA	NA	NA
Verification of order entry by pharmacists, entering prescribers' orders, is done by …	24	17 (71)	7 (41)	1 (6)	0 (0)	9 (53)
Order entry is done by pharmacy technicians, entering prescribers' orders	24	17 (71)	NA	17 (100)	NA	NA
Verification of order entry by pharmacy technicians, entering prescribers' orders, is done by …	24	17 (71)	14 (82)	3 (18)	0 (0)	0 (0)
Order entry is done by other prescribers (e.g., nurse prescribers)	24	5 (21)	NA	NA	NA	NA
Verification of order entry by other prescribers (e.g., nurse prescribers), is done by …	24	10 (42)	7 (70)	0 (0)	0 (0)	3 (30)

NA = not applicable.
[a]Basis for analysis: all respondents.

nonhazardous compounds were supplied by external providers. Moreover, 59% (10/17) of respondents reported that their facility's infrastructure did not support sterile compounding services for hazardous compounds to meet compliance standards. Adherence to USP General Chapter <797> standards[9] for beyond-use dating of sterile compounded nonhazardous and hazardous products was reported by 38% (5/13) and 50% (6/12) of respondents, respectively.

Drug Costs and Inventory Management

None of the small hospitals responding to this survey could provide data about drug costs; however, based on data from 5 hospitals, the median reported inventory turnover rate was 4.9 (interquartile range 4–6.5) per year.

Human Resources

With the exception of a 7% vacancy rate for staff pharmacists, no hospitals reported unfilled pharmacy services positions. The typical staff composition, based on FTE positions, consisted of 20% staff pharmacists, 53% registered pharmacy technicians, 16% pharmacy assistants, and 11% pharmacy department managers (10% of whom were pharmacists). Analysis showed that if all pharmacy positions were considered, regardless of existing within respective pharmacy departments (reported FTE position ≥ 0; Table 9), the median total pharmacy department staffing was 2.8 FTEs. Medians by professional group were 0.5 FTE for staff pharmacists, 1.5 FTEs for technicians, 0 FTEs for pharmacy assistants, 0 FTEs for pharmacy nurses, and 0.3 FTE for pharmacist managers, with an overall ratio of pharmacists to nonpharmacists (technicians, pharmacy assistants, pharmacy nurses) of 0.5:1.8. In this analysis, total budgeted hours, expressed in terms of FTE, per acute and non-acute patient-day for technicians was considerably higher than for all other pharmacy positions (0.5 versus 0–0.1, Table 9).

According to further analysis of data from respondents who reported FTE staffing for specific pharmacy positions that existed within their pharmacy departments (a reported FTE position > 0, Table 10), the median total departmental staffing was 2.7 FTEs. Of the allocated total 2.7 FTEs, the median FTEs for staff positions were 0.6 for pharmacists, 1.9 for technicians, 0.8 for pharmacy assistants, 0.5 for pharmacy nurses, and 0.5 for pharmacist managers. The ratio of pharmacists to nonpharmacists (technicians, pharmacy assistants, pharmacy nurses) was 0.6:1.8. Total budgeted hours, expressed in terms of FTE, per acute and non-acute patient-day for technicians was 5 times higher than for all other pharmacy positions (0.5 versus 0.1, Table 10). Total budgeted hours for non-acute plus acute patient-days was 0.7 FTE and for acute patient-days was 1.3 FTE (Table 11).

DISCUSSION

This survey, with its high response rate, provides a snapshot of Canadian community hospitals with fewer than 50 acute care beds that are supported by third-party telepharmacy services. To our knowledge, this is the first survey assessing pharmacy distribution, clinical, and management services in small Canadian hospitals.

The results revealed that the numbers of both inpatient and outpatient programs and the proportion of these programs with a pharmacist assigned were far lower than in larger hospitals surveyed in 2016/17, as documented in the *Hospital Pharmacy in Canada Report*.[3] We found that the pharmacist clinical practice models in small hospitals echoed those of hospitals with 50–200 acute care beds,[3] as did the extent of a broad range of clinical pharmacy activities provided. Relative to their larger counterparts, a much higher proportion of the small hospitals had a "mostly distributive pharmacists with limited clinical services" model

TABLE 9. Budgeted Pharmacy Staffing and Staffing Ratios, as Budgeted Hours/Patient-Day, for All Facilities (FTE ≥ 0)[a]

Staff Type	Budgeted Hours, as Median FTEs (IQR)		Total Budgeted Hours per Acute + Non-acute Patient-Day, as Median FTEs (IQR)	
Pharmacy technician	1.5	(1.0–2.1)	0.5	(0.3–0.7)
Pharmacy assistant	0.0	(0.0)	0.0	(0.0)
Pharmacist	0.5	(0.3–0.8)	0.1	(0.1–0.2)
Pharmacy manager	0.3	(0.0–0.5)	0.1	(0.0–0.1)
Pharmacy nurse	0.0	(0.0)	0.0	(0.0)
Subtotals				
Pharmacists	0.5	(0.3–0.8)	0.1	(0.1–0.2)
Pharmacy technicians, pharmacy assistants, pharmacy nurses	1.8	(1.0–2.1)	0.7	(0.5–0.8)
Total pharmacy staff	2.8	(1.8–3.3)	0.5	(0.3–0.7)

FTE = full-time equivalent, IQR = interquartile range.
[a]Basis for analysis: all respondents that reported staffing FTEs ≥ 0 for assigned positions (n = 23) and patient-day information (n = 16) (i.e., reported data include facilities with and without budgeted hours for the specified positions).

TABLE 10. Budgeted Pharmacy Staffing and Staffing Ratios, as Budgeted Hours/Patient-Day, for Facilities with Budgeted Positions (FTE > 0)[a]

Staff Type	Budgeted Hours			Total Budgeted Hours per Acute + Non-acute Patient-Day		
	No. of Respondents	Median FTEs (IQR)		No. of Respondents	Median FTEs/ Patient-Day (IQR)	
Pharmacy technician	20	1.9	(1.0–2.5)	15	0.5	(0.3–0.7)
Pharmacy assistant	7	0.8	(0.7–2.5)	2	0.1	(0.0–0.1)
Pharmacist	21	0.6	(0.4–1.0)	15	0.1	(0.1–0.2)
Pharmacy manager	12	0.5	(0.2–1.0)	11	0.1	(0.0–0.1)
Pharmacy nurse	1	0.5	NA	1	0.1	NA
Subtotals						
Pharmacists	21	0.6	(0.4–1.0)	15	0.1	(0.1–0.2)
Pharmacy technicians, pharmacy assistants, pharmacy nurses	23	1.8	(1.0–2.5)	16	0.5	(0.3–0.7)
Total pharmacy staff	23	2.7	(1.8–3.4)	16	0.7	(0.5–1.0)

FTE = full-time equivalent, IQR = interquartile range, NA = not applicable.
[a]Basis for analysis: all respondents that reported staffing FTEs > 0 for assigned positions, along with patient-day information (i.e., reported data are limited to facilities with budgeted hours for the specified positions).

(10% versus 33%). In contrast to facilities with 50–200 beds, pharmacists' clinical activities were vast, despite the small size of responding hospitals. In hospitals with 50–200 beds, medication reconciliation was primarily conducted by pharmacists, whereas this task was often conducted by nonpharmacy staff in the smaller hospitals in our survey. Despite the support of telepharmacy services, we think that low overall pharmacy staffing and limited hours of operation meant that pharmacists working at small hospitals were less involved in performing daily medication review, developing patient care plans, monitoring therapy, and facilitating medication-related continuity of care when patients transitioned within and out of hospital, including discharge patient education.

In these small hospitals, medication reconciliation at the time of admission was the highest cpKPI, similar to that of hospitals with 50–200 beds and 3 times that of hospitals with more than 500 beds.[3] Moreover, our study found that hospitals with fewer than 50 acute care beds exceeded all other categories of hospital size and type in terms of medication reconciliation on discharge. As indicators of evidence-based processes of care, cpKPIs are in "the domain of clinical pharmacy services that are associated with a meaningful impact on patient outcomes".[3] In responding to our survey, hospital and pharmacy leadership often retrieved medication reconciliation frequencies from hospital data, as opposed to identifying medication reconciliation completed specifically by pharmacists. Despite our attempt to compare medication reconciliation cpKPI frequencies with data for larger hospitals in the *Hospital Pharmacy in Canada Report*,[3] it remains unclear whether the data for larger hospitals are based on medication reconciliation conducted by pharmacists only or if they represent hospital-wide data. Clarity will be needed in future surveys of small and larger hospitals to distinguish between medication reconciliation conducted by pharmacists and medication reconciliation conducted by other providers.

In the small hospitals responding to this survey, evaluation of pharmacists' provision of direct patient care was often by self-evaluation, most likely because of limited resources for peer or management review; furthermore, if an aspect of pharmacist clinical practice was to be evaluated, it was primarily an assessment of conformity of documentation.

Unit-dose drug distribution, ADCs, and traditional drug distribution systems were used at the same frequencies as in larger facilities. In contrast, smaller hospitals had less decentralized unit-dose satellites and higher use of the outdated wardstock distribution system.

The greatest disparity in pharmacy services between small and larger hospitals lay in weekly hours of operation

TABLE 11. Staffing Ratios[a]

Ratio	No. of Respondents	Ratio
Total budgeted hours per acute patient-day	7	1.3
Total budgeted hours per acute + non-acute patient-day	16	0.7

[a]Basis for analysis: all respondents who provided staffing and patient-day information.

of the pharmacy: 41.5 compared with 84 hours/week. However, when we explored pharmacy departments included in our survey that were supported by telepharmacist medication order verification outside the standard hours of operation of the hospital pharmacy department reported by respondents, the mean total weekly hours of pharmacist order verification was 66.4 hours (unpublished internal data), demonstrating that telepharmacists could extend the pharmacy's usual weekly hours of operation.

Parallel to larger facilities, most medication order entry was performed by pharmacists and pharmacy technicians, with verification performed primarily by pharmacists. Our survey found that small hospitals, like larger Canadian hospitals, continued to lag behind facilities in the United States, where more than 90% of medication orders are received electronically through computerized prescriber order entry.[6] As might have been expected, with the support of after-hours telepharmacy services for some of the small hospitals surveyed, a greater proportion of these sites, relative to larger hospitals (12%–18% versus 1%–3%), had at least 95% of medication orders reviewed for appropriateness before ADC access, night cupboard access, or appearance of the order on the MAR, regardless of the pharmacy's hours of operation. Despite similar standards in Canada and the United States, 90% of respondents to the 2016 ASHP survey[5] indicated that all medication orders, regardless of time of day, were reviewed by a pharmacist before administration, including 81% of respondents in hospitals with fewer than 50 beds.

Unlike their larger counterparts in Canada, small hospitals did not provide the majority of sterile compounding unless these products were obtained from an external provider. The reasons for this situation were not identified in this survey, although they may include a lack of pharmacy resources, the facility's particular patient population, or the available hospital programs and services.

Total budgeted hours per acute patient-day (which excludes non-acute care beds from the denominator but includes budgeted hours for non-acute care beds and ambulatory care services) was 1.3 FTE, higher than for all hospital size categories in the *Hospital Pharmacy in Canada Report* (0.99 FTE).[3] However, the ratio of total budgeted hours to total (acute + non-acute) patient-days was aligned with that stated in the Report (0.7 FTE).[3] This ratio should be interpreted with caution given the potential broad distribution in the proportion of acute care beds. As mentioned in the Report,[3] the most accurate view of resources used specifically for staffing inpatient acute care beds is inpatient budgeted hours per acute inpatient day. The majority of respondents to our survey were unable to provide data for non-acute care and acute care workloads separately. Nevertheless, reported median total pharmacy staff composition in the small hospitals was drastically below that for hospitals with 50–200 beds (2.7 FTE versus 17 FTE).[3] Moreover, the difference in ratio of pharmacists to pharmacy technicians, pharmacy assistants, and pharmacy nurses in small hospitals compared with larger facilities (1:2.0 versus 1:1.5) is worth some attention. This difference may suggest that pharmacy departments in small hospitals could benefit from an increased FTE pharmacist complement to more closely mirror the pharmacist activities and services provided in larger hospitals. In addition, the pharmacy staffing complement differed substantially between the small hospitals and larger facilities in terms of pharmacists (20% versus 40%), technicians (53% versus 28%), assistants (16% versus 23%), and managers (11% versus 5%). These results suggest that small hospitals may be in need of increased human resources and that realignment of pharmacy staffing may be warranted.

Limitations

This survey collected data from 3 Canadian provinces on distribution, clinical, and management services of pharmacy departments in hospitals with fewer than 50 acute care beds that had such services provided, either fully or in part, by a single telepharmacy provider. The results may not be generalizable to hospitals outside the 2 large provinces and the small prairie province where the survey was conducted; similarly, the results may not be generalizable to small hospital pharmacies with on-site pharmacist support only or to those with a different telepharmacy provider. Nonetheless, based on the high response rate and congruence of many of the results with the most recent (2016/17) *Hospital Pharmacy in Canada Report*, the present study design and data analysis are likely reproducible and applicable to a broader group of pharmacy departments in small hospitals across Canada. A larger study of small hospitals across Canada, with and without the support of telepharmacy services, is very much needed.

CONCLUSION

To the authors' knowledge, this is the first study to describe pharmacy distribution, clinical, and management services in small Canadian hospitals. Representing approximately 12% of hospitals with fewer than 50 acute care beds in Canada, our survey has provided valuable quantitative data on pharmacy distribution, clinical, and management information previously unknown to hospital and pharmacy leadership. Although small hospitals have many similarities to larger facilities in terms of the broad services provided by their pharmacy departments, there are many substantial gaps between small and large hospitals in the extent of resources and services available. Human resource metrics for small hospitals, such as staffing ratios, are well below those of larger hospitals, and significant differences in staffing complements require attention. Not surprisingly, given the small size of participating hospitals, many program and service questions mirroring the most recent CSHP Hospital

Pharmacy in Canada Survey were not applicable. Customization and dissemination of a survey specifically designed for smaller hospitals may be more efficient and provide much-needed data. It is paramount that the data necessary to benchmark, plan, and expand pharmacy services of small and often remote community hospitals be collected and disseminated, to help ensure that all Canadians have access to equitable care.

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Treatment of Mild Hyperkalemia in Hospitalized Patients: An Unnecessary Practice?

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ABSTRACT

Background: Sodium polystyrene sulfonate (SPS) is one of the most commonly used treatments for mild hyperkalemia. Other treatments include insulin, sodium bicarbonate, and salbutamol, which may be given alone or in combination. The results of research examining treatment effectiveness for mild hyperkalemia (e.g., the ability of SPS to achieve normokalemia) thus far have been inconsistent. Given that the effectiveness of treatment for mild hyperkalemia is debatable, new research is needed.

Objective: To determine whether treatment of hospitalized patients with mild hyperkalemia (using SPS or another approach, relative to no treatment) was associated with achievement of normokalemia (serum potassium < 5.1 mmol/L).

Methods: For this retrospective, quasi-experimental study, hospitalized patients with index serum potassium level between 5.1 and 6.4 mmol/L were identified. Post-index serum potassium level within 24 hours was dichotomized (< 5.1 or ≥ 5.1 mmol/L). Pre-index serum creatinine and serum potassium levels were recorded as the average of the first 5 values immediately before the index potassium value. For each patient, treatment was categorized as no treatment, SPS treatment, or other treatment strategy.

Results: Among the 1944 patients included in the analysis, the average age was 66.8 (standard deviation 13.5) years; 605 (31.1%) of the patients were women and 1339 (68.9%) were men. Logistic regression results indicated that patients who were female and/or had higher pre-index serum potassium were less likely to return to normokalemia within 24 hours after the time of the index serum potassium value. Treatment category was not a statistically significant predictor of the achievement of normokalemia. Most patients with mild hyperkalemia (> 74.5% in each treatment category) achieved normokalemia, whether or not they received treatment.

