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The Dose Makes the Poison*

Marc M Perreault

IV fluid therapy is ubiquitous in hospitals. It is part of any patient's admission orders, either as resuscitation therapy for patients receiving emergency or postoperative care and patients with sepsis or as maintenance therapy for patients with compromised oral intake; alternatively, IV fluid may be used as the diluent for most parenteral medications administered to patients. IV fluids are not usually purchased or stocked by the department of pharmacy, and we hospital pharmacists often do not view them as medications, with a dose–response relationship, or as a cause of potential harm to our patients. Despite the guidelines of the UK National Institute for Health and Care Excellence (published in 2013 and updated in 2017),[1] which outline general principles for managing IV fluids, they continue to be poorly prescribed overall.[2,3] The time has come that we pharmacists change our mindset about fluids and start considering this form of therapy as we would any other medication, that is, a treatment requiring individualization and proper monitoring.

A conceptual model for fluid therapy has been proposed to help prevent its inappropriate use.[4] This model consists of 4 distinct phases of fluid therapy, starting with rescue (resuscitation), proceeding to optimization and stabilization, and ending with de-escalation, thus mimicking the decreasing severity of illness over time.[4] During each of these phases, individualization—in terms of type of fluid and amount provided—is required to maintain organ perfusion while minimizing significant "third spacing". There is increased recognition of the detrimental consequences of giving too much fluid, as well as giving too much of the same fluid (e.g., normal saline [0.9% sodium chloride]), to patients.[5-10]

We have all either witnessed or been involved in cases where too much fluid was administered, for example, patients admitted from the emergency department and ending up on a medical or surgical floor days later with an excess of fluid, in the amount of 5 L or even up to 10 L. These patients have typically undergone aggressive resuscitation with boluses of fluid and are also given maintenance fluids; as their hemodynamic condition stabilizes and the inflammatory cascade abates, diuresis begins on its own or an intervention is required to initiate diuresis (e.g., administration of a loop diuretic or institution of renal replacement therapy). Unfortunately, this approach seems to be the usual and expected patient trajectory during a hospital stay; in other words, "the patient needs to swell before getting well."

This aggressive approach with fluids has been promoted through early goal-directed therapy aimed at providing fluids and vasopressors according to defined protocols in the management of severe sepsis and shock.[11] Prompt implementation of such protocols has resulted in significant improvement in clinical outcomes[11] and is currently a best practice within the Surviving Sepsis Campaign.[12]

However, evidence is now emerging of potential harm associated with providing too much fluid (positive fluid balance) to critically ill patients. Several retrospective studies have found an association between positive cumulative fluid balance at discharge from the intensive care unit (ICU) and death (whether in the ICU or elsewhere in the hospital),[5,6] raising the possibility that intervening on fluid balance might improve patient outcomes.[7] At this point, it is only an association, and no causation is implied; however, the evidence is building. In a recent systematic review and meta-analysis of randomized controlled trials and observational studies, Silversides and others[8] showed that a conservative fluid strategy in patients with sepsis or acute respiratory distress syndrome increases the number of ventilator-free days and reduces the ICU length of stay with no change in mortality, relative to a more liberal fluid strategy or standard care, setting the foundation for large randomized trials to determine optimal fluid strategies in critical illness.

*Paracelsus, dritte defensio [*Third Defense*], 1538.

In most circumstances, the fluid of choice for resuscitation, maintenance, and dilution of medications remains normal saline, also referred to as physiologic fluid. It contains 154 mmol of sodium and chloride and has a pH of 5.5. As such, it is anything but physiologic and on that basis, should be considered abnormal rather than "normal". A well-known metabolic complication of administering too much saline is hyperchloremia and its associated non-anion gap metabolic acidosis. Over the last decade, the potential for inducing acute kidney injury by chloride overload from normal saline has been recognized. However, 2 recent large clinical trials comparing saline and balanced crystalloids have failed to prove such a link.[9,10] For now, the optimal crystalloid remains to be determined.

It should be obvious that I do not pretend to solve any of the controversies associated with fluid therapy, but I do want to emphasize the growing evidence that too much fluid (in general) and too much normal saline (in particular) do not represent optimal pharmacotherapy. However, the optimal doses of fluids and of normal saline for a patient are currently unknown.

In addition, there are specific issues regarding fluids that we pharmacists face and that deserve to be addressed. The first is the need to recognize when to de-escalate fluid therapy, similar to the need to reduce a broad-spectrum antibiotic in a patient whose infection is improving. Triggers exist for giving fluid as a bolus, such as the presence of shock, a drop in systolic blood pressure, or a rise in serum lactate. However, triggers for slowing or stopping maintenance fluids have not yet been defined. For me, initiation of diuretics by the team serves as a trigger to reassess maintenance fluids. Unfortunately, without such triggers, infusion of fluids is continued for longer than required, and patients experience even greater volume overload.

A second issue that is emerging in the literature is the contribution to the overall fluid balance of fluids used to dilute medications. In a large retrospective study involving critically ill patients in the United Kingdom and Canada, the largest contributor of fluids over ICU days 1 to 3 was, surprisingly, from medication (34.5% of all fluids), whereas maintenance therapy and fluid boluses accounted for about 26.5% and 24.4% of fluids, respectively.[7] A similar observation was made in a medical ICU population where medication diluent accounted for 63% of the total parenteral volume in the first 7 days of ICU admission and was responsible for a greater incidence of hyperchloremia.[13] Hence, if fluids are to be restricted, pharmacists need to acknowledge the contribution from medication diluents to the overall fluid burden and must become involved in developing fluid-restrictive strategies.

So, the next time you are participating in patient rounds, take a moment to reassess your patient's maintenance fluid therapy and consider administering medications in smaller volumes of diluent, if possible, or transitioning IV medications to the enteral or oral route. Doing so will make the fluids less poisonous!

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La dose fait le poison*

par Marc M. Perreault

Le traitement liquidien par voie intraveineuse est omniprésent dans les hôpitaux. Il fait partie des ordonnances d'admission de tout patient, que ce soit sous la forme d'un traitement de réanimation, de soins d'urgence ou de soins postopératoires ou pour les patients atteints de sepsis ou encore comme traitement d'entretien destiné aux patients qui sont dans l'impossibilité de prendre des médicaments oraux; mais les solutions intraveineuses peuvent aussi servir à diluer la plupart des médicaments à usage parentéral. Normalement, le service de pharmacie n'achète ni ne stocke les liquides intraveineux et nous, pharmaciens d'hôpitaux, ne les considérons habituellement pas comme des médicaments, c'est-à-dire, comme un produit pourvu d'une relation dose-effet ou comme une cause potentielle de danger pour nos patients. Malgré la présence des lignes directrices de l'UK National Institute for Health and Care Excellence (publiées en 2013 et mises à jour en 2017)[1], qui décrivent les principes généraux de gestion des liquides administrés par voie intraveineuse, ceux-ci sont, dans l'ensemble, toujours mal prescrits[2,3]. Il est temps pour nous, pharmaciens, de changer notre perspective en ce qui concerne les liquides et de commencer à considérer cette forme de traitement comme n'importe quelle autre pharmacothérapie, c'est-à-dire, un traitement nécessitant une individualisation et un suivi adéquat.