Conclusions: The findings of this study suggest that although follow-up is required for mild hyperkalemia in hospitalized patients, active treatment may be unnecessary.

Keywords: creatinine, hyperkalemia, potassium, treatment outcome, polystyrenes

RÉSUMÉ

Contexte : Le sulfonate de polystyrène de sodium (SPS) est l'un des traitements les plus communément utilisés pour l'hyperkaliémie légère. D'autres traitements comprennent l'insuline, le bicarbonate de sodium et le salbutamol, qui peuvent être administrés seuls ou ensemble. Les résultats des recherches se penchant sur l'efficacité des traitements de l'hyperkaliémie légère (p. ex., la capacité du SPS à rétablir la normokaliémie) sont contradictoires jusqu'à présent. Étant donné que l'efficacité du traitement de l'hyperkaliémie légère est discutable, de nouvelles recherches sont nécessaires.

Objectif : Déterminer si le traitement des patients hospitalisés, présentant une hyperkaliémie légère, (à l'aide de SPS ou d'une autre approche, comparativement à l'absence de traitement) était associé à l'atteinte de la normokaliémie (potassium sérique < 5,1 mmol/L).

Méthodes : Des patients hospitalisés, dont l'indice de concentration sérique de potassium se situait entre 5,1 et 6,4 mmol/L, ont été identifiés pour participer à cette étude rétrospective quasi expérimentale. La concentration sérique de potassium mesurée dans les 24 heures après le diagnostic d'hyperkaliémie légère a été dichotomisée (< 5,1 ou ≥ 5,1 mmol/L). Les indices de concentrations sériques de créatinine et de potassium avant le diagnostic d'hyperkaliémie légère ont été obtenus par la moyenne des cinq premières valeurs situées immédiatement avant celle de la concentration de potassium. Le classement du traitement de chaque patient était le suivant : Aucun traitement, Traitement par SPS ou Autre stratégie de traitement.

Résultats : L'âge moyen des 1944 patients inclus dans l'analyse était de 66,8 ans (écart type 13,5); 605 (31,1 %) d'entre eux étaient des femmes et 1339 (68,9 %) des hommes. Les résultats de la régression logistique indiquaient que les patientes, donc les femmes, qui avaient un indice sérique de potassium plus élevé au moment du diagnostic, avaient moins de chances de retourner à la normokaliémie dans les 24 heures après l'instant de la mesure de la valeur de l'indice sérique de potassium. La catégorie de traitement n'était pas une variable prédictive statistiquement significative de l'atteinte de la normokaliémie. La plupart des patients présentant une hyperkaliémie légère (> 74,5 % dans chaque catégorie de traitement) atteignaient la normokaliémie, qu'ils aient reçu ou non un traitement.

Conclusions : Les résultats de cette étude laissent entendre que, malgré la nécessité d'un suivi des patients hospitalisés en cas d'hyperkaliémie légère, un traitement actif pourrait s'avérer inutile.

Mots-clés : créatinine, hyperkaliémie, potassium, résultat du traitement, polystyrènes

INTRODUCTION

Hyperkalemia, or levels of serum potassium above the normal range,[1,2] is a potentially serious condition.[3-6] According to one Canadian study, hyperkalemia was associated with 2.6% of emergency department visits and 3.5% of hospital admissions.[7] One of the most harmful consequences of hyperkalemia is its potential impact on cardiac activity (e.g., serious acute cardiac arrhythmias, conduction abnormalities).[8,9] Thus, severe hyperkalemia is considered a medical emergency that requires urgent treatment.[8,9] For patients with severe hyperkalemia, clinicians administer medication to reduce potassium levels as quickly as possible.[10] For patients with mild hyperkalemia, clinicians may administer medication, or they may wait to see if the patient's serum potassium returns to normal levels without pharmaceutical intervention.[11] Although previous research supports intervention for severe hyperkalemia (i.e., in cases of medical emergency),[12] there is a lack of research about the treatment of mild hyperkalemia.[4,13]

Pharmaceutical treatments for hyperkalemia include insulin, sodium bicarbonate, and salbutamol, administered alone or in combination.[14,15,] However, the most commonly used pharmaceutical intervention for the treatment of hyperkalemia is administration of the cation exchange resin sodium polystyrene sulfonate (SPS).[16] This agent works by removing excess potassium from the body. Following administration, SPS takes effect within approximately 2 hours.[17-19] The pharmacological effects last about 4 to 6 hours, although the duration of action varies with factors such as gastrointestinal (GI) transit time.[1,17,20] Given the delay in pharmaceutical effect, SPS is not used independently to manage hyperkalemia in cases where the patient is having a medical emergency that requires immediate treatment.[12]

Treatment with SPS carries some risk,[9] as its use has been associated with adverse GI events in previous research. For instance, in a recent Canadian study of older adults, use of SPS was associated with a greater risk of hospital admission for severe GI issues within 30 days, relative to non-use.[16] Similarly, Laureati and colleagues[21] found that SPS initiation, without concomitant sorbitol, was related to a higher incidence of severe GI events among patients with advanced chronic kidney disease (CKD).

Despite common use of SPS for reducing serum potassium levels and its known potential risks, the effectiveness of this agent, especially for mild hyperkalemia, has been questioned.[6,9,20] For instance, in a randomized controlled trial of 33 patients with CKD and mild hyperkalemia, treatment with 30 g of SPS by oral administration for 7 days was effective in reducing potassium levels but was not more effective than placebo in achieving normokalemia.[22] Therefore, it is also important to consider and weigh the evidence concerning this drug's safety in addition to its small therapeutic effects.[2]

Previous research on the treatment of hyperkalemia has focused on non-mild hyperkalemia and patients with CKD. Few studies, if any, have examined treatment in a broader range of patients or the achievement of normokalemia in patients with mild hyperkalemia. The primary purpose of this study was to determine whether treatment, primarily SPS, was associated with achievement of normokalemia (serum potassium < 5.1 mmol/L) in hospitalized patients with mild hyperkalemia. Given that Lepage and others[22] found no statistically significant difference in the achievement of normokalemia between groups receiving either a placebo or SPS, we hypothesized that there would be no statistically significant differences among groups receiving either no treatment, SPS alone, or other treatment (e.g., salbutamol, salbutamol and SPS combined) in a sample of patients with mild hyperkalemia.

METHODS

Data Source and Procedure

Approval for this retrospective quasi-experimental cohort study was obtained, before study initiation, through the Research Ethics Board (REB) of Horizon Health Network. A waiver of informed consent for secondary use of data was approved by the REB. The study site was a tertiary care hospital in Saint John, New Brunswick, with 524 inpatient beds. Data were retrieved from electronic hospital records for patients older than 19 years of age who were admitted to hospital between November 2009 and December 2018 and who had at least 1 serum potassium level of 5.1 mmol/L or above. The retrospective study period was selected on the basis of availability of electronic patient data; such data were unavailable for patients admitted before November 2009. For patients who were admitted more than once during the study period, only the first admission was included.

For this study, normokalemia was defined as serum potassium levels between 3.5 and 5.09 mmol/L, and mild hyperkalemia as levels between 5.1 and 6.4 mmol/L. These categories follow the work of Fordjour and others.[23] Patients with pseudohyperkalemia (as identified by a laboratory hemolysis tag), end-stage renal disease (e.g., patients with CKD, needing dialysis or kidney transplant to survive), acidosis (arterial or venous blood pH < 7.2), severe hyperkalemia (potassium serum level > 6.4 mmol/L), or missing data (e.g., pre-index serum creatinine [SCr]; see below for the definition of "index") and those undergoing hemodialysis were excluded from the analyses.

Study Variables

The covariates collected for the current study included age, sex, pre-index serum potassium level, and pre- and post-index SCr levels. The index serum potassium level was defined as the first valid serum potassium value of 5.1 mmol/L

or above during a patient's first hospital admission. The pre-index serum potassium and pre-index SCr levels were defined as the averages of the 5 serum potassium values and the 5 SCr values, respectively, immediately preceding the index potassium value. The post-index SCr value was the average of all SCr values measured in the 24-hour period after the index serum potassium level. The pre-index values were collected because of their potential clinical relevance and possible relation to treatment outcomes. They were included as covariates to statistically control for potential confounders related to differences in illness severity.

The independent variable was treatment for mild hyperkalemia. The 3 groups were no treatment, SPS treatment, and other treatment. The "other treatment" category consisted of treatments other than SPS alone; treatments in this category could include SPS in combination with other treatments for mild hyperkalemia (e.g., SPS, insulin, and salbutamol within the 24-hour follow-up period). Patients who were also receiving concurrent treatment for diseases such as diabetes and asthma were included in the analyses. For example, a patient who was receiving insulin on a regular basis for diabetes but did not receive any treatment for mild hyperkalemia was included in the "no treatment" category.

The dependent variable was the achievement of normokalemia, determined by the post-index serum potassium value. If the final serum potassium value was less than 5.1 mmol/L, normokalemia was deemed to have been achieved. If the post-index serum potassium was 5.1 mmol/L or above, normokalemia was deemed not to have been achieved.

Data Preparation

Before the analysis, the data were examined for accuracy using descriptive statistics.[24] Although there were outliers in the serum potassium and SCr levels, the data were determined to be accurate. Bivariate scatter plots and Q–Q plots were examined for normality, linearity, and homoscedasticity. Pre- and post-index SCr values displayed evidence of non-normality, nonlinearity, and heteroscedasticity. Given the large number of outliers and the accuracy of these data, a log transformation was performed. Subsequent testing indicated that the log-transformed pre- and post-index SCr values were relatively normally distributed and linear, although some minor heteroscedasticity remained. There were no missing values, as any case that did not include essential values was excluded, as per the research protocol. Multivariate outliers were identified using Mahalanobis distance measurements.

Data Analysis

A binary logistic regression analysis was conducted, with serum potassium within 24 hours after the index value (categorized as ≥ 5.1 or < 5.1 mmol/L) as the dependent variable and treatment category (i.e., no treatment, SPS treatment, other treatment) as the independent variable. All assumptions of binary logistic regression analysis were examined, including multicollinearity, adequacy of expected frequencies, and ratio of cases to variables. Covariates were entered stepwise before testing of the independent variable. The covariates were pre-index serum potassium, transformed pre-index SCr, age, and sex. Post-index SCr was not included due to issues with multicollinearity, as described below. Linearity in the logit was tested according to the procedures outlined by Tabachnick and Fidell,[24] and no serious violations were observed. An analysis of residuals indicated that there were no outliers in the solution.

RESULTS

Descriptive Analyses

Of the initial sample of 11 014 patients, only 1997 met the study criteria (see Figure 1 for flow chart). Fifty-three patients were identified as multivariate outliers, and these were excluded from the final analysis. These multivariate outliers differed from the rest of the sample in terms of having extreme values for both pre- and post-index SCr. As a result, after removal of the outliers, the maximum pre-index SCr declined from 1528 to 506 µmol/L and the maximum post-index SCr declined from 1332 to 731 µmol/L.

The final sample of 1944 patients consisted of 605 women (31.1%) and 1339 men (68.9%), with a mean age of 66.8 (standard deviation [SD] 13.5) years. Table 1 outlines patients' demographic characteristics and median serum potassium levels by sex and treatment group, along with other outcomes. Only 22.8% of the patients received treatment (n_{SPS} = 203; n_{Other} = 240) (Table 1). The most common SPS dose was 30 g (n = 126), and the most common method of administration was oral (n = 163). Other doses included 15 g (n = 21), 20 g (n = 4), 25 g (n = 1), 40 g (n = 2), and 60 g (n = 39), and other administration methods included rectal (n = 35) and enteral (n = 4). Insulin was the most commonly administered treatment in the "other treatment" category (80.4%, n = 193). The remaining treatments in the "other treatment" category were salbutamol and sodium bicarbonate alone or in combination with either insulin and/or SPS (19.6%, n = 47).

For all 3 groups, the median serum potassium levels decreased from index to post-index measurement, and most patients achieved normokalemia, regardless of treatment category (1171 [78.0%] of 1501 in the "no treatment" group; 160 [78.8%] of 203 in the SPS treatment group; 179 [74.6%] of 240 in the "other treatment" group).

The median time from initial pre-index SCr value to index potassium value was 2.89 (interquartile range [IQR] 1.20–6.22) days, and the median time from initial pre-index to index potassium value was 2.73 (IQR 1.14–6.08) days. For the patients who received SPS or other treatment, the average time from treatment to post-index serum potassium value was 13.85 (SD 5.81) hours.

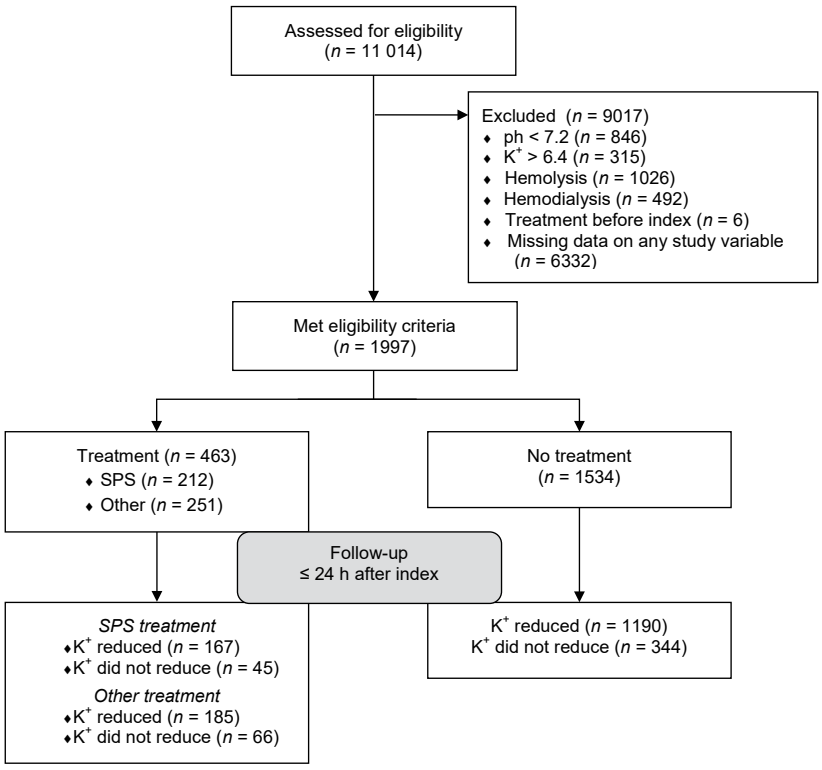

FIGURE 1. Participant flow diagram for study cohort before data analysis. SPS = sodium polystyrene sulfonate.

TABLE 1. Characteristics of 1944 Participants Included in the Final Analysis, by Treatment for Mild Hyperkalemia and Sex

	Treatment Group; Median (IQR)[a]						
	No Treatment (*n* = 1501)		SPS (*n* = 203)		Other (*n* = 240)		Total (*n* = 1944)
Characteristic	Women	Men	Women	Men	Women	Men	
Demographic							
Age (years) (mean ± SD)	69.6 ± 14.7	65. 3 ± 13.2	71.9 ± 13.1	67.4 ± 10.9	65.8 ± 14.5	65.1 ± 11.6	66.8 ± 13.5
Weight[b] (kg)	69.8 (57.6–82.3)	84.5 (73.6–97.6)	77.4 (58.0–95.2)	87.7 (78.7–102.7)	76.3 (62.9–86.5)	89.3 (78.6–102.5)	84.3 (70.0–96.0)
Height[c] (m)	1.6 (1.5–1.7)	1.7 (1.7–1.8)	1.6 (1.5–1.7)	1.7 (1.7–1.8)	1.6 (1.5–1.6)	1.7 (1.7–1.8)	1.7 (1.6–1.8)
Potassium (mmol/L)							
Pre-index	4.4 (4.1–4.6)	4.4 (4.2–4.6)	4.5 (4.3–4.7)	4.5 (4.3–4.6)	4.4 (4.2–4.6)	4.5 (4.3–4.6)	4.4 (4.2–4.6)
Index	5.2 (5.1–5.4)	5.2 (5.1–5.4)	5.5 (5.3–5.8)	5.4 (5.2–5.6)	5.4 (5.2–5.7)	5.4 (5.3–5.8)	5.3 (5.1–5.5)
Post-index	4.7 (4.4–5.1)	4.7 (4.4–5.0)	4.8 (4.3–5.1)	4.6 (4.2–4.9)	4.7 (4.3–5.0)	4.8 (4.6–5.1)	4.7 (4.4–5.0)
Creatinine (μmol/L)							
Pre-index	82.0 (60.5–117.0)	88.6 (73.5–114.9)	107.7 (77.8–146.5)	98.7 (80.5–133.6)	88.0 (64.05–128.8)	98.0 (82.0–124.0)	90.0 (71.8–118.0)
Post-index	85.0 (57.5–127.0)	91.0 (73.0–122.7)	122.0 (81.5–187.7)	123.0 (85.0–180.0)	120.0 (74.0–173.0)	120.5 (93.0–162.0)	95.7 (72.0–135.0)
Post-index potassium (no. of participants)							
≥ 5.1 mmol/L	126	204	21	22	7	54	434
< 5.1 mmol/L	371	800	42	118	38	141	1510
Total *n*	497	1004	63	140	45	195	1944

IQR = interquartile range, SD = standard deviation, SPS = sodium polystyrene sulfonate.
[a]Except where indicated otherwise.
[b]Data for weight were missing for 312 participants.
[c]Data for height were missing for 518 participants.

Statistical Analyses

A correlational analysis indicated potential issues with collinearity. More specifically, pre- and post-index SCr values were highly correlated ($r = 0.81$, $p < 0.001$ for the nontransformed scores; $r = 0.83$, $p < 0.001$ for the transformed scores). Therefore, transformed post-index SCr was not included in the statistical analysis. A test of the stepwise model of covariates against a constant-only model was statistically significant ($\chi^2 = 19.67$, $p < 0.001$) with transformed pre-index SCr entered first into the model, followed by sex and pre-index serum potassium value. Given that stepwise regression analyses remove variables unassociated with outcome, and given that age was unassociated with the outcome, age was removed from the analysis. The Nagelkerke R^2 was 0.015 (95% confidence interval [CI] 0.005–0.026),[25] indicating that approximately 1.5% of the variance in whether or not serum potassium levels declined within 24 hours was due to the 3 covariates of transformed pre-index SCr, sex, and pre-index serum potassium levels. Furthermore, the result of the Hosmer and Lemeshow test was nonsignificant ($\chi^2 = 7.57$, $p = 0.48$). Classification was acceptable, with 77.7% of the cases correctly classified. However, although 100% of the cases with reduced serum potassium levels were correctly classified, none of the cases with nonreduction in serum potassium levels were correctly classified. The addition of treatment did not improve the model ($\chi^2 = 2.03$, $p = 0.36$). In other words, neither of the 2 active treatment groups predicted the achievement of normokalemia relative to no treatment.

Table 2 presents the regression coefficients, Wald statistics, and odds ratios (ORs) with 95% CIs for each of the predictors. The pre-index serum potassium level significantly predicted the outcome: $\chi^2(1, n = 1944) = 3.88$, $p = 0.049$. The OR for pre-index serum potassium level was 0.72, indicating that the odds of a reduction in serum potassium to below 5.1 mmol/L within 24 hours was decreased with higher pre-index serum potassium levels. Sex significantly predicted outcome: $\chi^2(1, n = 1944) = 6.76$, $p = 0.009$. The OR for male sex was 1.35. Therefore, being male was associated with a 1.35 times greater odds of reduction of serum potassium to below 5.1 mmol/L within 24 hours. Finally, the transformed value for pre-index SCr significantly predicted outcome: $\chi^2(1, n = 1944) = 7.66$, $p = 0.006$. The OR was 0.43, indicating that the odds of a reduction in serum potassium to below 5.1 mmol/L within 24 hours were decreased with higher levels of the transformed pre-index SCr.

Follow-up independent-sample t tests indicated a statistically significant difference in index serum potassium levels between each of the 2 treatment groups and the "no treatment" group ($t_{SPS} = -8.93$, $p < 0.001$; $t_{Other} = -7.25$, $p < 0.001$). However, logistic regression examining the ability of treatment to predict outcome after controlling for index serum potassium level was nonsignificant: $\chi^2(2, n = 1944) = 1.01$, $p = 0.60$.

DISCUSSION

This study provides a detailed description of the treatment of mild hyperkalemia in a tertiary care hospital. The main finding was that neither SPS nor other treatment strategies predicted the achievement of potassium levels less than 5.1 mmol/L (normokalemia) relative to no treatment. Although neither treatment category had a statistically significant result, certain patient characteristics were found to be statistically significant predictors of the outcome, including pre-index serum potassium level, sex, and the transformed pre-index SCr level. Specifically, the odds of attaining normokalemia within 24 hours declined with higher pre-index serum potassium levels, higher levels of the transformed pre-index SCr, and female sex. Additionally, fewer patients than expected were treated for mild hyperkalemia. Of the 1944 patients included in the analysis, only 22.8% received either SPS or another form of treatment. Whether they received treatment or not, 74.6%

TABLE 2. Stepwise Sequential Binary Logistic Regression Analysis of Potassium (K^+) Reduction, as a Function of Patient Characteristics and Treatment

Variable	*B*	SE	Wald χ^2	Odds Ratio (95% CI)		*p* Value
Block 1						
Pre-index K^+	−0.32	0.16	3.88	0.72	(0.52–0.97)	0.049
Pre-index SCr[a]	−0.83	0.30	7.66	0.43	(0.24–0.78)	0.006
Male sex	0.30	0.12	6.76	1.35	(1.08–1.70)	0.009
Block 2						
SPS treatment[b]	0.13	0.18	0.52	1.14	(0.79–1.64)	0.47
Other treatment[c]	−0.18	0.16	1.25	0.83	(0.61–1.15)	0.26

CI = confidence interval, SCr = serum creatinine, SE = standard error, SPS = sodium polystyrene sulfonate.
[a]Pre-index SCr = transformed pre-index SCr.
[b]SPS compared with no treatment.
[c]Treatment other than SPS alone compared with no treatment.

to 78.8% of hospitalized patients with mild hyperkalemia achieved normokalemia within 24 hours.

Our main finding of no significant difference between treatment and no treatment in the achievement of normokalemia, even after controlling for pre-index serum potassium and SCr levels, does not support previous research, which has found SPS to be effective.[6,20,26,27] However, the previous studies had limitations that our study addresses. For instance, most of the previous studies had small sample sizes and no comparison group (e.g., placebo or no treatment), whereas our study had a large sample size and direct comparison with a group that received no treatment. At the same time, our research supports and extends the work of Lepage and others,[22] who conducted a clinical trial with placebo comparison and, although the sample size was underpowered ($n = 33$), found no statistically significant difference between placebo and SPS in the reduction of serum potassium in patients with CKD. Our study had a much larger sample consisting of a wide range of hospitalized patients with mild hyperkalemia. Our findings also support the conclusions of Batterink and others,[28] who conducted a retrospective review of hospital records for 138 patients. Although their findings indicated a statistically significant difference between no treatment and treatment with SPS, they noted that the treatment effect was small and might not be clinically important.

Nevertheless, it could be argued that differences in index serum potassium levels might account for our finding that treatment was not associated with achievement of normokalemia. In other words, perhaps patients with higher index serum potassium levels were treated and patients with lower index serum potassium levels were not treated, leading to confounding of the results by index serum potassium level. However, follow-up analyses, as described in the Results section, indicated that group differences in index serum potassium did not explain why treatment was not associated with the achievement of normokalemia. Furthermore, by using pre-index serum potassium and SCr levels as statistical controls, this study eliminated variability between groups that might have been due to differences in illness severity.

The finding that women were at greater risk of not achieving normokalemia within 24 hours of the index serum potassium was surprising, given that previous research has found that male sex is a risk factor for hyperkalemia.[12] Overall, in our study, approximately 1 in 5 men (20.9%) and 1 in 4 women (25.4%) did not experience a return to normokalemia. The sex-based rates were similar for the patients who received no treatment, but different for the patients who received SPS or other treatment. Among patients who received SPS, 33.3% of women and 15.7% of men did not achieve normokalemia. Among patients in the "other treatment" group, 15.6% of women and 27.7% of men did not achieve normokalemia. Women in our study differed from men in other respects as well. For instance, women were older than men (average age 69.6 and 65.5 years, respectively). The age difference was most prominent for the SPS treatment group (71.9 and 67.4 years, respectively). In addition, the median transformed pre-index SCr was higher for women in the SPS treatment group than the overall median transformed pre-index SCr for the entire study group. Therefore, the finding that women were at higher risk of not achieving normokalemia might have been due to the age or pre-index SCr of the women in our sample and not to sex-related differences. Nonetheless, other researchers have found some evidence that women are at higher risk of hyperkalemia. For instance, Turgutalp and others,[29] in their sample of Turkish patients, found that women were at higher risk of community-acquired hyperkalemia.

Strengths and Limitations

Relative to previous studies of this topic, this study was strengthened by the large sample of hospitalized patients with mild hyperkalemia. The larger sample enhanced our ability to generalize beyond the study sample and reduced the likelihood of type II error. Generalization was also improved by not limiting our sample to select patient populations (e.g., patients with CKD). In addition to including broad patient populations, our research had other pragmatic design features,[30] such as the real-world examination of treatment versus no treatment in the reduction of serum potassium to below 5.1 mmol/L.

Despite the many strengths of this study, its retrospective nature necessitates a discussion of limitations. One limitation of this real-world retrospective study was the lack of control over when blood samples were taken. Any serum potassium level reported within the 24-hour period following the index value was included; therefore, the timing of blood samples varied considerably among study participants. For patients who were given treatment, the follow-up serum potassium level may have been measured before the treatment could have any effect. Furthermore, if follow-up serum potassium was not reported within 24 hours after the index, it was not included in our analysis. Although it is possible that serum potassium decreased beyond the 24-hour time limit, the UK guidelines suggest that 6 hours is adequate time for treatment to be effective,[3] and the average time from treatment to follow-up in the current study was more than 13 hours.

Another limitation of this study was lack of control over the dose of SPS (or other treatments). Variation in dose across the study sample and the use of different doses for the same patient within the 24-hour period of interest were possible, but most patients in the SPS group received the typical dose of 30 g by oral administration, and most patients in the "other treatment" group received insulin alone. In addition, patients might have been receiving medications for other illnesses. For instance, many of the

patients had other illnesses (e.g., diabetes) and could have been receiving medications (e.g., insulin) for these illnesses as well. Although this lack of control over other medications and illnesses is a limitation, it may also be considered a strength of the study, given that it allows for the real-word examination of treatment for mild hyperkalemia.[31]

This study did not examine the effectiveness of administration of fluids or any of the more recent pharmaceutical treatments for hyperkalemia. Research on patiromer sorbitex calcium and sodium zirconium cyclosilicate (also known as ZS-9) has indicated that these medications are effective in managing hyperkalemia.[32] Future research could investigate the administration of fluids and newer pharmaceutical treatments in the management of mild hyperkalemia, although our evidence suggests that pharmaceutical intervention may be unnecessary for most patients with mild hyperkalemia, given that 78% of those with no intervention achieved normokalemia. Investigating unobserved group differences in the trajectory of serum potassium change could also be addressed in future studies. If unobserved groups (i.e., latent classes) are found, variables differentiating the groups could be assessed to help identify patients with mild hyperkalemia who are at risk of further exacerbation or non-normalization of serum potassium levels. Identifying these patients would have important clinical implications and could help identify those patients who are in need of intervention.

CONCLUSION

The findings of this study demonstrated that most patients were not treated for mild hyperkalemia in the 24-hour follow-up period after documentation of hyperkalemia, and there was no statistically significant association between treatment and achievement of normokalemia relative to no treatment, regardless of whether patients were treated with SPS or another hyperkalemia-reducing strategy. In a recent editorial, Parks and Grady remarked that SPS should not be used to reduce serum potassium levels.[30] Our research supports that conclusion, at least for patients with mild hyperkalemia. For these patients, our research suggests that, although follow-up is required, elevated serum potassium levels may resolve within 24 hours without intervention. Thus, for most hospitalized patients, treatment of mild hyperkalemia may be unnecessary.

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Pénuries de médicaments en établissement de santé : une étude qualitative à partir de cas réels pris en charge par les pharmaciens hospitaliers

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INTRODUCTION

En 2019, l'Association des pharmaciens du Canada a noté que « les pénuries de médicaments continuent d'être une source de vive inquiétude qui ne cesse de s'amplifier au sein du système canadien de soins de santé. La gestion des problèmes d'approvisionnement en médicaments est devenue une activité malvenue dans l'exercice quotidien de la profession de pharmacien; elle monopolise du temps et des ressources qui ne peuvent être consacrés à la prestation de soins directs »[1].

Dans une enquête menée en 2018 auprès de 1 500 citoyens canadiens, on a observé qu'un Canadien sur quatre a été touché personnellement par une pénurie de médicaments au cours des trois dernières années ou connaît quelqu'un qui l'a été[2]. Dans une autre enquête menée en 2018 auprès des pharmaciens, on a remarqué que les pénuries de médicaments ont augmenté, voire beaucoup augmenté, au cours des trois à cinq dernières années, d'après 79 % des répondants[3].

Les pénuries de médicaments font partie du quotidien des pharmaciens communautaires et hospitaliers depuis au moins deux décennies[4]. La crise vécue avec Sandoz Canada en 2012 a laissé sa marque et changé les pratiques au sein des établissements de santé[5]. Au fil des années, le nombre d'épisodes de pénurie n'a fait qu'augmenter. Videau et collab. ont mentionné qu'en l'espace de 12 mois, soit du 31 août 2016 au 4 septembre 2017, il y a eu 2 129 ruptures d'approvisionnement de différents médicaments au Canada selon le site web canadien consacré à la déclaration obligatoire des ruptures de fourniture de médicaments par les fabricants. Ces interruptions ont duré en moyenne 118 jours (écart-type 113 jours) et concernaient la plupart des classes thérapeutiques[6]. D'autres études ont confirmé l'importance et la croissance du nombre de pénuries de médicaments au Canada[7,8].

S'il existe plusieurs études permettant d'établir le nombre et la variété des médicaments en pénurie au Canada, il existe peu de travaux mettant en évidence les actions mises en place par les pharmaciens hospitaliers pour limiter les impacts de ces pénuries. Nous nous sommes intéressés à décrire ces actions au sein des établissements de santé d'un groupe d'approvisionnement en commun au Canada.

MÉTHODE

Il s'agit d'une étude descriptive rétrospective.

L'objectif principal est de décrire et de quantifier l'impact de la gestion des pénuries de médicaments en établissement de santé sur la charge de travail et la complexité des actions pharmaceutiques des pharmaciens hospitaliers d'un même groupe d'approvisionnement en commun (GAC).

Au Québec, trois GAC assurent la gestion des ententes contractuelles entre les fabricants de médicaments, les grossistes de médicaments et les établissements de santé. Le chef du département de pharmacie de chaque établissement est responsable d'établir la liste locale des médicaments disponibles et de mandater les quantités annuelles de médicaments requises pour assurer les soins des patients. L'étude cible le chef du département de pharmacie (ou son représentant) des 12 établissements de santé membres de Sigma-santé (GAC représentant la région de Montréal et de Laval). L'étude a été menée en septembre 2019. Les participants ont été avisés que la participation à l'étude était volontaire et que les résultats agrégés seraient publiés. L'étude cible l'exercice financier du 1er avril 2018 au 31 mars 2019.