Un modèle conceptuel pour le traitement liquidien a été proposé afin d'en éviter l'utilisation inadéquate[4]. Ce modèle compte quatre phases distinctes de traitement liquidien : la première étant le secours (réanimation), suivie de l'optimisation et de la stabilisation et enfin la désescalade, un processus qui s'ajuste avec le temps à la diminution de la gravité de la maladie[4]. Au cours de chacune des phases, l'individualisation (c'est-à-dire le type de liquide et la quantité administrée) est nécessaire au maintien de l'irrigation de l'organe tout en réduisant de façon significative le « troisième secteur ». Or, on est de plus en plus conscient des conséquences néfastes de donner une trop grande quantité de liquide, voire même d'administrer aux patients une trop grande quantité d'un même liquide (par exemple, la solution physiologique salée [chlorure de sodium à 0,9 %])[5-10].

Nous avons tous vu ou vécu des cas où un excès de liquide avait été administré, par exemple à des patients admis au service des urgences qui se retrouvent quelques jours plus tard dans le service d'une autre unité médicale ou à l'unité de soins chirurgicaux et qui présentent un excédent de liquide de cinq, voire même de dix litres. Ces patients ont habituellement subi des traitements de réanimation énergiques à l'aide de bolus liquidiens et ils reçoivent aussi des liquides comme traitement d'entretien; alors que leur état hémodynamique se stabilise et que la cascade inflammatoire régresse, la diurèse se déclenche d'elle-même ou une intervention est nécessaire pour la déclencher (à l'aide, par exemple, de l'administration d'un diurétique de l'anse ou de l'amorce d'un traitement de suppléance rénale). Malheureusement, cette approche semble être celle utilisée par défaut et produire le résultat auquel on s'attend pendant un séjour hospitalier, autrement dit : « Le patient doit enfler avant d'aller mieux. »

Cette utilisation énergique des liquides a été encouragée par le recours à des traitements précoces orientés vers des objectifs visant à fournir des liquides et des vasopresseurs selon les protocoles prédéfinis pour la gestion des sepsis sévères et chocs septiques[11]. La mise en œuvre rapide de tels protocoles a mené à des améliorations significatives des résultats cliniques[11] et est actuellement l'une des meilleures pratiques dans la campagne « Surviving Sepsis » (survivre au sepsis)[12].

Or, on constate l'apparition de nouvelles données sur les dommages potentiels associés au fait d'administrer trop de liquides (bilan hydrique positif) à des patients gravement malades. Plusieurs études rétrospectives ont découvert une association entre les cas de bilan hydrique cumulatif positif au moment du congé de l'unité de soins intensifs (USI) et les cas de décès (à l'USI ou ailleurs dans l'hôpital)[5,6], ce qui laisse entrevoir que le fait d'intervenir sur le bilan hydrique pourrait améliorer les résultats thérapeutiques[7]. Jusqu'ici, il ne s'agit que d'une association et non d'un lien de causalité; cependant, de plus en plus de données probantes vont dans ce sens. Lors d'une analyse systématique et d'une méta-analyse d'études contrôlées à répartition aléatoire et d'études observationnelles, Silversides et collab.[8] ont montré qu'une stratégie plus prudente concernant les liquides pour les patients atteints de sepsis ou d'un syndrome de détresse respiratoire aiguë permet d'accroître le nombre de journées sans respirateur et de réduire la durée des séjours à l'USI sans qu'il y ait de changement aux taux de mortalité, comparativement à une approche plus libre concernant les liquides ou des soins classiques, ce qui jette les bases d'importantes études à répartition aléatoire dans le but de déterminer la stratégie optimale concernant les liquides pour les maladies graves.

*Paracelsus, dritte defensio [*Troisième défense*], 1538.

Dans la plupart des cas, le liquide de choix pour la réanimation, l'entretien et la dilution de médicaments demeurait la solution physiologique salée, aussi appelée « liquide physiologique ». Il contient 154 mmol de chlorure et de sodium et possède un pH de 5,5. Il n'est donc en rien physiologique et il devrait donc être considéré comme anormal et non « normal » comme le veut le terme anglais « normal saline ». Un trouble métabolique bien connu, qui est produit par l'administration d'une trop grande quantité de solution physiologique salée, est l'hyperchlorémie et l'acidose métabolique à trou non anionique qui lui est associée. Au cours de la dernière décennie, on a reconnu qu'une surdose de chlorure provenant de solution physiologique salée a le potentiel de provoquer l'insuffisance rénale aiguë. Cependant, deux importantes études cliniques comparant la solution physiologique salée aux solutions cristalloïdes équilibrées ne sont pas arrivées à prouver l'existence d'un tel lien[9,10]. Pour l'instant, il reste à déterminer quel est le cristalloïde optimal.

Je ne prétends évidemment pas résoudre les controverses associées au traitement liquidien, mais je cherche à mettre de l'avant l'accumulation de données indiquant qu'un excès de liquides (en général) et trop de solution physiologique salée (en particulier) ne représentent pas une pharmacothérapie optimale. Cependant, les doses optimales de liquides et de solution physiologique salée pour un patient restent inconnues.

Par ailleurs, il y a des enjeux précis concernant les liquides auxquels nous, pharmaciens, faisons face et qui méritent d'être abordés. Le premier est la nécessité de reconnaître à quel moment on doit alléger un traitement liquidien, tout comme il est nécessaire d'accélérer le passage à un antibiotique à spectre plus étroit pour un patient dont l'infection se résorbe progressivement. Il y a des indicateurs spécifiant le moment de l'administration d'un bolus de liquide, dont un choc, une chute de pression artérielle systolique ou une augmentation du taux de lactate sérique. Par contre, il n'y a toujours pas d'indicateurs définis signalant le moment de réduire ou de cesser l'administration de liquide d'entretien. Selon moi, l'amorce de l'administration de diurétiques par l'équipe sert de repère indiquant qu'il est temps de réévaluer le traitement d'entretien. Malheureusement, sans de tels indicateurs, l'infusion de liquides se poursuit plus longtemps que nécessaire et les patients subissent une surdose de fluides encore plus importante.

Un deuxième enjeu apparaissant dans la littérature est la place des liquides utilisés pour diluer les médicaments dans le bilan hydrique total. Dans une importante étude rétrospective menée auprès de patients gravement malades au Royaume-Uni et au Canada, les raisons motivant l'administration de liquides pendant les jours 1 à 3 aux USI étaient, étonnamment, en premier lieu la dilution de médicaments (34,5 % de tous les liquides) alors que le traitement d'entretien et les bolus comptaient respectivement pour 26,5 % et 24,4 % des liquides[7]. Une observation semblable a été faite auprès d'une population à l'USI médicale, où les diluants de médicaments comptaient pour 63 % du volume parentéral total dans les sept premiers jours suivant l'admission à l'USI et étaient responsables d'une plus grande incidence d'hyperchlorémie[13]. Ainsi, pour limiter l'administration de liquides, les pharmaciens doivent tenir compte du poids des diluants dans le bilan hydrique total et aussi participer à l'élaboration de stratégies de restriction de l'utilisation des liquides.

Par conséquent, la prochaine fois que vous participerez à une tournée médicale, prenez le temps de réévaluer le traitement d'entretien et songez à administrer les médicaments à l'aide de plus faibles volumes de diluants, si possible, ou à passer de médicaments administrés par voie intraveineuse à des médicaments administrés par voie orale ou parentérale. Ces précautions empêcheront les liquides de devenir des poisons!

[Traduction par l'éditeur]

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Evaluation of Pharmacist Intervention on Discharge Medication Reconciliation

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ABSTRACT

Background: Discharge medication reconciliation (Discharge MedRec) was implemented on one unit at a large urban teaching hospital, and was to be expanded across the rest of the hospital and the health authority's various sites by the end of 2018. Clinical pharmacists on the Acute Care for the Elderly unit carried out discharge planning and led Discharge MedRec during a pilot period, to inform the future implementation.

Objectives: The primary objective was to examine the number and type of medication discrepancies before and after implementation of Discharge MedRec. The secondary objectives were to compare documented medication changes, pharmacist recommendations, discharge counselling, communication with community pharmacists, polypharmacy, and 30-day readmission rates.

Methods: Patients seen in December 2015 constituted the control (pre-implementation) group, who received usual care. Patients seen from January to April 2016 constituted the intervention group, for whom pharmacists performed Discharge MedRec and other discharge activities as per the hospital-to-home checklist of the Institute for Safe Medication Practices Canada.

Results: There were 66 patients in the control group and 306 in the intervention group. Median discrepancies per patient decreased from 6.5 to 3 (p = 0.007), median number of documented changes without rationale increased from 2 to 3 (p = 0.01), and median number of documented changes with rationale increased from 1 to 2 (p < 0.001). Pharmacists made a per-patient median of 1 progress note recommendation in the control group and 2 progress note recommendations in the intervention group (p = 0.007), and a per-patient median of 2 orders in both the control and intervention groups (p = 0.62). Median recommendation acceptance was 100% for both groups, but twice as many recommendations were made per patient for the intervention group. Discharge counselling increased from 22.7% to 65%. Communication with community pharmacists increased from 10.6% to 60.8%.

Conclusions: Clinical pharmacist involvement improved Discharge MedRec planning and documentation. Decreases in medication discrepancies, combined with an increase in discharge counselling, should improve continuity of care across the health care team and increase patient adherence with medication therapy. This study further demonstrates the leadership role that pharmacists play in the assessment and clear documentation of medication changes at all transitions of care.

Keywords: discharge medication reconciliation, clinical pharmacist, polypharmacy, elderly

RÉSUMÉ

Contexte : Le processus de bilan comparatif des médicaments au moment du congé a été mis en place dans une unité d'un important hôpital universitaire en milieu urbain et devait être mis en place dans le reste de l'hôpital et dans les différents sites de la régie de santé avant la fin de 2018. Des pharmaciens cliniciens de l'Unité de soins gériatriques de courte durée ont réalisé la planification des congés et ont dirigé le processus de bilan comparatif des médicaments au moment du congé, au cours d'une période d'essai, afin de contribuer à une future mise en place d'un tel processus.

Objectifs : L'objectif principal consistait en l'étude du nombre et du type de divergences relatives aux médicaments avant et après la mise en place du processus de bilan comparatif des médicaments au moment du congé. Les objectifs secondaires portaient sur la comparaison des éléments suivants : les changements apportés à la pharmacothérapie, les recommandations des pharmaciens, l'offre de conseils au moment du congé, les échanges avec les pharmaciens communautaires, la polypharmacie et les taux de réadmissions dans les 30 jours suivant le congé.

Méthodes : Les patients rencontrés en décembre 2015 constituaient le groupe témoin (avant la mise en place du processus) ayant reçu les soins habituels. Les patients rencontrés entre janvier et avril 2016 formaient le groupe expérimental pour lequel les pharmaciens avaient réalisé un processus de bilan comparatif des médicaments au moment du congé et d'autres activités en lien avec le congé, en fonction de la liste de vérification du transfert de l'hôpital à la maison de l'Institut pour la sécurité des médicaments aux patients du Canada.

Résultats : Il y avait 66 patients dans le groupe témoin et 306 dans le groupe expérimental. Le nombre médian de divergences par patient a diminué et est passé de 6,5 à 3 (p = 0,007), le nombre médian de changements consignés, apportés sans raison apparente a augmenté et est passé de 2 à 3 (p = 0,01) et le nombre médian de changements consignés, dont la raison apparaissait aux dossiers a augmenté et est passé de 1 à 2 (p < 0,001). Le nombre médian de recommandations par patient dans les notes d'évolution réalisées par les pharmaciens était de un dans le groupe témoin et de deux dans le groupe expérimental (p = 0,007) et le nombre médian d'ordonnances par patient réalisées par des pharmaciens était de deux, tant dans le groupe témoin que dans le groupe expérimental (p = 0,62). Les taux médians d'acceptation des recommandations étaient de 100 % dans les deux groupes, mais il y a eu deux fois plus de recommandations par patient réalisées dans le groupe expérimental. L'offre de conseils au moment du congé a augmenté et est passée de 22,7 % à 65 %. Les échanges avec les pharmaciens communautaires ont augmenté et sont passés de 10,6 % à 60,8 %.

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Conclusions : La participation des pharmaciens cliniciens a amélioré la planification et l'enregistrement du bilan comparatif des médicaments au moment du congé. Une réduction des divergences concernant les médicaments, associée à une augmentation de l'offre de conseils au moment du congé, devrait améliorer la continuité des soins au sein de l'équipe de soins de santé et accroître l'observance thérapeutique du patient. La présente étude est un nouvel exemple du rôle de leader que les pharmaciens jouent dans l'évaluation et la description claire des changements apportés à la pharmacothérapie à chaque transfert des soins.

Mots clés : bilan comparatif des médicaments au moment du congé, pharmacien clinicien, polypharmacie, aînés

INTRODUCTION

Medication reconciliation (MedRec) is described as the "systematic and comprehensive review of all the medications a patient is taking (known as a BPMH [best possible medication history]) to ensure that medications being added, changed or discontinued are carefully evaluated."[1] Rozich and Resar[2] estimated that 60% of all medication errors occur at admission, at interfaces of transfer, or at discharge. When a patient is transferred from one care setting to another, medications may be stopped or started, or long-term medications may be changed. Unintentional changes at these interfaces lead to discrepancies, which may in turn lead to adverse drug reactions.