À partir d'une séance de remue-méninges sur les ruptures d'approvisionnement les plus importantes vécues au cours des dernières années et d'une revue documentaire sur la gestion des pénuries, nous avons déterminé quatorze variables permettant de qualifier l'organisation, la gestion des stocks, les sources de données consultées et les pratiques d'approvisionnement de chaque établissement. De plus, nous avons établi 26 actions pharmaceutiques liées à la gestion des pénuries.

Afin de faciliter la réflexion des pharmaciens, les investigateurs ont retenu dix médicaments injectables (sauf un) ayant été en pénurie en 2018-2019 soit : alcaloïde de la vinca (c.-à-d. vincristine, vinblastine), bleu de méthylène, céfazoline, cisatracurium, corticostéroïdes (c.-à-d. hydrocortisone,

méthylprednisolone, dexaméthasone), dexmédétomidine, érythromycine pommade ophtalmique, leucovorin, chlorure de potassium, succinylcholine. Ces médicaments ont été retenus parce qu'ils représentent diverses classes thérapeutiques et qu'ils ont probablement eu un impact sur la plupart des membres du GAC.

Les membres de l'équipe de recherche (MF, DL, SA, SR, JFB) ont développé un questionnaire sous forme de fichier texte (Word, Microsoft) et l'ont soumis à la discussion. Ce questionnaire suit la chronologie d'une pénurie, de la prise de connaissance de la pénurie jusqu'à son impact ou non sur le patient, ce qui favorise l'évaluation de chaque étape et la détermination de moyens d'atténuation des conséquences à chacune d'elles. Il vise à répertorier et à mettre en évidence l'impact des pénuries sur la charge de travail et sur la complexité des actions pharmaceutiques découlant des pénuries de médicaments. L'équipe de recherche comporte au moins un pharmacien représentant un établissement pour adultes et un établissement pédiatrique. Le questionnaire a été envoyé à chacun des 12 chefs de département de pharmacie des établissements de santé affiliés à Sigmasanté.

Seules des statistiques descriptives ont été effectuées.

RÉSULTATS

Dix pharmaciens d'établissements associés au GAC Sigmasanté ont participé à l'étude (taux de participation de 83 %, 10/12); ils provenaient de centres hospitaliers universitaires (n = 3), d'un institut universitaire (n = 1), de centres intégrés universitaires de santé et de services sociaux (n = 5) ou de centres intégrés de santé et de services sociaux (n = 1).

Les pharmaciens désignés pour répondre au questionnaire s'occupaient de la gestion des pénuries de médicaments depuis moins de cinq ans (3/10) ou plus de cinq ans (7/10). Les répondants, tous titres d'emploi confondus, ont estimé le temps moyen par semaine consacré à la gestion des pénuries de médicaments comme étant inférieur à 6 heures (n = 4), de 6 à 20 heures (n = 5) et de plus de 20 heures (n = 1).

Afin de se tenir au courant des pénuries, les répondants consultent la liste des médicaments en rupture de stocks provenant du grossiste Mckesson Canada (n = 10/10), les listes que fournissent directement les fabricants par courriel (n = 8/10), des communications par courriel provenant du GAC et de collègues (n = 7/10) et le site Pénuries de médicaments Canada (www.penuriesdemedicaments.ca) (n = 5/10).

Les répondants déclarent maintenir un stock de produits pour 10 à 90 jours selon le caractère critique du produit, l'espace et les pratiques.

Les répondants n'ont pas tous été affectés de la même façon par la pénurie des 10 médicaments ciblés dans notre étude : 10 produits (n = 4), neuf produits (n = 1), huit produits (n = 1), sept produits (n = 1), six produits (n = 2) pour un total de 76 épisodes de pénurie commentés par les répondants.

Les répondants disposent d'une politique et procédure encadrant la gestion des pénuries de médicaments (n = 5), discutent en comité des actions à entreprendre (n = 6), effectuent des prêts et des emprunts auprès d'autres établissements de santé (n = 7) ou des pharmacies d'officine (n = 2). Une majorité de répondants (n = 9) achètent le maximum des produits qui leur sont alloués lorsque cela est applicable.

Ces 25 actions envisagées ont été mises en place dans 4 % à 83 % des situations durant les 76 épisodes de pénurie. Un seul épisode de pénurie de médicament a été associé à une déclaration d'incident-accident médicamenteux.

Le tableau 1 présente un profil des actions pharmaceutiques liées à la gestion des pénuries de médicaments en établissement de santé. Comme toutes les pénuries n'ont pas forcément affecté chacun des répondants, compte tenu des stocks disponibles et des patientèles traitées, l'étude met en évidence un total de 76 épisodes de pénurie sur une possibilité de 100 (c.-à-d. 10 médicaments proposés à 10 répondants).

Le tableau 2 présente le profil du degré d'accord des répondants avec les énoncés entourant la gestion des pénuries de médicaments.

DISCUSSION

Cette enquête menée auprès de pharmaciens hospitaliers d'un groupe d'approvisionnement en commun d'une des principales villes canadiennes (Montréal) met en évidence l'impact des pénuries sur la charge de travail et la complexité des actions pharmaceutiques découlant des pénuries de médicaments.

En ce qui concerne la charge de travail, tous les répondants ont indiqué avoir désigné un pharmacien affecté à la gestion des pénuries des médicaments. De plus, sept des dix répondants y travaillent depuis plus de cinq ans et une majorité consacre plus de six heures par semaine à la gestion de ces ruptures de stocks. Shaban et collab. ont sondé des départements de pharmacie des établissements de santé du programme des vétérans américains [9]. Des 17 répondants, près de la moitié des établissements interrogés ont reconnu avoir mis en place un groupe de travail (n = 8) pour gérer les pénuries de médicaments et atténuer leur impact. Claus et collab. ont évalué l'effet des pénuries de médicaments en Belgique et confirmé qu'elles avaient un impact important sur la charge de travail et les coûts d'acquisition[10]. De Weerdt et collab. se sont également intéressés de plus près à la charge de travail des pharmaciens belges exposés à des ruptures d'approvisionnement de médicaments[11]. Les auteurs ont noté que les pharmaciens d'hôpitaux ont consacré une médiane de 109 minutes par semaine aux problèmes d'approvisionnement en médicaments (min. 40; max. 216). Cinquante-neuf pour cent (59 %) du temps total consacré aux problèmes d'approvisionnement en médicaments relevait des pharmaciens d'hôpitaux, 27 % des techniciens en pharmacie ; le reste a été effectué par du personnel logistique ou administratif.

TABLEAU 1. Profil des actions pharmaceutiques liées à la gestion des pénuries de médicaments en établissement de santé

Action pharmaceutique	Nombre (%) des répondants (*n* = 76)	
Envoi d'un avis courriel (note) aux pharmaciens	63	(83)
Envoi d'un avis courriel (note) aux médecins	56	(74)
Consultation des pharmaciens dans les équipes cliniques touchées par la pénurie	52	(68)
Envoi d'un avis courriel (note) aux infirmières	49	(64)
Mise en place d'un changement de pratique auprès des prescripteurs afin de réserver les quantités à certaines indications ou pratiques	37	(49)
Utilisation d'un autre format	37	(49)
Tenue d'une ou de plusieurs réunions avec les cliniciens concernés	37	(49)
Création d'une nouvelle fiche « produit » dans le logiciel d'approvisionnement	26	(34)
Révision des quotas des produits concernés dans le logiciel des cabinets ou des réserves d'étage (min.-max.)	26	(34)
Création d'une nouvelle fiche « produit » dans le logiciel « dossier clinique informatisé »	24	(32)
Révision des quotas des produits concernés dans le logiciel d'approvisionnement (min.-max.)	24	(32)
Utilisation d'une autre molécule	23	(30)
Mise en place d'un changement de pratique auprès des utilisateurs (infirmières) afin de réserver les quantités à certaines indications ou pratiques	22	(29)
Ajout d'une alerte dans le dossier pharmacologique informatisé	20	(26)
Réemballage / manipulation pour servir d'une façon différente (p. ex. préparation en seringues *vs* service en fiole)	18	(24)
Utilisation d'une autre teneur	15	(20)
Création d'une nouvelle fiche « produit » dans le logiciel de gestion des cabinets	13	(17)
Demande d'importation d'un produit de remplacement au Programme d'accès spécial de Santé Canada	12	(16)
Report d'activités cliniques (p. ex. dose omise, activité médicale reportée)	8	(11)
Modification requise à la pompe d'alimentation parentérale	6	(8)
Modification requise aux plateaux de réanimation	4	(5)
Modification requise aux protocoles (p. ex. feuilles d'ordonnances prérédigées)	4	(5)
Modification requise aux plateaux d'anesthésie	3	(4)
Prolongation de la date de péremption de stocks périmés résiduels	3	(4)
Mise en place d'une substitution automatique par un autre produit	3	(4)

TABLEAU 2. Profil du degré d'accord des répondants aux énoncés entourant la gestion des pénuries de médicaments

Énoncé	TA	PA	PD	TD	PR
Les équipes de gestion des départements de pharmacie sont les mieux placées pour planifier les besoins en médicaments et tous les médicaments jugés importants pour la pratique devraient être stockés pour 90 jours ou plus en inventaire de l'établissement	8	2	0	0	0
Il est essentiel de préserver le rôle et le pouvoir d'achat des groupes d'approvisionnement en commun au Québec pour assurer la sécurité des stocks de médicaments en établissement de santé	10	0	0	0	0
La baisse forcée des prix des médicaments génériques n'est pas étrangère à la réduction des marges d'inventaire des fabricants de médicaments génériques au Canada	5	4	0	0	1

TA = totalement en accord, PA = partiellement en accord, PD = partiellement en désaccord, TD = totalement en désaccord, PR = pas de réponse.

Environ un tiers du temps total a été consacré à la collecte d'informations sur le problème d'approvisionnement. Deux enquêtes menées auprès de pharmaciens hospitaliers européens ont également confirmé l'impact des pénuries sur la charge de travail des pharmaciens[12,13].

En ce qui concerne la complexité des actions pharmaceutiques mises en place, notre étude met en évidence un total de 25 actions pharmaceutiques potentielles, appliquées dans une proportion variant entre 4 % et 83 % selon les dix médicaments ciblés dans notre enquête. Une partie importante de ces actions n'est pas visible à l'extérieur du département de pharmacie. Dans de nombreux cas, le patient ne souffre pas du manque de médicament, grâce au pharmacien désigné qui entreprend de nombreuses actions pour trouver des stratégies permettant d'utiliser des quantités résiduelles du médicament en pénurie sur le marché. Dans 49 % des cas, les répondants ont dû demander aux prescripteurs un changement de pratique afin de réserver les quantités nécessaires à certaines indications ou de modifier leur approvisionnement (p. ex. changement de format [49 %], changement de molécule [30 %], changement de teneur [20 %]). Bien que certains de ces changements semblent banals, ils accroissent tous le risque d'incidents et d'accidents. De plus, chaque changement affecte des dizaines de personnes de titres d'emplois différents (p. ex. pharmaciens, assistants techniques en pharmacie, médecins, infirmières, infirmières auxiliaires) qui travaillent dans plusieurs quarts de travail ; il faut souvent de deux à quatre semaines pour réussir à joindre tous les intervenants concernés. Dans un établissement de santé, des milliers de gestes cliniques sont posés chaque jour et de nombreux changements de pratique liés à la gestion des pénuries de médicaments augmentent les risques d'erreurs médicamenteuses.

Des 25 actions déterminées, cinq sont effectuées dans au moins 45 % des cas ciblés, soit l'envoi de courriels aux pharmaciens, aux médecins et aux infirmières, souvent précédé d'une consultation des pharmaciens dans les équipes cliniques touchées et de la tenue d'une ou de plusieurs réunions avec les cliniciens concernés. En termes de charge de travail et de complexité, la difficulté ne réside pas dans la rédaction de courriels, mais bien dans la détermination de toutes les actions requises, leur coordination et leur implantation. Plusieurs actions décrites semblent à priori uniquement techniques (p. ex. création de nouvelles fiches de produits dans un logiciel, révision de quotas, ajout d'une alerte dans un logiciel, modification d'un processus de préparation par pompe). Dans un département de pharmacie, de nombreux logiciels sont utilisés pour la gestion des approvisionnements, pour le dossier clinique informatisé, pour le fonctionnement de différents automates, pour les armoires automatisées, etc. Chaque modification faite à la réserve des produits se répercute dans plusieurs systèmes. Un seul changement de produit peut nécessiter des heures de travail. Certains médicaments sont plus dangereux à manipuler que d'autres et si tous ces changements sont mal communiqués au personnel, ils peuvent entraîner des risques pour les patients. Il est souvent difficile de joindre tous les membres des équipes par un simple courriel. Dans certains cas ciblés, il faut augmenter le nombre de rencontres et de réunions pour mieux diffuser l'information au sujet de la rupture de stocks et des mesures prises pour en réduire les effets néfastes.

Fait rassurant, les dix pénuries ciblées dans notre enquête ont mené à un report d'activités cliniques chez 11 % des répondants et un seul événement indésirable a été noté au cours de l'année de l'étude. Bien que ces données soient basées sur la mémoire des répondants, toutes les actions concertées menées par les pharmaciens hospitaliers ont porté des fruits, et les conséquences de ces pénuries sont négligeables pour les patients traités dans ces établissements de santé.

Enfin, les répondants étaient invités à faire part de leur degré d'accord à trois énoncés entourant la gestion des pénuries de médicaments. Tous s'accordent pour dire que les équipes de gestion des départements de pharmacie sont les mieux placées pour planifier les besoins en médicaments et tous les médicaments jugés importants pour la pratique devraient être stockés pour au moins 90 jours dans les réserves de l'établissement. Ceci contrevient aux pratiques financières et de gestion, qui visent une réserve minimale et un roulement des stocks élevé. Dans l'enquête canadienne sur la pharmacie hospitalière de 2016-2017, le taux moyen de roulement des stocks de médicaments est de 9,7 à l'échelle du Canada et de 11,2 au Québec[14]. En favorisant des stocks de médicaments pour une période d'au moins 90 jours, le taux de roulement devra diminuer de façon significative et des espaces supplémentaires devront être consentis aux départements de pharmacie. De plus, les répondants notent qu'il est essentiel de préserver le rôle et le pouvoir d'achat des groupes d'approvisionnement en commun au Québec pour assurer la sécurité des stocks de médicaments en établissement de santé. Les ententes de partenariat négociées par l'Alliance pharmaceutique pancanadienne sont signées par les autorités provinciales et ceci contribue à fragmenter le pouvoir de négociation et le rapport de forces des GAC. Tous les répondants considèrent que le rôle et le pouvoir d'achat des GAC sont des éléments cruciaux pour la gestion des pénuries de médicaments. Enfin, neuf répondants sur dix considèrent que la baisse forcée des prix des médicaments génériques n'est pas étrangère à la réduction des marges des stocks des fabricants de médicaments génériques au Canada. Les pharmaciens hospitaliers peuvent stocker davantage de produits, pour autant que ces médicaments demeurent disponibles sur le marché canadien. Une réflexion politique devrait s'engager sur les conditions permettant de préserver une disponibilité suffisante de médicaments sur le territoire canadien.

Cette étude comporte des limites. L'étude ne cible qu'un GAC ; ce serait peut-être intéressant de répéter l'étude à plus grande échelle au Canada. Toutefois, les pénuries de médicaments sont le plus souvent nationales et non locales. Il est toutefois possible que les pratiques de gestion varient d'une

région à l'autre. L'étude ne cible que dix médicaments. Étant donné les centaines de produits en pénurie chaque année, il est possible que les actions à entreprendre diffèrent selon la sélection des produits utilisés pour une telle enquête. En outre, les répondants ont été invités à décrire et à quantifier les actions effectuées au cours de la dernière année. Un biais de mémoire est possible, bien que les données des répondants convergent.