Older patients are particularly at risk of such discrepancies, because they are more likely to be receiving multiple concurrent medications (polypharmacy) and to visit a multitude of health care providers.[3] Evidence has suggested that most adverse drug events leading to readmission among elderly patients occurred within 14 days after discharge, and 8.4% of such readmissions were due to preventable adverse drug events.[4,5] Prescribers may be reluctant to change or modify drugs initiated by other prescribers, which leads to the risk of a prescribing cascade (whereby new drugs are prescribed to treat the side effects of previously prescribed drugs).

Clinical pharmacists' recommendations during the patient stay and at discharge could have substantial benefits for patient care. Proactive involvement of a pharmacist during the hospital stay and at discharge has led to recommendations to change doses or to adapt or stop medications.[3,6-9]

Discharge medication reconciliation (Discharge MedRec) is the final checkpoint in the reconciliation process before a patient leaves the hospital. Conflicting information and errors on discharge documents are often problematic, especially for elderly patients and their caregivers. The Institute for Safe Medication Practices Canada found that 67% of discharge prescriptions were incomplete or contained errors.[5] The benefits of Discharge MedRec have been cited as increased potential to discover discrepancies,[3,10] increased opportunities to prevent prescribing cascades,[9] cost savings as a result of pharmacist interventions,[11,12] and potentially decreased readmission rates.[11,13]

An accurate medication history is foundational for MedRec and increases patient safety at transitions of care (or at discharge).[14] The involvement of pharmacists in obtaining a patient's medication history and in the discharge process have shown that they are well suited for identifying medication errors.[15-21] In several previous studies, the involvement of clinical pharmacists during admission and discharge reduced medication-related problems and readmissions.[5,22-24] In addition, pharmacist involvement in Discharge MedRec has led to significant cost savings.[5,8]

Across our health authority, Discharge MedRec data focusing on high-risk patients, such as the geriatric population, have not been extensively studied. In a Canadian study performed on an internal medicine unit in 2006, pharmacist involvement revealed unintentional discrepancies that might have been missed on discharge.[9] Global studies have also demonstrated the benefits of pharmacist involvement in Discharge MedRec, indicating improvements in documentation, increased quality and efficiency of MedRec practices, and increased detection of drug-related problems.[3,6,7,12,21] These benefits could be attributed in part to pharmacists' special training in managing medications and their potential side effects. It is important to emphasize pharmacy involvement in Discharge MedRec and to continue to advocate for pharmacist involvement at all interfaces of care.

This single-centre, consecutive-cohort study piloted the Discharge MedRec model on the Acute Care for the Elderly (ACE) unit at a large urban teaching hospital, with the aim of measuring the effectiveness of additional pharmacist support at discharge.

METHODS

Study Design

This quality assurance initiative was conducted on a single ACE unit. The control group consisted of patients discharged

from the ACE unit between December 1 and December 31, 2015. The intervention group consisted of patients discharged between January 1 and April 30, 2016. Patients who left against medical advice, who were discharged before pharmacist work-up, or who died in hospital were excluded. The analysis therefore included patients who were undergoing care during the study timeframe and who received pharmacist work-up. The intervention was routine involvement of a clinical pharmacist to assist with Discharge MedRec according to all aspects of the hospital-to-home checklist of the Institute for Safe Medical Practices Canada.[5] During the intervention phase, an additional pharmacist was staffed to the ward on weekdays to aid with the increased workload associated with this comprehensive care; as such, the patient-to-pharmacist ratio decreased from 36:1 to 18:1 during the intervention phase. Pharmacists were instructed to document, in the patient chart and/or the pharmacy's patient monitoring form, all recommendations, recommendations accepted, cases of patient counselling, and cases of communication with community pharmacists. Both types of documentation were reviewed by a single reviewer (R.L.).

Data collected for analysis included the following:

- total medication changes at discharge
- medication changes documented with and without rationale
- medication changes not documented
- total number of pharmacist recommendations documented through chart notes and orders, subdivided as to type of recommendation (medication started, changed, stopped, other)
- total number of drugs
- total number of patients with medication tapering
- presence or absence of discharge counselling
- communication with community pharmacists

Pre-intervention (Control) Group

Patients in the control group underwent standard admission and discharge practices in accordance with existing hospital policy. At discharge, the discharge prescription was generated from the list of active medications, and the physician manually filled in preadmission medications that were to be restarted. Pharmacists were consulted as needed during the discharge process, and they contacted the province-wide public drug plan to obtain special authority as needed. The discharge prescription was given to the patient upon discharge.

Intervention Group

Patients in the intervention group underwent the same admission process as patients in the control group and received the same level of care during their stay in hospital. Pharmacists involved in the study were responsible for medication-related care during each patient's entire stay on the unit. During Discharge MedRec in the intervention phase, the pharmacist reviewed all medications with the physician, ensuring that preadmission and current medications were restarted or continued as necessary. Indications, reversal of auto-substitutions, dose changes, and additions or discontinuations of medications were noted on the Discharge MedRec form. Counselling of patients and communication with community pharmacists were provided at discharge as appropriate. Copies of the resulting Discharge MedRec form were kept in the patient's chart, sent by fax to the patient's community pharmacist, and given to the patient.

Outcomes

The primary outcome was changes in the number and type of discrepancies (undocumented changes without rationale). The secondary outcomes were changes in the number and type of documented changes (with or without rationale), rate of pharmacist involvement in making recommendations, provision of patient counselling, communication with community pharmacists, and rate of polypharmacy. Thirty-day readmission rates were also examined.

Data Collection

Pharmacist involvement during the hospital stay and at discharge was evaluated to determine the effect of pharmacist-led Discharge MedRec and to measure pharmacist impact in terms of various medication-related variables (Table 1). Recommendations and discrepancies were categorized in terms of medications started, stopped, or changed (Table 1), with comparisons between the control and intervention groups. Data for recommendations were collected by examining the patient chart and the patient monitoring form. Recommendation acceptance was identified either by documentation (in orders, the patient chart, or the patient monitoring form) of the prescriber's acknowledgement of a pharmacist's recommendation, or by a prescriber's verbal order as transcribed by a pharmacist. Data for discrepancies and medication changes were collected by comparing the Admission MedRec and Discharge MedRec forms.

Data for patient counselling and communication with community pharmacists were collected from indications of such activity either on the Discharge MedRec form, the patient chart, or the patient monitoring form. Data on polypharmacy were collected by tabulating medications listed on the Admission MedRec form and comparing these medications with the Discharge MedRec form. Data regarding tapering of medications were found by examining the patient chart and the Discharge MedRec form. Readmission data were collected at least 1 month after discharge by reviewing the patient's electronic health record for any readmissions throughout the health authority within 30 days of the discharge date.