CONCLUSION

Cette étude descriptive présente une analyse qualitative originale de la gestion des pénuries des médicaments et des actions mises en place en établissement de santé. L'étude met en évidence la variété et la complexité des actions requises pour assurer une prestation sécuritaire de soins. Les pénuries ont un impact sérieux sur le travail des pharmaciens hospitaliers et 25 actions pharmaceutiques peuvent être envisagées afin de limiter les conséquences des pénuries de médicaments.

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Optimizing Pharmacy Learner Rotations to Improve Clinical Productivity: A Study to Assess 3 Pharmacy Layered Learning Practice Models in an Inpatient Tertiary Care Oncology Unit

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INTRODUCTION

The provision of quality experiential learning is an imperative component of pharmacy education.[1] However, some academic pharmacy programs and institutional pharmacy departments may find the growing demand for experiential education rotations difficult to accommodate.[2] The layered learning practice model (LLPM) is a practice structure that can facilitate the accommodation and incorporation of more learners into a given practice site during academic rotations. Within the pharmacy context, the LLPM structure could emulate that of a common medicine-based teaching and practice environment and would consist of staff pharmacists, pharmacy residents, and pharmacy students.[3]

Within the LLPM, direct patient care activities are delegated to students, both to impart more clinical responsibility and to encourage near-peer learning and development as clinical pharmacists.[4] The pharmacy residents gain supervised opportunities to act as preceptors for junior learners in a safe environment, in addition to providing direct patient care themselves, which encourages their further development as independent practitioners.[5] One or more staff pharmacist preceptors coordinate and facilitate the activities of the group and are responsible for completed interventions and ultimately the care delivered by the pharmacy residents and students.[4] While ensuring that learners meet their educational requirements, the presence of students should not compromise clinical services or productivity.[6] The positive impact of LLPMs involving pharmacy learners has been demonstrated previously. Those earlier studies found improvement in resolution of medication-related problems, patient education, and patient satisfaction scores.[7-9]

Evaluating the clinical productivity of pharmacists using standardized performance indicators is encouraged to yield generalizable and reproducible performance results, which are ultimately used as a basis for clinical service or operational decisions. Using a modified Delphi process, a Canadian working group of pharmacy leaders and hospital pharmacists developed a list of 8 consensus-based clinical pharmacy key performance indicators (cpKPIs) (Table 1), which are supported by the Canadian Society of Hospital Pharmacists (CSHP).[10-13]

Yung and others[14] were the first to assess the impact of an LLPM on clinical productivity through quantification of the CSHP cpKPIs across a spectrum of LLPM scenarios. Their study demonstrated that the structured LLPM, comprising pharmacists, pharmacy residents, and pharmacy students in an inpatient oncology unit, did not impair the delivery of pharmaceutical care relative to standard practice, as measured by the cpKPIs. The study compared the following 3 scenarios: pharmacists alone; pharmacists and pharmacy students; and pharmacists, pharmacy residents, and pharmacy students. The scenarios had comparable total numbers of cpKPIs standardized to 20 pharmacist workdays. Although the total number of cpKPIs was similar across scenarios, there was a trend toward a reduction in discharge medication reconciliation and patient education at discharge when pharmacy learners were present. It was hypothesized that this trend was due to the occurrence of daily afternoon academic debriefing and patient review sessions, which took place at a time when many patients are discharged.

Yung and others[14] showed that it is possible to maintain clinical efficiency while offering pharmacy learner rotations within an LLPM structure. Although maintenance of clinical efficiency is an acceptable outcome, the next logical step is to attempt to improve the clinical capacity of pharmaceutical care delivery by optimizing the structure and performance of activities within the LLPM. The current study aimed to improve the cpKPIs of discharge medication reconciliation and patient education at discharge by involving Doctor of Pharmacy (PharmD) students in the role of medication

TABLE 1. Canadian Consensus Clinical Pharmacy Key Performance Indicators (cpKPIs) and Definitions[a]

cpKPI	Definition
1. Medication reconciliation on admission	Proportion of patients who received documented medication reconciliation on admission (and had resolution of identified discrepancies), performed by a pharmacist
2. Pharmaceutical care plan	Proportion of patients for whom a pharmacist has developed and initiated a pharmaceutical care plan
3. Drug therapy problems (DTPs)	Number of DTPs resolved by a pharmacist per admission
4. Interprofessional patient care rounds	Proportion of patients for whom a pharmacist participated in interprofessional patient care rounds to improve medication management
5. Patient education during hospital stay	Proportion of patients who received education from a pharmacist about their disease(s) and medication(s) during their hospital stay
6. Patient education at discharge	Proportion of patients who received medication education from a pharmacist at discharge
7. Medication reconciliation at discharge	Proportion of patients who received documented medication reconciliation at discharge (and had resolution of identified discrepancies), performed by a pharmacist
8. Bundled patient care interventions	Proportion of patients who received bundled care by a pharmacist as defined by the following criteria: • Medication reconciliation on admission • Pharmaceutical care plan AND/OR resolution of DTPs • Pharmacist's participation in interprofessional patient care rounds • Patient education during hospital stay AND/OR at discharge • Medication reconciliation at discharge

[a]Adapted, with permission of the Canadian cpKPI Collaborative, from *Canadian Consensus on Clinical Pharmacy Key Performance Indicators: Knowledge Mobilization Guide*.[10]

safety facilitators at hospital discharge and assigning them to work with the health team to complete these discharge activities. This role involved performing the steps in the checklist for medication safety at transitions, developed by the Institute for Safe Medication Practices Canada (ISMP Canada).[15]

A principal question that this study aimed to address was how to structure an LLPM to optimize capacity for care delivery, as measured by cpKPIs. Three distinct 8-week LLPM rotations were designed to provide insight into this question. The model was similar to that of the previous study, with pharmacists, residents, and students in various combinations; however, the number of pharmacy students (2, 3, or 4) was varied across 3 intervention groups (termed "blocks"). By modifying the number of students involved, we explored whether there is an optimal number of students within an LLPM that represents a practical balance between the preceptor's time and other workplace responsibilities and the students' clinical contributions to patient care.

This study advances the exploratory research completed by Yung and others[14] to help identify strategies to optimize structured experiential learning and may guide the clinical teaching and role assignment associated with pharmacy-learner rotations. Additionally, the patient care contributions of each pharmacy professional were measured through quantification of completed cpKPI-related activities, which elucidated areas that may require emphasis in the design of future rotations to ensure a balanced clinical experience.

The primary objective of the current study was to determine and compare the percentage of all eligible cpKPI-related activities completed for patients between intervention groups and standard practice. In addition, the study had 4 secondary objectives: to determine the percentage of eligible patients receiving care related to 6 of the cpKPIs and to compare these proportions between intervention groups and standard practice; to compare the number of drug therapy problems (DTPs) resolved per patient between intervention groups and standard practice; to compare the total number of cpKPIs, standardized to 20 pharmacist workdays, between intervention groups and standard practice; and to describe the contributions of each pharmacy professional to pharmaceutical care, as measured by cpKPIs.

METHODS

This retrospective quality assurance study assessed a pharmacy practice intervention that took place over a 6-month period, from March 7 to August 20, 2018, corresponding to 3 planned 8-week PharmD student rotation blocks. The study setting was an inpatient medical oncology unit in The Ottawa Hospital in Ottawa, Ontario. The unit had 35 to 40 dedicated medical oncology beds throughout the study period. At the time of the study, the hospital was using a paper-based charting system. The study was approved by the institution's research ethics board.

Study participants consisted of 2 full-time equivalent (FTE) oncology pharmacists (J.W., S.L.), 3 pharmacy residents (including J.Y.), and 8 PharmD students organized in 3 LLPMs. Each LLPM was composed of the 2 pharmacists, one of the residents, and 2, 3, or 4 students (with one of the students spanning 2 rotations) (Table 2). All of the residents were licensed pharmacists during the period of the study. The 2 pharmacists were experienced residency and pharmacy student preceptors and had previously been involved in LLPM rotations at the same institution.[14] Comparator data were collected from a nonconsecutive 10-week period, including 7 weeks of data previously collected by Yung and others[14] (September 5 to 15, 2017, and January 8 to February 9, 2018) with an extension of 3 weeks (February 12 to March 2, 2018) before the intervention periods. This extension of the comparator period was intended to improve data robustness, with data from the extension being combined with data from the original period using dataset totals. These collective data were representative of the standard practice of the 2 FTE pharmacists without learners present.

The roles and scopes of practice of students, residents, and pharmacists in this study reflected those described previously.[7-9] Learners were incorporated within the oncology practice, providing direct patient care on the unit, and were also given suitable access to office computers and workspaces.

The PharmD students provided longitudinal patient care for 2 to 5 patients at a time. They also alternated in fulfilling the additional responsibility of facilitating patient discharges, whereby the assigned student carried a "discharge pager" and was notified when patients were ready for discharge, at which time patient education and medication reconciliation were to be performed. On their first day before the data collection period, the students underwent a 1-hour training session with their preceptors on the use of the ISMP Canada checklist for medication safety at transitions.[15] Completion of the checklist indicated fulfilment of the cpKPIs for patient education at discharge and medication reconciliation at discharge. If the assigned PharmD student was unavailable at the time of a patient's discharge, a resident or pharmacist would perform these activities.

The residents provided care to 3 to 6 patients at a time while also providing direct instruction to the students, facilitating debriefing sessions, and teaching. The oncology pharmacists carried out the roles of supervisor and teacher. In addition to their distribution and clinical practices, they coordinated the activities of the team, modelled patient care duties for learners, conducted therapeutic discussions, and facilitated debriefing sessions for all learners. All of the learners practised within the scope of their authority and debriefed daily with preceptors to ask questions and review work. All orders placed in the paper-based charts were cosigned by one of the pharmacist preceptors. The pharmacists were responsible for all medication-related outcomes of the patients and participated in direct care activities for patients on the unit who were not assigned to a particular learner.

Recording of cpKPIs

All participating pharmacists, residents, and students underwent training to recognize and record the cpKPIs as defined by the CSHP consensus guidelines.[10] Training consisted of a 1-hour presentation given by one of the study investigators (J.W.) on the first day of each rotation. This presentation was additional to the training described above for the student role of discharge facilitator. The training materials and procedures were similar to the process described by Yung and others.[14] A concise instruction sheet and project manual were provided, which included examples of the DTPs (available as Appendix 2 of the previous article by Yung and others[14]). The data collection period started within the first day after completion of training.

The participants were given stickers that were colour-coded according to their role (student, resident, or pharmacist) and labelled from 1 to 7, representing each of the cpKPIs investigated in this study (Table 3). Labels were attached to daily inpatient rosters adjacent to the patient who received the corresponding cpKPI-related care. The appropriate affixing of cpKPI labels was reviewed and

TABLE 2. Composition of Control and Intervention Groups

	Block No. and Dates[a]; No. of Persons (Duration of Participation)			
Role	Control	Block 1 March 7 to April 27	Block 2 April 30 to June 22	Block 3 June 25 to Aug 20
Pharmacist	Historical data (10 weeks)[b]	*n* = 2 (8 weeks)	*n* = 2 (8 weeks)	*n* = 2 (8 weeks)
Pharmacy resident	NA	*n* = 1 (5 weeks)	*n* = 1 (5 weeks)	*n* = 1 (5 weeks)
PharmD student	NA	*n* = 1 (8 weeks) *n* = 1 (5 weeks)	*n* = 2 (8 weeks) *n* = 1 (4 weeks)	*n* = 3 (8 weeks) *n* = 1 (4 weeks)

NA = not applicable, PharmD = Doctor of Pharmacy.
[a]All dates in calendar year 2018.
[b]Control group data were collected during 10 nonconsecutive weeks, including 7 weeks of data previously reported by Yung and others.[14]

TABLE 3. Additional Requirements for Sticker Documentation for Tracking Clinical Pharmacy Key Performance Indicators (cpKPIs) on Patient Care Rosters

cpKPI Label	Additional Documentation
1. Admission medication reconciliation	• Reviewed the admission medication reconciliation • Identified and resolved discrepancies
2. Pharmaceutical care plan	None
3. Drug therapy problems (DTPs)	Reported 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
4. Interprofessional patient care rounds	• Attended bullet rounds • Attended other rounds
5. Patient education during hospital stay	None
6. Patient education at discharge	None
7. Discharge medication reconciliation	• Reviewed the discharge medication reconciliation • Identified and resolved discrepancies

confirmed daily by the pharmacists, to ensure the accuracy and standardization of coding. For all patients, pharmacists were assumed to have participated in patient care rounds (cpKPI 4), since standard practice on the unit is to attend interprofessional bullet rounds.

Study participants generally worked from 0800 to 1600 on weekdays, and cpKPIs were recorded daily during these working clinical hours. At the study institution, the role of the pharmacist on evening and weekend shifts differs significantly from that of pharmacists working the daytime clinical shift; therefore, no study interventions were recorded in the evenings, on weekends, or on provincial holidays.

Data Analysis

Patient lists were collected and stored in a secure area in the pharmacy at the end of each week. The data were transcribed from patient rosters into a deidentified, password-protected quality assurance database (Excel version 1808, Microsoft Corporation) by one of the authors (L.S.).

The data collected were used to calculate the percentage of eligible cpKPI-related activities that were completed for patients in each of the 3 intervention periods (primary objective). To account for patients admitted across multiple study blocks, patients were considered ineligible for cpKPIs previously documented, with the exception of DTPs identified and resolved. Patients who died were not discharged and therefore were not considered eligible for assessment of education at discharge or medication reconciliation at discharge. Mean percentages were compared between intervention and control groups using χ^2 statistical tests. The Student *t* test was used to compare the number of DTPs resolved per patient. Overall productivity was assessed using total cpKPIs completed by a given group, standardized to 20 pharmacist workdays. Standardization helps to adjust for any practical differences in staffing or vacations that occurred across the 6-month study period, and 20 days was selected to represent approximately 1 month of pharmacist time. Total cpKPIs represent an absolute value and were used to account for unequal distribution of patient load between groups; these data are reported descriptively as well.

RESULTS

The results of this study were synthesized using data from 666 patient admissions over three 8-week intervention blocks between March 7 and August 20, 2018. Patient admission characteristics of the intervention groups can be found in Table 4. The total proportions of eligible cpKPIs completed for the standard practice (control) group and the 2-, 3-, and 4-student blocks were 47%, 41%, 50%, and 52%, respectively (Table 5). The total proportion of patients receiving eligible cpKPI-related care with the 2-student model (block 1) was significantly lower than with the control group (absolute difference 6%, 95% confidence interval [CI] −9.3 to −2.7; $p < 0.001$), suggesting reduced productivity with this LLPM relative to standard practice. In contrast, the total proportion of patients receiving eligible cpKPI-related care with the 4-student model (block 3) was significantly higher than with the control group (absolute difference 5%, 95% CI 1.8 to 8.2; $p = 0.002$), indicating higher productivity with this model relative to pharmacists working alone. There was no significant difference between the 3-student model and standard

TABLE 4. Baseline Characteristics of Patient Admissions during Study Blocks

Characteristic	Block 1	Block 2	Block 3
Duration of block (d) [no. of workdays][a]	51 [74]	53 [67]	56 [65]
No. of admissions	205	223	238
Patient age (years) (mean ± SD)	63.0 ± 13.4	63.5 ± 14.0	63.0 ± 15.0
Length of stay (days) (mean ± SD)	16.2 ± 20.3	13.8 ± 18.3	12.1 ± 14.3

SD = standard deviation.
[a]The number of workdays refers to the number of days worked by pharmacists during the period of the block. This number takes into account the Monday-to-Friday work week of the 2 full-time pharmacists.

TABLE 5. Total Proportions of Eligible Clinical Pharmacy Key Performance Indicators Completed for Patients in Each Block, Relative to Standard Practice (Control)

Study Block	Total Proportion Completed (%)	Absolute % Difference (95% CI)		*p* Value
Control	47	NA		NA
Block 1 (2 students)	41	−6	(−9.3 to −2.7)	< 0.001
Block 2 (3 students)	50	3	(−0.2 to 6.2)	0.07
Block 3 (4 students)	52	5	(1.8 to 8.2)	0.002

CI = confidence interval, NA = not applicable.

practice, although there was a trend toward higher productivity (absolute difference 3%, 95% CI −0.2 to 6.2; $p = 0.07$).

The results for proportions of patients in each block receiving each type of cpKPI-related care (compared with standard practice) are presented in Table 6 and depicted in Figure 1. Significantly higher proportions of patients received a pharmaceutical care plan and education during their admission with the 4-student model (block 3) than with standard practice. The absolute differences were 16% (95% CI 8 to 24; $p < 0.001$) and 20% (95% CI 12 to 27; $p < 0.001$), respectively.

The results for education at discharge and discharge medication reconciliation were more variable (Table 6). A significantly higher proportion of patients received education at discharge with the 3-student model (block 2; absolute difference 9%, 95% CI 2 to 17; $p = 0.016$), and there was a trend toward higher productivity with the 4-student model (block 3). Significantly smaller proportions of eligible patients received medication reconciliation at discharge with the 2- and 4-student models (blocks 1 and 3, respectively), with no difference observed with the 3-student model (block 2).

The average number of DTPs resolved per eligible patient were calculated and compared between intervention and control groups (Table 7). There was a statistically significant reduction in mean DTPs resolved per patient with the

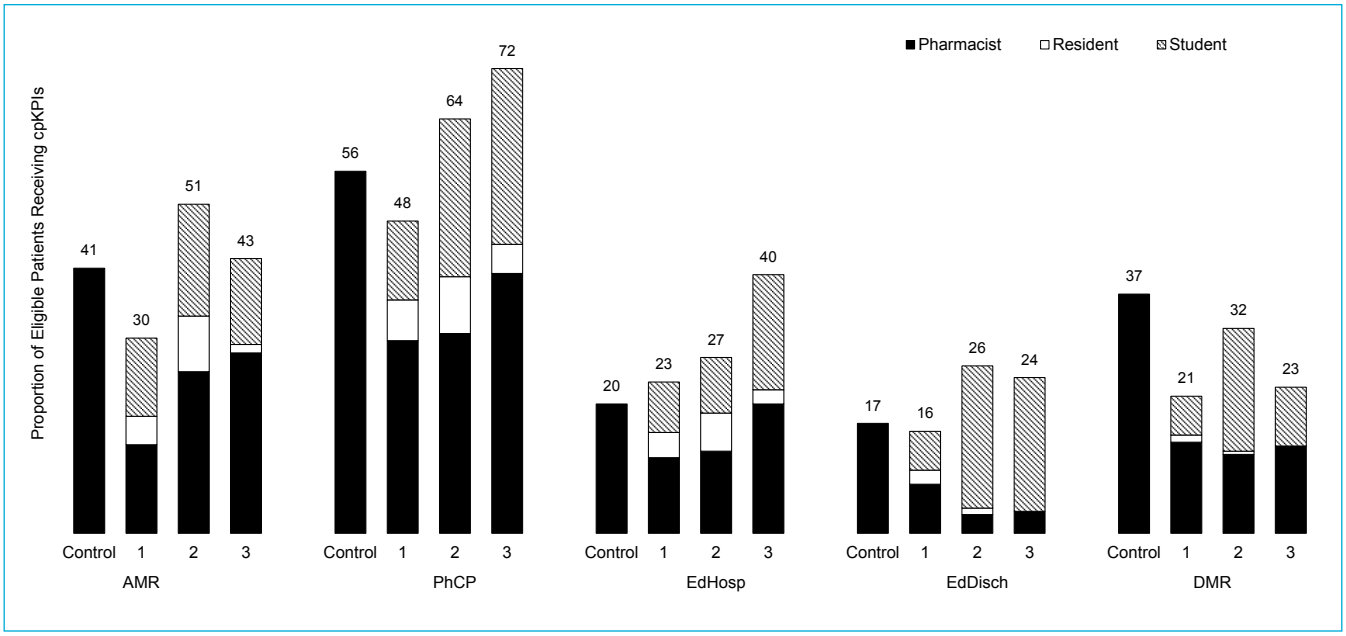

FIGURE 1. Proportion of eligible patients receiving care associated with clinical pharmacy key performance indicators (cpKPIs) for each intervention group (block) and standard practice (control), by type of cpKPI. The numbers 1, 2, and 3 designate blocks 1, 2, and 3, respectively, where blocks were distinguished by the number of PharmD students. AMR = admission medication reconciliation, DMR = discharge medication reconciliation, EdDisch = patient education at discharge, EdHosp = patient education during hospital stay, PhCP = pharmaceutical care plan.

TABLE 6. Proportions of Eligible cpKPIs Completed for Patients in Each Block, Relative to Standard Practice

	Block No.; % Difference[a] (95% CI)		
cpKPI	**Block 1**	**Block 2**	**Block 3**
1. Admission medication reconciliation	–11 (–19 to –3) $p = 0.01$	10 (6 to 23) $p < 0.001$	1 (–7 to 9) $p = 0.81$
2. Pharmaceutical care plan	–8 (–17 to 1) $p = 0.073$	8 (–1 to 16) $p = 0.064$	16 (8 to 24) $p < 0.001$
3. Drug therapy problems	–8 (–16 to 1) $p = 0.066$	–6 (–14 to 2) $p = 0.16$	–2 (–10 to 6) $p = 0.63$
5. Patient education during hospital stay	3 (–4 to 10) $p = 0.4$	7 (0 to 14) $p = 0.05$	20 (12 to 27) $p < 0.001$
6. Patient education at discharge	–1 (–8 to 6) $p = 0.78$	9 (2 to 17) $p = 0.016$	7 (0 to 14) $p = 0.057$
7. Discharge medication reconciliation	–16 (–24 to –8) $p < 0.001$	–5 (–13 to 4) $p = 0.26$	–14 (–22 to –6) $p = 0.001$

CI = confidence interval, cpKPI = clinical pharmacy key performance indicator.
[a]Percent difference was calculated as intervention group minus standard practice (control).

2-student model (block 1) relative to standard practice (mean difference –0.4, 95% CI –1 to 0; $p = 0.048$). However, there was a successive increase in the number of DTPs resolved for the 3- and 4-student models (blocks 2 and 3). This trend can also be seen in Figure 2, which depicts the number of DTPs resolved, standardized to 20 pharmacist workdays.

The absolute total numbers of activities associated with cpKPIs 1, 2, 5, 6, and 7, standardized to 20 pharmacist workdays, for standard practice and blocks 1, 2, and 3 were 93, 75, 117, and 135, respectively (Figure 3). The pattern for these results was similar to that for number of DTPs resolved, with a reduction in productivity with the 2-student model (block 1) and a subsequent trend toward increasing productivity when more learners were present (blocks 2 and 3).

Overall contributions by pharmacy students, pharmacy residents, and clinical pharmacists are visually depicted in Figure 3. Overall, the pharmacists' productivity was reduced when learners were present relative to working alone, which is representative of the shared workload between pharmacists and learners and the increase in pharmacists' time spent performing preceptor activities.

TABLE 7. Number of DTPs Resolved per Eligible Patient in Each Block, Relative to Standard Practice (Control)

Study Block	No. of DTPs Resolved (Mean ± SD)	Mean Difference (95% CI)	*p* Value
Control	1.9 ± 3.0	NA	NA
Block 1 (2 students)	1.4 ± 2.4	–0.4 (–1 to 0)	0.048
Block 2 (3 students)	1.9 ± 3.9	0 (–0.6 to 0.6)	> 0.99
Block 3 (4 students)	2.0 ± 3.5	0.08 (–0.4 to 0.6)	0.7

CI = confidence interval, DTP = drug therapy problem, NA = not applicable, SD = standard deviation.

DISCUSSION

The involvement of more pharmacy students in a structured LLPM appeared to improve clinical productivity as measured by cpKPIs. The absolute differences between proportions of eligible patients receiving cpKPI-related care suggest that overall clinical productivity was reduced with the 2-student model but improved with the 4-student model.

These findings are also reflected in cpKPIs measured in terms of absolute numbers standardized to 20 pharmacist workdays. Using these standardized absolute numbers allows assessment of clinical productivity, regardless of the volume of patient admissions. Because more eligible patients would result in a smaller calculated proportion, the results for the 3- and 4-student models would be conservative, as patient admissions were higher during these blocks (Table 4).

Two cpKPIs with significant improvements in the 4-student model relative to standard practice were provision of pharmaceutical care plans and provision of education during the hospital stay. Both activities are typically emphasized in pharmacy school and are high-yield learning opportunities for students, which may explain the positive correlation with the higher student models.

In addition to the theory that the presence of more students results in higher productivity, a possible confounder could be the clinical experience gained by learners as they progressed through rotations before entering the study. This

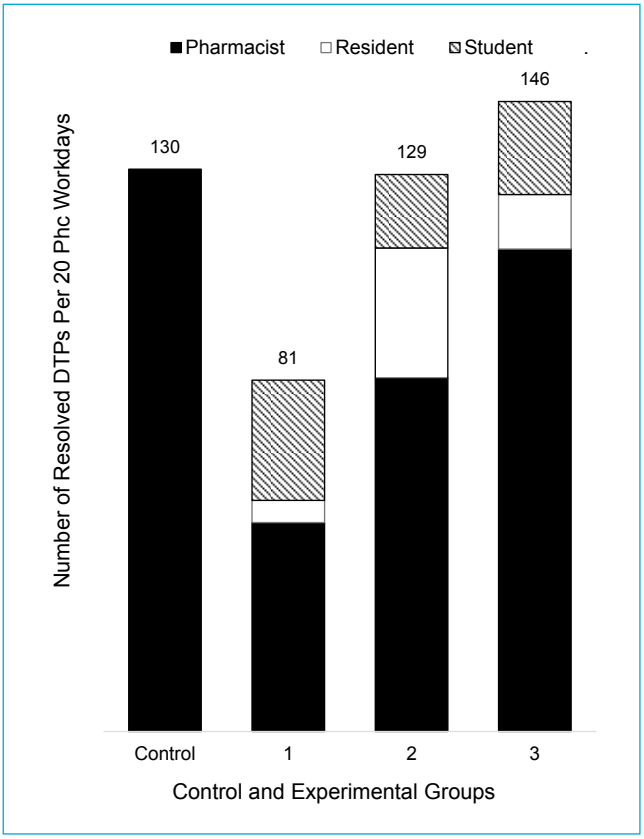

FIGURE 2. Total number of resolved drug-therapy problems (DTPs), standardized to 20 pharmacist (Phc) workdays, for each intervention group (block) and standard practice (control). The numbers 1, 2, and 3 designate blocks 1, 2, and 3, respectively, where blocks were distinguished by the number of PharmD students.

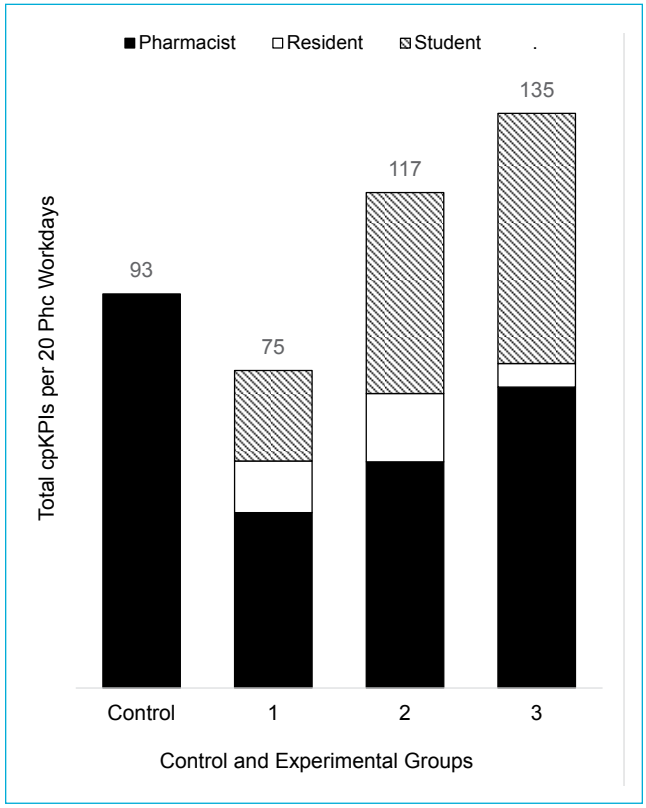

FIGURE 3. Total number of clinical pharmacy key performance indicators (cpKPIs), standardized to 20 pharmacist (Phc) workdays, for each intervention group (block) and standard practice (control). The numbers 1, 2, and 3 designate blocks 1, 2, and 3, respectively, where blocks were distinguished by the number of PharmD students.

study also did not account for individual differences in student skill level or previous clinical or rotational experiences. Clinical efficiencies may also be gained through increased familiarity, experience, and comfort with the LLPM on the part of the pharmacist preceptors. Although this confounder was not formally accounted for, the pharmacists involved were experienced with the preceptor role within an LLPM and did not drastically modify their practice from one block to another.

The level of contributions by pharmacists while engaged in preceptor activities increased with the number of students, contrary to the popular belief that the presence of more students reduces the clinical productivity of pharmacists. One reason may be increased peer-learning time, as learners may initially be more likely to bring issues to each other than to the pharmacists. No trends in the contributions of residents were observed, as each LLPM involved only a single resident. Individual clinical proficiency and ability to manage first-time preceptor responsibilities may have resulted in highly variable data.

Yung and others[14] found that the provision of discharge education and discharge medication reconciliation declined when learners were present, most likely due to the timing of afternoon debriefing sessions. The role of medication safety facilitator at discharge was created to mitigate this reduction and to improve pharmacy-based care at discharge. The results indicated a trend toward an increase in the provision of education at discharge but a significant reduction in discharge medication reconciliation relative to standard practice. This may reflect the fact that discharge medication reconciliation can be completed remotely, whereas education at discharge requires an in-person meeting with the patient, which can be difficult to coordinate as the patient prepares to leave the hospital. Introduction of the role of medication safety facilitator at discharge presumably facilitated coordination of discharge counselling sessions, in addition to having a pharmacy team member with available time dedicated to the activity, thus improving education at discharge compared with standard practice.

Conducting a proper assessment of trends in discharge-related activities is challenging. Discharges may occur outside of rotation practice hours during the daytime, and such discharges were not recorded in our study. For example, if a higher number of discharges occurred during student

hours during block 3, this LLPM would appear to have more instances of education at discharge and discharge medication reconciliation. The patients who died during their respective admissions were not considered eligible for discharge-related activities and were censored from assessment of the corresponding cpKPIs. However, patients who were transferred to another institution and palliative patients being discharged for end-of-life care were not routinely eligible for discharge activities provided by pharmacy learners, and education at discharge and discharge medication reconciliation outcomes were not routinely censored for these patients.

One limitation of this study was the dependence of data collection on physical recording of cpKPIs. Electronic recording of cpKPIs might increase the accuracy of results. Consequently, a potential confounder could be the improved consistency of cpKPI recording by the 2 FTE pharmacists as the study progressed. In addition, the teaching and mentoring time of pharmacists and residents was not adequately recorded; therefore, any potential differences in preceptor time requirements across the 3 blocks cannot be described. Preceptor time outside of the expected work hours was also not captured, but this was not thought to be significantly different across blocks, and preceptors made an effort to finish daily duties on time. Variations in overlap of learners were not reliably recorded. Additionally, 1 student was present for an extra week in the 2-student model, providing a potential productivity advantage. Although this might have affected the magnitude of effect, a meaningful impact on the results is unlikely.

The findings of this study suggest an increase in cpKPI performance with a greater number of learners. However, it is unknown whether cpKPI-related activities performed by learners are equivalent in quality to those performed by pharmacists. Previous studies have demonstrated that clinical pharmacist activities are associated with outcomes such as reductions in hospital length of stay, mortality, adverse drug reactions, health care costs, and readmissions.[16-18] Learners are under the supervision of a pharmacist and are taught to practise as a fully qualified pharmacist would, which is facilitated by a smaller patient load. One study showed that implementation of a pharmacy LLPM resulted in improved patient satisfaction scores.[9] Pharmacy learners may arguably be more meticulous in their patient care plans, given that their performance is being assessed.