Table 1. Definitions

Type of Change*	Definition	Example†
Documented change with rationale	Medication changes that were documented and included clear rationale	**NEW** gliclazide SR 30-mg tab PO daily for diabetes
Documented change without rationale	Medication changes that were documented, but did not include a rationale	**NEW** calcium carbonate 1250 mg PO daily
Undocumented change without rationale	Medication changes from the Admission MedRec form that were not addressed on the Discharge MedRec form or changes that appeared on the Discharge MedRec form without explanation	1. acetaminophen 1 g PO TID (not present on Admission MedRec form but present on Discharge MedRec form, with no indication of "**NEW**") 2. ASA 81 mg PO daily (on Admission MedRec form, but not addressed on Discharge MedRec form)
Total number of changes (documented + undocumented)	Sum of all changes listed above	Based on the examples above, the total number of changes is 4

MedRec = medication reconciliation.
*Changes made to any of the progress notes, orders, or the Discharge MedRec form were included. If the recommendation or order was present in multiple places, the note of higher quality (i.e., more complete) was used in the evaluation.
†This column shows information as it appears on the MedRec form, which is available to both the patient and to health care providers. Any entry for a medication that is newly prescribed is to be highlighted, most especially for the patient's benefit.

Statistical Analysis

All data were coded into a password-protected spreadsheet (Excel 2016 for Windows, Microsoft Corporation). The responses were manually reviewed by one of the investigators (R.L.) in the spreadsheet and verified with the primary investigator (S.M.) before the analyses were performed. All statistical analyses were performed with statistical software (JMP version 12, SAS Institute). Descriptive statistics (medians, totals) were calculated to compare pharmacist notes, types of pharmacist recommendations, involvement in discharge counselling, changes in polypharmacy, and changes in readmission rates. The Fisher exact test was used to analyze differences in baseline characteristics. Mann–Whitney *U* tests were used to analyze differences in baseline age, medication changes (documented, undocumented, and discrepancies), number of recommendations made and accepted, tapering of medications, and number of active medications on the Admission and Discharge MedRec forms. The χ^2 test was used to analyze differences in rates of discharge counselling, communication with community pharmacists, and readmission.

RESULTS

In total, 72 patients were discharged from the ACE unit in December 2015, of whom 66 met the criteria for inclusion in the control group (i.e., discharged during study timeframe and received pharmacist work-up; Figure 1). In addition, 317 patients were discharged from the ACE unit between January and April 2016, of whom 306 met the inclusion criteria. The small number of patients who left against medical advice or died in hospital were excluded from the analysis. None of the patients who received pharmacist work-up left against medical advice. The median age of patients in the control and intervention groups was 83 and 83.5 years respectively (Table 2). The control group had 28.8% men (19/66), and the intervention group had 47.1% men (144/306). The median length of stay was 18.5 days in the control group and 9.5 days in the intervention group ($p < 0.001$).

When medication changes were analyzed (Table 3), the median number of discrepancies (undocumented changes without rationale) was 6.5 in the control group and 3 in the intervention group ($p = 0.007$). The median number of documented changes without rationale was 2 in the control group and 3 in the intervention group ($p = 0.01$), and the median number of documented changes with rationale was 1 in the control group and 2 in the intervention group ($p < 0.001$). The median number of pharmacist recommendations doubled between the control and intervention phases of the study (Table 3). The median acceptance rate for recommendations was 100% in both groups ($p < 0.001$), with twice the number of recommendations per patient in the intervention group. The median number of pharmacist orders was the same in the 2 groups.

Polypharmacy data are also shown in Table 3. The rate of tapering was 4.5% (3/66) in the control group and 6.9% (21/306) in the intervention group ($p = 0.75$). Patients in the control group had a median of 8.5 active medications upon admission and a median of 9 medications at discharge, whereas patients in the intervention group had a median of 6 medications upon admission and 9 medications upon discharge.

Discharge counselling was provided for 22.7% (15/66) of patients in the control group and for 65.0% (199/306) of patients in the intervention group ($p < 0.001$). Communication with community pharmacists increased from 10.6% (7/66) in the control group to 60.8% (186/306) in the intervention group ($p < 0.001$). Thirty-day readmission rates were 28.8% (19/66) in the control group and 21.2% (65/306) in the intervention group ($p = 0.17$).

DISCUSSION

Previous studies of MedRec have acknowledged the importance of pharmacist involvement at both admission and discharge. In the current study, clinical pharmacist involvement in Discharge

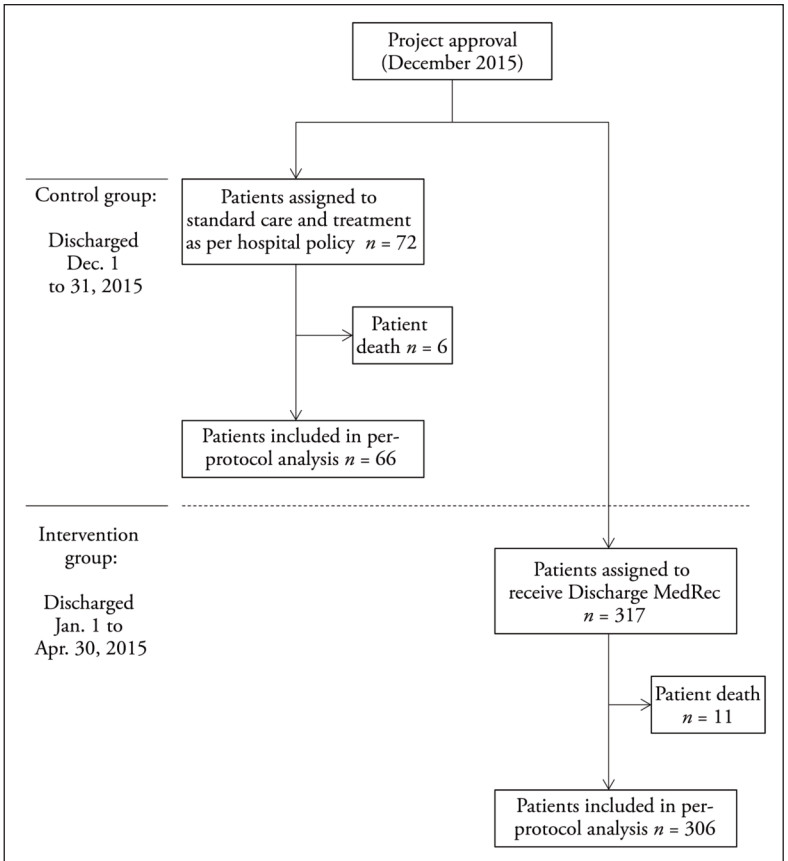

Figure 1. Timeline of study.

Table 2. Baseline Characteristics of Study Groups

Characteristic	No. (%) of Patients*				*p* Value
	Control (*n* = 66)		Intervention (*n* = 306)		
Age (years) (median, IQR)	83	(77–89)	83.5	(78–89)	0.13‡
Sex					0.16§
Men	19	(28.8)	144	(47.1)	
Women	47	(71.2)	162	(52.9)	
Admission diagnoses†					
Infectious disease	25	(37.9)	108	(35.3)	0.78¶
Cardiovascular condition	15	(22.7)	62	(20.3)	0.62¶
Failure to thrive/weakness	5	(7.6)	50	(16.3)	0.08¶
Respiratory condition	8	(12.1)	36	(11.8)	> 0.99¶
Fluid/electrolyte problem	1	(1.5)	20	(6.5)	0.14¶
Blood/renal condition	2	(3.0)	17	(5.6)	0.55¶
Gastrointestinal/genitourinary condition	3	(4.5)	12	(3.9)	0.74¶
Neurologic condition	6	(9.1)	11	(3.6)	0.09¶
Endocrine condition	2	(3.0)	3	(1.0)	0.22¶
Liver/pancreas problem	2	(3.0)	1	(0.3)	0.08¶
Other	10	(15.2)	74	(24.2)	0.14¶

IQR = interquartile range.
*Except where indicated otherwise.
†Medical conditions that encompassed ≥ 2% of the patient population on the Acute Care for the Elderly unit are listed; some patients had more than one condition.
‡Calculated with Mann–Whitney *U* test.
§Calculated with χ^2 test.
¶Calculated with the Fisher exact test.

Table 3. Outcomes

Outcome	Median Value (IQR)* Control (*n* = 66)		Intervention (*n* = 306)		*p* Value
No. of discrepancies					
Undocumented changes without rationale	6.5	(1–11)	3	(1–6)	0.007†
Total "medications started"	6.5	(1–11)	3	(1–6)	0.006†
Total "medications changed"	0	(0)	0	(0)	Not tested
Total "medications stopped"	0	(0)	0	(0)	Not tested
Documented changes without rationale	2	(1–3)	3	(1–6)	0.01†
Documented changes with rationale	1	(0–2)	2	(1–4)	< 0.001†
Total changes (documented + undocumented)	10	(6–14.75)	10	(5.25–14)	0.84†
No. of pharmacist recommendations					
Made in progress notes	1	(1–2)	2	(1–4)	0.007†
Accepted in progress notes	1	(0–2)	2	(0–4)	< 0.001†
Pharmacist orders (in orders and directives)	2	(1–3)	2	(0–4)	0.62†
Polypharmacy					
No. of active medications identified on Admission MedRec form	8.5	(4.25–10.75)	6	(3–10)	0.81†
No. of medications upon discharge	9	(5–13)	9	(6–12)	Not tested
Total no. (%) of patients with tapering upon discharge	3	(4.5)	21	(6.9)	0.75†
Patient outcomes					
No. (%) of patients who received counselling	15	(22.7)	199	(65.0)	< 0.001‡
No. (%) of patients with communication between hospital pharmacist and patient's community pharmacists	7	(10.6)	186	(60.8)	< 0.001‡
No. (%) of patients readmitted within 30 days	19	(28.8)	65	(21.2)	0.17‡

IQR = interquartile range, MedRec = medication reconciliation.
*Except where indicated otherwise.
†Calculated with Mann–Whitney *U* test.
‡Calculated with χ^2 test.

MedRec improved medication discharge planning and documentation. This study has further demonstrated the leadership role that pharmacists play in the assessment, clarification, and clear documentation of medication changes during a patient's stay and, more importantly, during the discharge process. These findings reinforce calls for additional pharmacist support in maintaining MedRec at care transitions, the use of pharmacists as educators to demonstrate Discharge MedRec best practices, and the continued affirmation of the pharmacist's role as a medication manager. These findings are also consistent with previous research in this area.[11,12]

In this study, the median number of discrepancies decreased by 54% (from 6.5 to 3; $p = 0.007$). Levels of documented changes both with and without rationale increased in the intervention group relative to the control group: by 100% ($p < 0.001$) and by 50% ($p < 0.01$), respectively. The median number of changes overall was the same in the 2 groups ($p = 0.84$); however, more documentation and rationale were provided for changes in the intervention group. "Medications started" discrepancies decreased by 54% in the intervention group (Table 3). "Medication changed" and "medication stopped" discrepancies were so few that the median remained unchanged at zero. This is possibly because changes are usually initiated during the stay rather than at point of discharge, and there is usually some form of documentation for such changes.

Relative to the control group, the median number of pharmacist recommendations per patient doubled in the intervention group, whereas the median number of pharmacist orders per patient was unchanged. The median proportion of pharmacist recommendations accepted was 100% in both groups, but twice the number of recommendations were made in the intervention group ($p = 0.007$). These trends matched both the Belgian and global studies.[3,6,7,14,25] Other studies have also suggested that pharmacist recommendations may help in avoiding potential medication discrepancies.[7,10]

Medications were tapered for 4.6% of patients in the control group and 6.9% of those in the intervention group ($p = 0.75$); however, the total number of discharge medications increased in both groups. The overall increase in the number of discharge medications may be explained by several factors. The current Admission MedRec process captures province-wide prescription medications, whereas most over-the-counter medications must be manually added to the patient's record and are sometimes missed. Discharge medication lists are generated from in-hospital databases and include all active over-the-counter medications, which might explain the higher number of medications upon discharge. Over-the-counter medications, such as calcium for bone health,[26] vitamin D for reducing falls risk,[26,27] and acetaminophen for osteoarthritis-related pain,[28] are often prescribed for geriatric patients. Concerted efforts to increase training regarding documentation of over-the-counter medications and to increase efforts to monitor and discontinue medications are particularly important for optimizing therapy for geriatric patients.

Relative to the control group, there was an absolute increase of 42% in provision of discharge counselling to patients in the intervention group ($p < 0.001$), and an absolute increase of 50% in contact with community pharmacies ($p < 0.001$). These actions should improve continuity of care across the health care team, patient satisfaction, and adherence with medication therapy, and ultimately should decrease medication discrepancies.[29] Pharmacist involvement may be increased by the introduction of a formal Discharge MedRec process.

The median rate of readmission was 28.8% for the control group and 21.2% for the intervention group ($p = 0.17$); however, this aspect of the analysis was not sufficiently powered to detect a significant difference had it been present. Many factors can affect readmission rates, including medication discrepancies, but also severity of condition, comorbid conditions, race, economic status, age, and previous hospital admissions.[30] A larger study with multivariate analysis specifically designed to examine readmission rates as a result of Discharge MedRec (i.e., preventing and resolving medication discrepancies) might show a statistically significant difference. Sebaaly and others[11] suggested that 30-day readmission rates dropped 2% as a result of Discharge MedRec, and they predicted that the decrease in readmission rates due to pharmacist interventions would result in significant cost savings.

Further cost savings could be achieved with the inclusion of pharmacy technicians in the MedRec process. The basis for any good MedRec process is a best possible medication history, and there is a clear role for pharmacy technicians in obtaining best possible medication histories.[12,31] Depending on the jurisdiction, pharmacy technicians may have other roles; however, in our area, the current scope of practice of pharmacy technicians limits their clinical involvement to taking medication histories and clerical functions such as preparation of dosing calendars and sending faxes to community pharmacies.