Two important considerations for studies involving experiential learning rotations are the learners' satisfaction with their experience and the quality of their education. In their qualitative study, Bates and others[5] assessed perceptions of learners practising within an LLPM. Residents described development of their time management skills through the balancing of clinical and preceptorship activities, and assessments demonstrated that learning outcomes were met. The students also reported a preference for practising directly under a resident, given the recency of the latter's student experience,[5] a preference that was echoed in a Canadian study evaluating the experience of pharmacy students practising within an LLPM.[19]

Although the current study focused on the impact of an LLPM on clinical productivity, future studies could include participant satisfaction surveys for both learners and preceptors and an evaluation of the learning outcomes achieved, to ensure the delivery of a high-quality educational rotation.

CONCLUSION

Implementation of an LLPM involving pharmacists, a resident, and 3 or 4 pharmacy students on an inpatient oncology unit appeared to improve clinical productivity relative to standard practice, as measured by cpKPIs. Although this study had several limitations, it is the first of its kind, and the results will be valuable in structuring pharmacy experiential learning rotations and will provide a platform for future research.

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Ceftriaxone-Induced Pancreatitis

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INTRODUCTION

Ceftriaxone, a widely used third-generation cephalosporin, has been implicated in causing acute pancreatitis.[1] Risk factors for ceftriaxone-induced acute pancreatitis include biliary stasis, renal failure, and fluid restriction.[2,3] Ceftriaxone-induced acute pancreatitis can be managed conservatively, but in some cases more invasive interventions, such as endoscopic retrograde cholangiopancreatography (ERCP), may be required.[3-7] We describe a 70-year-old man with ceftriaxone-induced acute pancreatitis, which was treated with conservative therapy.

CASE REPORT

A 70-year-old man presented with undocumented fever and cough of several days' duration.* His history was significant for nasopharyngeal carcinoma, which was in remission, adrenal insufficiency, hypothyroidism, and vocal cord paralysis. His home medications consisted of levothyroxine 75 µg daily, omeprazole 20 mg once daily, cholecalciferol 1000 units daily, calcium carbonate 600 mg twice daily, and hydrocortisone orally 15 mg in the morning and 5 mg in the evening.

Upon admission, the patient was afebrile and hypoxic, with blood pressure of 97/65 mm Hg, heart rate of 86/min, and respiratory rate of 22/min. He was underweight, with a body mass index of 18.2 kg/m^2. Laboratory tests on admission revealed white blood cells 15.5 × 10^9/L (normal range 3.6–9.6 × 10^9/L), hemoglobin 132 g/L (normal range 129–169 g/L), and platelets 156 × 10^9/L (normal range 140–380 × 10^9/L. His hepatic profile was normal. He had acute kidney injury secondary to dehydration, with a serum creatinine of 136 µmol/L and creatinine clearance of 30 mL/min.

Radiography and computed tomography (CT) of the chest showed evidence of bilateral infiltration. Community-acquired pneumonia or aspiration pneumonia was diagnosed. The results of respiratory viral screening and culture of sputum and blood were all negative. Antibiotic therapy was started, consisting of ceftriaxone 2 g IV daily for 14 days and azithromycin 500 mg orally once daily for 3 days. In addition, IV fluid therapy, in the form of sodium chloride 0.9%, was started at a rate of 100 mL/h. The patient's home medications were continued at the same doses, with the exception of hydrocortisone, for which the dose was doubled because of the infection.

On day 14 of the admission, the patient reported sudden onset of dyspepsia, nausea, vomiting, epigastric pain, and fever. He denied dysuria, change in the colour of urine or stools, or change in bowel habits. On examination, he was thin with a nontoxic appearance; he was afebrile and tachycardic, with blood pressure of 110/61 mm Hg. His abdomen was tender all over, most notable in the epigastric area, but otherwise soft and lax, with no organomegaly. There were no signs of jaundice, and the findings for other aspects of the physical examination were unremarkable.

The patient's past medical history was negative for liver disease and hemolysis. Additionally, there was no family or personal history of gallstones, and the patient denied any history of alcohol consumption or smoking. The patient had never undergone ERCP, nor was there recent surgical history that might have pointed to the cause of pancreatitis. The laboratory results showed a significant increase in transaminases (aminotransferases), amylase, and lipase levels, relative to values on day 1 of the admission (Table 1).

Ultrasonography of the abdomen revealed mild thickening of the gallbladder wall, with no hyperemia, pericholecystic fluid, or gallstones. The patient was treated conservatively, with IV fluids in the form of sodium chloride 0.9%; in addition, the ceftriaxone was discontinued. Within 48 hours (day 16 of the admission), serum lipase levels and hepatic function improved significantly, with rapid resolution of his symptoms.

A diagnosis of ceftriaxone-induced acute biliary pancreatitis was made. Elevation of liver enzymes in the setting of acute pancreatitis was suggestive of ceftriaxone-associated biliary pseudolithiasis. We could not find any other factors that might have explained the acute pancreatitis. The Naranjo probability scale[8] indicated a probable relationship (Naranjo score of 7) between the ceftriaxone therapy and the adverse effect of acute pancreatitis in this patient. The patient recovered and was discharged in a stable condition.

*The patient provided consent for publication of this report.

TABLE 1. Laboratory Data during Hospital Admission

Laboratory Value	Normal Range	Day 1	Day 14	Day 16
Renal profile				
Creatinine (μmol/L)	64–115	136	86	81
Urea (mmol/L)	2.5–7.5	9.6	5.5	5.7
Hepatic profile and enzymes				
Alanine aminotransferase (U/L)	10–45	10	285.7	131
Aspartate aminotransferase (U/L)	10–45	20.1	211.1	48.8
Alkaline phosphatase (U/L)	50–116	84	246	174
Amylase (U/L)	30–110	–	3250	–
Lipase (U/L)	0–60	–	1644	67
Triglycerides (mmol/L)	< 1.7	–	1.05	0.77

DISCUSSION

Acute pancreatitis is an acute inflammatory condition of the pancreas. Gallstones and alcohol are the most common causes, accounting for the majority of cases in adult patients.[9] Medications have also been recognized as a possible cause.[10] Reports of drug-induced acute pancreatitis range from 0.1% to 2% of overall cases.[10-12] There is no specific test for establishing a diagnosis of drug-induced acute pancreatitis; instead, the diagnosis is often based on exclusion of all other common causes of acute pancreatitis.

Globally, few cases of ceftriaxone-associated pancreatitis have been reported.[1,4-7,13,14] Ceftriaxone is primarily excreted through the kidneys, and 10% to 20% of the drug is excreted in the bile.[13] Precipitation of ceftriaxone in the bile causes the formation of biliary sludge, leading to the development of cholangitis, cholecystitis, or acute pancreatitis.[13] Ceftriaxone harbours high calcium-binding affinity, and the solubility of the calcium–ceftriaxone complex is low; as such, the bound substance tends to be retained in the bile.[12] Ceftriaxone forms a precipitate after excretion and concentration in bile in the gallbladder, the major constituent of which is a calcium–ceftriaxone salt.[4]

Pseudolithiasis is a term used for imaging abnormalities observed in the gallbladder or common bile duct in patients treated with ceftriaxone, to differentiate these ceftriaxone-induced reversible abnormalities from those related to truly operable stones.[1] It is difficult to differentiate ceftriaxone-associated sludge from the usual gallbladder sludge on ultrasonographic or CT images, and the pseudolithiasis can rapidly disappear after discontinuation of ceftriaxone.[4] Long-term IV administration of high-dose ceftriaxone has been associated with the transient formation of biliary sludge, which is usually reversible upon discontinuation of the drug.[1]

Review of the existing case reports of ceftriaxone-induced acute pancreatitis revealed that it can occur in both men and women of any age. The duration of treatment with ceftriaxone in these cases varied from 2 days to several weeks, with typical adult doses of 2 to 4 g/day. Management of ceftriaxone-induced acute pancreatitis was variable and included conservative treatment, ERCP, or cholecystectomy.[1,4-7,13,14] Risk factors for acute pancreatitis associated with ceftriaxone include poor oral intake, hypoalbuminemia, and renal impairment, which can increase the incidence of pseudolithiasis. This is because about 90% of ceftriaxone is bound to serum albumin and about 55% of the drug is excreted by the kidney.[2,3] In the case reported here, the patient's poor oral intake and renal impairment put him at risk of acute pancreatitis. Renal dysfunction has been identified as an independent risk factor for ceftriaxone-associated acute pancreatitis in adults.[15] When ceftriaxone is administered to patients who have renal insufficiency or are receiving dialysis, it may be necessary to adjust the dosage because high concentrations of ceftriaxone in the blood and bile may cause biliary pseudolithiasis.[16] Additionally, macrolides have been associated with acute pancreatitis. Most reports have identified erythromycin as a leading cause, but other macrolides, such as roxitromycin and clarithromycin, have also been associated with acute pancreatitis.[16] The mechanism by which erythromycin can cause this adverse effect may be its prokinetic activity, which can lead to spasm of the sphincter of Oddi. The fact that our patient was being treated with azithromycin may have increased his risk of acute pancreatitis.

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Nécrolyse épidermique toxique due à l'ipilimumab et au nivolumab chez une patiente souffrant d'un mélanome métastatique

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INTRODUCTION

Depuis quelques années, l'immunothérapie est utilisée dans le traitement antinéoplasique et son efficacité se démontre pour un nombre grandissant d'indications. Un de ses effets est dû à la stimulation du système immunitaire par l'inhibition des points de contrôle, ce qui permet l'activation des lymphocytes T afin qu'ils exercent leur effet cytotoxique sur les cellules tumorales[1]. Cette stimulation du système immunitaire est toutefois associée à de possibles réactions indésirables à médiation immunitaire et à un risque de réactivation de maladies auto-immunes[1,2]. Le cas présenté dans cet article décrit une réaction rapide de nécrolyse épidermique toxique (NET) associée à la prise d'ipilimumab (anti-CTLA4) et de nivolumab (anti-PD1) par une patiente souffrant d'un mélanome métastatique.

DESCRIPTION DU CAS

Il s'agit d'une femme de 58 ans, pesant 90 kg, mesurant 158 cm et sans allergie médicamenteuse connue.* Elle souffre d'hypertension artérielle, de diabète de type II et d'hypothyroïdie. Elle a reçu un nouveau diagnostic de mélanome métastatique avec une mutation V600E sur le gène *BRAF*. Trois métastases cérébrales ont initialement causé deux épisodes convulsifs, ce pourquoi elle s'est vu prescrire du lévétiracétam. La patiente préférant la double immunothérapie à une simple immunothérapie ou à une thérapie anti-BRAF, elle entreprend un premier traitement constitué de quatre doses d'ipilumumab à raison de 3 mg/kg et de nivolumab à raison de 1 mg/kg toutes les trois semaines. Elle reçoit son premier cycle au jour 0 (J0).

*Le consentement écrit de la famille de la patiente a été obtenu pour publier ce rapport de cas et les images qui lui sont associées, conformément aux exigences du comité d'éthique de la recherche de l'établissement concerné.

Au J6, elle se présente à l'urgence pour une éruption cutanée qui progresse rapidement, apparue dans son dos au J3. Au J5, elle présente un épisode de lipothymie sans conséquence significative. À l'évaluation initiale, les lésions maculopapulaires érythémateuses s'étendent sur plus de 30 % de la surface corporelle (SC). La patiente reçoit un traitement de prednisone dosé à 90 mg (1 mg/kg/jour), de diprosone topique à appliquer deux fois par jour et de 50 mg de diphenhydramine intraveineux toutes les six heures au besoin. Elle a une créatinine sérique de base de 60 µmol/L, mais elle présente une insuffisance rénale aiguë avec une créatinine sérique de 108 µmol/L au J6, résolue par un soluté de réhydratation. Au J7, on note une augmentation légère de l'alanine aminotransférase (ALT) à 43 UI/L (valeur normale : 0–37 UI/L) comparativement à 22 UI/L une semaine avant l'immunothérapie. Ses autres résultats de laboratoire sont normaux. Une histoire médicamenteuse a été réalisée à l'arrivée de la patiente (tableau 1). Du J8 au J10, la réaction cutanée progresse jusqu'à atteindre 65 à 70 % de sa SC et des phlyctènes apparaissent sur 20 % de celle-ci. Le signe de Nikolsky est positif et les trois muqueuses sont atteintes. Son score de Scorten est estimé à 4/10 et est associé à 58 % de risque de décès[3]. Un dermatologue confirme la suspicion d'un syndrome de Stevens-Johnson (SSJ) évoluant vers une NET. Au J10, trois biopsies ont été réalisées et des photos de la réaction ont été prises (figure 1). Au J11, l'éruption cutanée couvre 90 % de la SC et les phlyctènes, plus de 20 %. Puisque la réaction progresse rapidement, la patiente est transférée à l'unité des grands brûlés d'un centre hospitalier tertiaire, où elle reçoit des soins de plaie adaptés et de la prednisone à raison de 2 mg/kg/jour. Elle n'a pas reçu de cyclosporine, d'etanercept ni d'immunoglobulines. Lors de ce séjour, les lésions cutanées évoluent en cellulite multigermes traitée avec du meropenem pendant 11 jours.

Après une évolution favorable des lésions, au J32, la patiente est à nouveau transférée à son hôpital

TABLEAU 1. Histoire médicamenteuse à l'admission

Médicament	Posologie	Date
Médication au jour 0[a]		Date de début de la médicament
Nivolumab	1 mg/kg intraveineux tous les 21 jours pour 4 doses, puis 3 mg/kg tous les 14 jours pour une durée indéterminée	Jour 0
Ipilimumab	3 mg/kg intraveineux tous les 21 jours pour 4 doses	Jour 0
Dexlansoprazole	60 mg une fois par jour	Jour –77
Tramadol / acétaminophène	37,5 / 325 mg 1 comprimé toutes les 6 heures au besoin Prise réelle : au besoin	Jour –77
Amlodipine	10 mg une fois par jour	Jour –14
Calcium / vitamine D	500 mg / 400 UI deux fois par jour	Plus de 2 mois
Lévétiracétam	500 mg deux fois par jour	Jour –112
Lévothyroxine	0,05 mg une fois par jour	Jour –112
Metformine	1000 mg deux fois par jour	Jour –126
Saxagliptine	5 mg une fois par jour	Jour –126
Insuline NPH[b]	20 unités le matin et 12 unités au coucher	Jour –112
Insuline lispro	10 unités le matin, le midi et au souper	Jour –112
Lorazépam	0,5 mg une fois par jour au besoin en cas d'insomnie Prise réelle : au besoin	Jour –112
Crème hydratante	Application sur la corne et la peau sèche des pieds et des mains deux fois par jour au besoin Prise réelle : au besoin	Jour –112
Changements récents de la médication		Date de fin de la médicament
Périndopril	4 mg une fois par jour	Jour –14
Labétalol	100 mg deux fois par jour	Jour –42
NaCl	1 g trois fois par jour	Jour –42
Dexaméthasone	3 mg deux fois par jour	Jour –14
Triméthoprime-sulfaméthoxazole	160 / 800 mg trois fois par semaine	Jour –14

[a]Jour 0 = premier cycle de la double immunothérapie.
[b]Neutral protamine Hagedorn.