The major strengths of this study include its large sample size, with a combined total of 372 patients followed during the entire study period. Multiple aspects of pharmacist involvement were examined, and a detailed analysis of pharmacist recommendations and orders was performed. However, the study also had some potential limitations. The control and intervention phases of the study ran consecutively, not simultaneously. Medication discrepancies identified in hospital were not rated in terms of their potential to cause harm. Comprehensive postdischarge follow-up was not conducted. At times, language posed a significant communication barrier between the pharmacist and the patient, although efforts were made to enhance communication, either by using translators or by speaking to a patient's community pharmacy or caregivers. We were unable to analyze characteristics of the minority of patients who left against medical advice or patients who were discharged from the ward before pharmacist work-up. Opportunities for future research include adverse events analysis, determination of patient satisfaction and patients' adherence to medication therapy plans after discharge, and involvement of pharmacy technicians in MedRec.

At the patient level, postdischarge adverse events could be examined in relation to high-risk medication classes and geriatric prescribing guidelines, such as the Beers criteria. Patient satisfaction could be assessed to inform MedRec processes. At the site level, time-and-motion studies and per-patient cost analyses before and after implementation of MedRec could be used to plan and evaluate Discharge MedRec. At the health authority level, multiple sites could attempt the same pilot study to determine practicality.

CONCLUSION

A pharmacist-led Discharge MedRec service was successful in decreasing discrepancies, providing more documented and accepted recommendations, and improving discharge planning. In light of the positive results of this pilot study and subsequent requests from physicians, additional pharmacist staffing has remained on the ACE unit, and work is under way to expand Discharge MedRec to high-risk patients on other wards.

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Leadership Succession Preparedness and Sense of Urgency in Canadian Hospital Pharmacy

Zack Dumont, Neil J MacKinnon, William Mueller, Kelly Babcock, and Jenelle Sobotka

ABSTRACT

Background: Leadership turnover is unavoidable in all organizations, including hospital pharmacy departments. Succession planning can promote organizational stability, among other benefits.

Objectives: To gather a contemporary, nationwide measure of the level of preparedness for department leadership succession and to gain related insight from a variety of pharmacy leaders.

Methods: This study was an environmental scan of Canadian hospital pharmacy leaders. An online survey was conducted to identify the current rate of succession planning; to describe existing succession plans; to determine the perceived need for succession planning; and to describe strategies for, barriers to, and facilitators of succession planning.

Results: Eighty-three responses were received. Thirteen respondents (16%) reported that their hospital pharmacy departments had a succession plan, and 13 (16%) of individuals had known successors. Most respondents (64/75 [85%]) perceived succession plans to be rare or nonexistent across Canada. However, 72% (54/75) felt that succession planning was needed for their own leadership position. The most common barriers to succession planning were a lack of formal structure or tools, lack of plan implementation, unionization, and lack of career ladder positions. Select facilitators to succession planning identified by respondents were having a strong existing leadership and having an abundant pool of capable successors.

Conclusions: Most Canadian hospital pharmacy departments and individual leaders represented in this survey were not prepared with succession plans. A collective effort to proactively enact succession planning in Canadian hospital pharmacy departments would have multiple benefits for existing and aspiring leaders and, ultimately, the profession as a whole.

Keywords: leadership, management, succession, human resources, competency

RÉSUMÉ

Contexte : Tout organisme, y compris les services de pharmacie d'hôpitaux, fait face au renouvellement inévitable de sa direction. La planification de la relève peut, entre autres avantages, favoriser la stabilité organisationnelle.

Objectifs : Brosser un portrait national et actuel de la capacité des services de pharmacie de faire face au renouvellement de leur direction et obtenir le point de vue de différents leaders en pharmacie sur le sujet.

Méthodes : La présente étude est une analyse du contexte des leaders en pharmacie hospitalière du Canada. Un sondage en ligne a permis de déterminer le degré actuel de planification de la relève, de décrire les plans de relève mis en place, de déterminer dans quelle mesure une planification de la relève est nécessaire et de décrire les stratégies à adopter pour mener une planification de la relève ainsi que les éléments y faisant obstacle ou la facilitant.

Résultats : Les investigateurs ont reçu 83 réponses. Treize répondants (16 %) ont indiqué que les services de pharmacie de leur hôpital possédaient un plan de relève et tous les 13 (16 %) connaissaient les successeurs. La plupart des répondants (64/75 [85 %]) croyaient que les plans de relève étaient rares, voire inexistants, au Canada. Cependant, 72 % (54/75) estimaient que leur poste de direction nécessitait une planification de la relève. Les obstacles à la planification de la relève le plus souvent évoqués étaient : l'absence de structure ou d'outils formels, l'absence de mise en œuvre d'un plan, la syndicalisation et le manque de postes offrant des possibilités d'avancement. Parmi les éléments facilitant la planification de la relève, les répondants ont mentionné : la présence d'un leadership fort et l'accès à un important bassin de candidats compétents.

Conclusions : La plupart des services de pharmacie d'hôpitaux canadiens et des dirigeants représentés dans le sondage n'étaient pas en mesure de s'appuyer sur un plan de relève. Un travail collectif de mise en œuvre proactive d'une planification de la relève dans les services de pharmacie d'hôpitaux canadiens aurait de multiples avantages pour les dirigeants en place et ceux appelés à le devenir et, ultimement, pour la profession dans son ensemble.

Mots clés : leadership, direction, succession, ressources humaines, compétence

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INTRODUCTION

The CSHP position statements on pharmacy practice in hospitals and other collaborative health care settings guide pharmacy departments to encourage lifelong learning in the provision of direct patient care, the refinement of personal practice skills, and the development of leadership skills.[1] Leadership development is carried out in many ways, including teaching, preceptorship, coaching, and mentoring. In question, however, is the degree of emphasis placed on truly "passing the torch" from one hospital pharmacist to another, through a formal succession plan. Because turnover in leadership can be unpredictable and no less unavoidable,[2] broadly applicable advantages can be realized by having a succession plan, which has been described as "a deliberate process designed to promote organizational stability during changes in leadership".[3]

Maintaining effective organizational performance, retaining knowledge assets,[3] and making transitions easier for the incoming leaders are only a few of the benefits of succession planning. In a retrospective analysis (not specific to pharmacy) published in 2011, Bidwell found that internally hired recruits performed better and were less likely to exhibit turnover than external recruits.[4] Yet other research suggests that many businesses and corporations are not prepared with a succession plan for the CEO position,[5,6] let alone other positions. As noted by the American Society of Health-System Pharmacists' Statement on Leadership as a Professional Obligation, "Leadership is a professional obligation of all pharmacists and not the exclusive responsibility of pharmacists who hold formal leadership roles or titles."[7] Given that leadership sets the culture and expectations for the rest of the organization, it may be surmised that key positions, from "the top" to the front line, are all vulnerable to the same lack of succession preparedness.