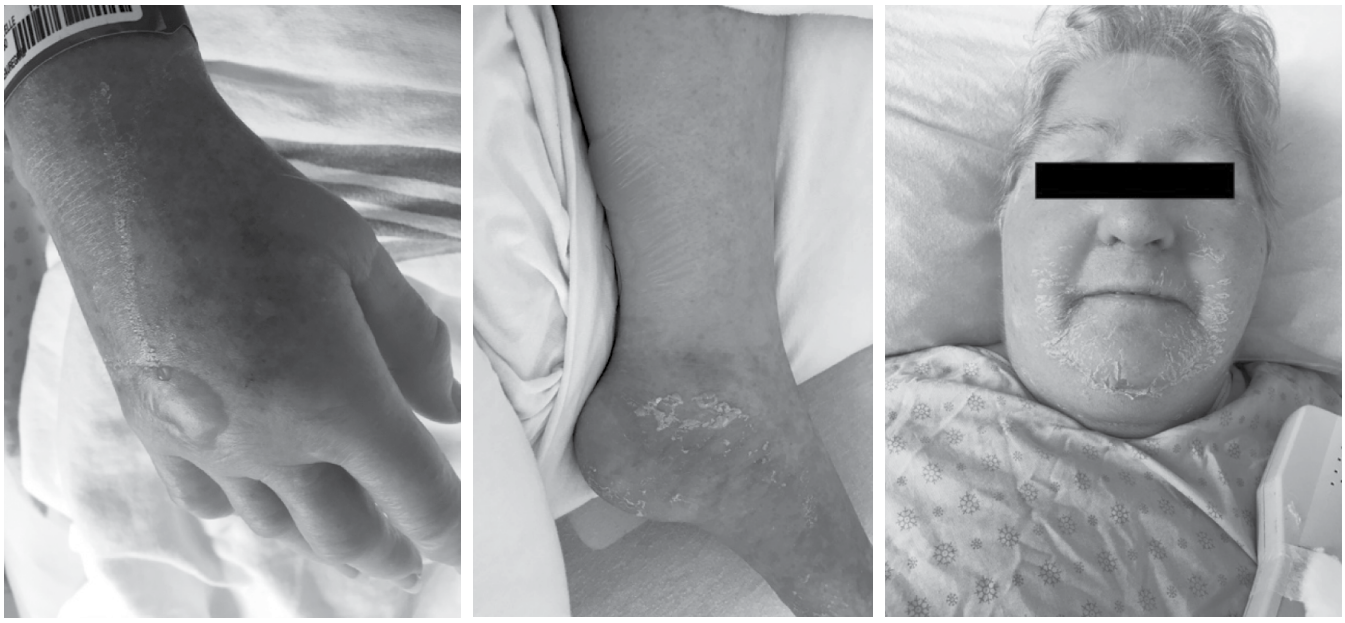

FIGURE 1. État de la réaction cutanée 10 jours après l'administration d'une première dose d'ipilimumab et de nivolumab.

d'appartenance. Un débalancement de son diabète sous corticostéroïdes suivi en endocrinologie et une pneumonie à *Pneumocystis jiroveci* pour laquelle elle a reçu un traitement de triméthoprime-sulfaméthoxazole de 21 jours prolongent son hospitalisation. Le traitement a été bien toléré et elle a obtenu son congé de l'hôpital au J56. À son départ, elle a reçu une ordonnance de sevrage de prednisone et de suivi en dermatologie. La patiente a reçu de la prednisone pendant cinq mois.

Le résultat des biopsies démontre une nécrose épidermique presque complète avec un discret infiltrat dermique lymphohistiocytaire périvasculaire et les immunofluorescences directes sont négatives; le résultat tend donc à confirmer la présence d'une NET.

DISCUSSION

Plusieurs éléments ont mené au diagnostic de NET chez cette patiente. Le malaise qui l'a menée à consulter à l'urgence s'apparente au prodrome précédant une NET, et l'éruption érythémateuse qui a rapidement progressé en phlyctènes et en desquamation est caractéristique d'une réaction cutanée causée par un médicament. Par ailleurs, l'atteinte des trois muqueuses et le signe de Nikolsky positif orientaient aussi vers ce diagnostic confirmé par une biopsie. Un score de Naranjo de sept indique que la NET a probablement été causée par la combinaison d'ipilimumab et de nivolumab[4] et c'est aussi ce qu'ont conclu les cliniciens.

Quelques rapports de cas de SSJ et de NET portant sur l'ipilimumab et le nivolumab sont présentés dans la littérature scientifique. Dans un premier cas, une femme de 64 ans traitée pour un mélanome métastatique réfractaire à l'ipilimumab a développé ces symptômes quatre semaines après le début d'un traitement au nivolumab[5]. Dans ce cas, l'ajout d'immunoglobulines et de cyclosporine à la cortisone à haute dose a permis de contenir la réaction. Dans un deuxième cas[6], un homme de 62 ans, traité pour un mélanome métastatique, a développé une NET au jour 4 après le deuxième cycle de double immunothérapie, soit 25 jours après le début du traitement. Malgré la prise en charge du patient par l'ajout d'immunoglobulines et de cyclosporine, il est décédé d'une défaillance d'organes multiples. Un autre patient de 54 ans traité pour un lymphome folliculaire a développé une NET 10 jours après la première dose de nivolumab[7]. Ce cas est intéressant, puisque le patient prenait d'autres médicaments qui pouvaient être associés à ce type de réaction, soit de l'allopurinol, le triméthoprime-sulfaméthoxazole et le fluconazole[7]. Finalement, un cas similaire à celui de notre patiente concerne un homme de 57 ans qui a développé une NET seulement six jours après la première administration d'ipilimumab et de nivolumab pour traiter un adénocarcinome gastro-œsophagien[8].

Environ 37 à 70 % des patients traités avec l'ipilimumab développent une toxicité cutanée, dont 1 à 3 % de grade 3 ou supérieur. De façon générale, 30 à 50 % des patients sous immunothérapie développent une toxicité cutanée durant leur traitement[2]. La monographie de l'ipilimumab[9] indique que le délai médian d'apparition d'une réaction cutanée à médiation immunitaire est de 3,1 semaines, ce qui correspond aussi au délai d'action du médicament sur les lymphocytes T. La monographie du nivolumab[10] indique que le délai médian d'apparition de réactions cutanées de grade 3 à médiation immunitaire lorsqu'il est combiné à l'ipilimumab pour le traitement d'un mélanome est de deux semaines et que la fréquence de telles réactions est plus élevée lorsqu'il est utilisé en combinaison.

Bien que le mécanisme sous-jacent à la NET induite par l'immunothérapie ne soit pas clairement élucidé, plusieurs hypothèses ont été émises. D'abord, l'augmentation de l'activité antitumorale des lymphocytes T pourrait être le déclencheur de réactions auto-immunes contre les kératinocytes. Ensuite, les anti PD-1 peuvent compromettre l'intégrité de l'épithélium, mais il est difficile de déterminer si ce phénomène peut contribuer au développement d'une NET[11]. Certains auteurs ont envisagé la possibilité que la comédication augmente les risques de développer une NET[10]. L'immunothérapie pourrait être le déclencheur d'une réaction d'hypersensibilité cutanée favorisée par la prise de médicaments connus pour en augmenter le risque.

Concernant les autres médicaments pris par la patiente, la mention du SSJ apparaît dans quelques monographies de produits, comme le dexlansoprazole[12], le tramadol-acétaminophène[13] et la saxagliptine[14], mais l'incidence n'est pas précisée. Concernant le lévétiracétam, l'incidence de SSJ serait supérieure à celle de la population générale et surviendrait en moyenne après 12 jours[15]. Toutefois, la patiente prenait ces médicaments depuis plus longtemps et aucun n'a été retiré durant le traitement. Concernant l'amlodipine, il y a moins de 0,1 % de cas de SSJ selon la monographie[16] et la littérature scientifique ne décrit que peu de cas portant sur cet agent. Dans le cas présent, l'amlodipine a d'abord été suspectée comme cause potentielle de la NET, puisque son administration avait débuté deux semaines avant la réaction. Mais cette hypothèse a été écartée, puisque le médicament a été repris pendant l'hospitalisation sans aggravation de la réaction. Il faut également prendre en considération le triméthoprime-sulfaméthoxazole que la patiente venait de commencer à prendre. Bien que le traitement se soit terminé 14 jours avant la réaction, le risque de SSJ est connu avec cet antibiotique[17]. Il est donc raisonnable d'affirmer qu'aucun de ces médicaments n'était directement en cause dans ce cas-ci, mais on ne peut exclure leur implication une fois l'inhibition lymphocytaire levée.

La revue de littérature confirme que des réactions de SSJ et de NET sont possibles avec la prise d'ipilimumab et de nivolumab, ce qui renforce la thèse postulant que cette patiente a réagi à cette double immunothérapie. L'intérêt du cas vient du fait que la réaction est survenue seulement

trois jours après l'exposition à ces agents, alors que des délais de 7 à 140 jours sont mentionnés dans les autres rapports de cas[18]. Selon plusieurs références, le délai d'apparition d'un SSJ ou d'une NET varierait d'une à quatre semaines après le début du traitement médicamenteux, mais pourrait aller jusqu'à huit semaines[19,20]. Devant l'incertitude à propos des rôles respectifs de l'immunothérapie et des autres médicaments augmentant le risque de réaction d'hypersensibilité cutanée, il conviendrait de prendre en considération ce risque de réaction sévère dans l'évaluation globale précédant la prescription d'une immunothérapie.

En conclusion, ce cas illustre la survenue d'une NET chez une femme de 58 ans traitée pour un mélanome métastatique avec la combinaison d'ipilimumab et de nivolumab. La rapidité de l'apparition de la réaction après le début de l'immunothérapie est surprenante lorsqu'on la compare avec ce que rapporte la littérature disponible.

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Reconstruire, en mieux

par Tania Mysak

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Veuillez pardonner ce titre un peu cliché et, tandis qu'approchent les derniers mois de mon mandat de présidente, permettez-moi, avant de partir, de vous livrer quelques réflexions concernant ce sur quoi la Société canadienne des pharmaciens d'hôpitaux (SCPH) pourrait concentrer ses efforts après la pandémie.

J'écris ces quelques lignes entre le congrès Ensemble, qui a remporté un franc succès, et une troisième vague évitable (et prévisible) de COVID-19 dans nos provinces les plus peuplées. C'est un moment intéressant situé dans un espace-temps favorable à la réflexion sur la manière dont nous tirons ou non des enseignements de ce que nous avons vécu et sur la façon dont l'année qui vient de s'écouler façonnera notre avenir.

Comme je l'écrivais il y a un an de cela, la COVID-19 a grandement perturbé nos vies, d'un point de vue personnel, professionnel et au sein même de notre Société. Nos sources traditionnelles de revenus et notre manière de gérer nos affaires et nos réseaux ayant été bouleversées, un retour aux normes d'avant 2019 semble très improbable. Comme beaucoup d'autres organismes, la SCPH devra adopter une « nouvelle normalité ».

Que nous a appris l'année dernière qui puisse nous guider dans notre parcours pour atteindre ce nouvel état futur?

Tout d'abord, les congrès. Pendant des dizaines d'années, nos congrès axés sur la pratique professionnelle ont servi de lieu de rencontre annuelle permettant d'apprendre, de réseauter et, franchement, de générer des recettes importantes pour la Société. Cependant, au cours de la dernière décennie, nous avons constaté un déclin régulier des commandites et de la participation; les revenus qui en ont résulté ont chuté en conséquence. La participation au Congrès de Banff (organisé par nos filiales dans l'Ouest) a connu un déclin similaire. La COVID-19 a remis en question l'avenir même des congrès en présentiel. Seront-ils aussi importants et aussi englobants? Doivent-ils se tenir en personne?

En nous réunissant virtuellement à l'occasion du congrès Ensemble, nous avons reçu d'étonnants commentaires concernant son contenu (le contenu des congrès de la SCPH est toujours excellent) et avons été félicités pour la facilité d'accès à la rencontre. Plusieurs membres ont pris le temps de nous indiquer que le format en ligne leur avait permis d'y participer, alors qu'ils ne pouvaient pas le faire auparavant. Ces commentaires sont importants, car ils touchent un élément sur lequel nous nous sommes concentrés dans notre Plan stratégique (https://cshp.ca/document/4123/CSHP-Strategic-Plan-2020.pdf) — l'apport des membres. S'ils accordent une grande valeur à l'accès à ces excellentes occasions d'apprentissage et de réseautage, nous ferions preuve de négligence si nous ne prenions pas en compte cet élément dans nos plans.

Bien sûr, comme cela a été le cas dans tous les domaines, la COVID-19 a aussi dynamisé notre réseautage en ligne, comme en témoigne l'augmentation de la participation à nos réseaux de spécialistes en pharmacie. Nous avons continué sur notre lancée en organisant plus de webinaires, en augmentant notre présence dans les médias sociaux et en utilisant tous les outils de participation et d'apprentissages ludiques qui nous étaient offerts sur notre plateforme de congrès en ligne.

Finalement, nous savons que l'une des raisons les plus importantes pour lesquelles nos membres apprécient la SCPH est le réseautage et l'impression de famille engendrée par le sentiment d'appartenance. Profitant de cette période qui nous a enseigné la valeur de la communauté, la SCPH s'engage à continuer à favoriser ces relations et ces amitiés qui nous ont unis et consolidés au cours de l'année dernière. Pour ce faire, nous comprenons la nécessité d'avoir des contacts humains en personne. Nous sommes donc résolus à entretenir ces relations qui jouent un rôle vital dans notre Société pour les années à venir.

Nous nous réjouissons de revoir vos visages à l'occasion de nos activités locales et nationales!

[Traduction par l'éditeur]

Tania Mysak, B.S.P., Pharm. D., est présidente sortante et agente de liaison pour la vision de la Société canadienne des pharmaciens d'hôpitaux.

Building Back Better

Tania Mysak

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Forgive the cliché of the title, and as the last months of my presidential term approach, allow me to offer some parting thoughts on what the Canadian Society of Hospital Pharmacists (CSHP) can focus its efforts on in a post-pandemic world.

I write this in the interregnum of a hugely successful Together conference and a preventable (and predictable) third wave of COVID-19 in our most populous provinces. It is an interesting place, in time and space, to reflect on how lessons are learned (or not) and how this past year will shape our future for years to come.

As I wrote a year ago, COVID-19 has been the great disruptor in our lives, personally, professionally, and within our Society. Our traditional revenue sources, manner of conducting business, and networks have been upturned in ways that are unlikely to return to pre-2019 norms. CSHP, like so much else, will require a "new normal".

What have we learned in the past year that will guide us on our journey to this future state?

First, conferences. For decades, our Professional Practice Conference served as an annual gathering to learn, network, and frankly, generate a significant amount of revenue for the Society. However, over the past decade, we have seen a steady decline in sponsorship and participation, and the resultant revenues have declined accordingly. Banff Conference (held by our Western Branches) has had similar declines in attendance. COVID-19 has thrown the future of in-person conferences into question. Will they be as large and encompassing? Do they need to be in person?

As we gathered online for Together, we received amazing feedback about the content (CSHP consistently hosts excellent content) and received kudos for accessibility. Several members took the time to reach out and note how the online format made attendance possible for them, whereas previously, they were unable to attend. This feedback is critical because it addresses something we have focused on in our Strategic Plan (https://cshp.ca/document/4123/CSHP-Strategic-Plan-2020.pdf)—member value. If our members value the ability to access this kind of excellent learning and networking opportunity, we would be remiss in not considering that in our plans.

Of course, as it has in all things, COVID-19 has also amped up our online networking, as witnessed by the increased level of engagement on our Pharmacy Specialty Networks. We were able to build on this momentum by including more webinars, having a stronger social media presence, and using every engagement and gamification tool available to us on our online conference platform.

Ultimately, we know that one of the most powerful reasons our members value CSHP is for the networking and sense of family that belonging brings. In a period that has taught us the value of community, CSHP is committed to continuing to foster those connections and friendships that have united and strengthened us over the past year. We understand that this takes in person human connection, and we remain resolved that those contacts will remain a vital part of our Society for years to come.

We can't wait to see all of your faces again at our local and national events.

Tania Mysak, BSP, PharmD, is Past President and Vision Liaison for the Canadian Society of Hospital Pharmacists.

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