The pharmacy profession is not protected from these potential deficiencies. In a prospective study published in 2013, White and Enright found that of the approximately 75% of managers or directors in US hospital pharmacies who planned to leave their positions within 10 years, fewer than half had a succession plan.[8] Furthermore, only 17% of these leaders felt they had someone who could fill vacant leadership positions within 2 months. In Canada, a 2007 leadership survey conducted by Musing and others[9] determined that only 24 (17.9%) of 134 respondents had a succession plan in place or in development. Shortly thereafter, a 2008 report by the Canadian Society of Hospital Pharmacists (CSHP) Hospital Pharmacy Management Task Force stated that "changing management roles, the appointment of nonpharmacist managers, and ongoing vacancies in formal leadership positions" corroborated the lack of preparation for succession planning, and pinpointed a looming leadership gap.[10] The report went on to explain that 20% to 40% of pharmacists holding manager-type positions at that time were projected to retire within 10 to 15 years.[10] With an aging workforce,[11] generational changes,[10] shifting public and stakeholder demands, increasing requirements for accountability and transparency, and a long-standing lack of formal leadership training or emphasis,[10] developing a succession plan had never been more important.

Performed about 10 years after the survey by Musing and others[9] and the report of the CSHP Task Force,[10] the purpose of this 2018 study was to gather a contemporary nationwide measure of the level of preparedness for pharmacy department leadership succession and to gain related insight from a variety of pharmacy leaders. The specific objectives were to identify the current rate of succession planning; to describe existing succession plans; to determine the perceived need for succession planning; and to describe strategies for, barriers to, and facilitators of succession planning.

METHODS

This study was a prospective environmental scan of Canadian hospital pharmacy leaders. There were 2 main components: telephone interviews followed by a survey. A preliminary set of telephone interview and survey questions was adapted by the research team (Z.D., N.J.M., W.M., and K.B.) from an earlier study.[12] The principal investigator (Z.D.) conducted telephone interviews with diverse leaders such as CSHP board members, pharmacy association leaders, directors of pharmacy, and new practitioners. The aim was to seek opinions and to help refine the survey, which was then carried out online, as described below. The study was approved by the University of Cincinnati Institutional Review Board.

Telephone Interviews

The interview participants, who were identified through non-probabilistic purposive sampling,[13] were targeted to encompass a diverse spectrum of demographic characteristics, backgrounds, and experience. Potential participants were contacted by e-mail and asked to sign a consent form. At the beginning of their interview, participants were presented with a synopsis of the research project, the purpose of the interview, and their roles and responsibilities as participants in the interview component of the study. The discussion covered the existence or absence of succession plans and factors used for identifying candidates, and participants were asked to consider the draft survey questions and to propose new questions. The interview questions are available in Appendix 1 (https://www.cjhp-online.ca/index.php/cjhp/issue/view/189/showToc). The sessions were audiorecorded and transcribed, and the transcripts were provided to participants upon request.

After the telephone interviews, the research team reviewed the findings to identify themes and incorporated participants' suggestions and comments into the survey.

Survey

The survey instrument was pilot tested by 3 pharmacists in leadership positions in hospital pharmacy who were not otherwise involved in this study. The testers were directed to provide feedback specifically related to survey logic, terminology, and instructions requiring clarification. The survey invitation and questions were revised before launch on the basis of feedback provided. The final survey, comprising 22 questions, was conducted with the online survey tool REDCap (https://www.project-redcap.org). One question was an ice-breaker regarding leadership, 15 of the questions were related specifically to succession planning, 5 questions were used to collect demographic characteristics such as location, facility type, and hospital size, and the last question was a call to action to forward the survey to other potential participants. The survey questions related to leadership and succession planning are available in Appendix 2 (https://www.cjhp-online.ca/index.php/cjhp/issue/view/189/showToc).

Once the survey was under way, participant recruitment was by nonprobabilistic, convenience, multiframe, and network sampling of Canadian hospital pharmacist leaders,[13] specifically those who held a leadership position or considered their role to be key to the organization. This definition of leadership was used to ensure inclusion of both formal and informal leaders, independent of official titles or designations.

Participants were given 2 weeks to complete the survey (March 12 to March 26, 2018). Completion of the survey was interpreted as provision of consent to participate. In preparation for launch of the survey, an e-mail invitation, which included a link to the online survey, was sent by the principal investigator (Z.D.) to the administrator of the CSHP Pharmacy Specialty Networks (PSNs) and the CSHP's publications administrator.[14] The PSNs are web-, app-, and e-mail-based communication networks for CSHP members. The CSHP employee responsible for PSN administration distributed the invitation to the members of 2 PSNs: Clinical Practice Leaders and Hospital Pharmacy Management.[15] On days 5 and 12, the publications administrator distributed the survey invitation in the regularly scheduled weekly CSHP newsletter (the *eBulletin*), which is sent to all members and supporters.[16] Reminder PSN and newsletter notifications were sent by CSHP staff at the midway mark (i.e., 1 week after the survey opened and before the survey closed). Also at the midpoint, the newsletter and survey link were forwarded by the principal investigator to the president of each of the 9 provincial CSHP branches and the equivalent representative from the affiliate Association des pharmaciens des établissements de santé du Québec, requesting that the survey invitation be shared with pharmacy directors, managers, and branch council members.

Data Analysis

Data from the survey are descriptive and were evaluated using Microsoft Excel. When the response option of "other" was selected, the response was categorized as "other", and free-text comments were aggregated.

RESULTS

Telephone Interviews

Interviews were completed (mean duration 32 min) with 8 participants from the CSHP board and branch councils: 2 CSHP staff members, 3 executive officers, 2 branch presidents, and 1 branch delegate. Of the 8 participants, 6 were women and 2 were men. One participant had less than 10 years of pharmacy experience, and the others had 10 years or more. Themes extracted from the telephone interviews are listed in Box 1. Barriers identified by interview participants were incorporated into the survey.

Survey Distribution and Respondents

The survey invitation was sent to the 168 members of the Clinical Practice Leaders PSN and the 130 members of the Hospital Pharmacy Management PSN.[17] The e-mail messages containing the *eBulletin* newsletter were received by 2983 members and supporters, of whom 1086 opened the first e-mail and 28 clicked on the link to the survey invitation; the second newsletter was opened by 1027 recipients and the survey link clicked 12 times (O. Chrzanowska, Web Administrator, CSHP, personal communication by e-mail, March 27, 2018). An additional 115 pharmacists were reported to have received the invitation through forwarding by initial survey respondents.

A total of 83 survey responses were received. Given the potential overlap between the PSNs, as well as overlap with newsletter and forwarding recipients, a denominator could not be determined and a response rate was therefore not calculated. The demographic characteristics of survey respondents are presented in Table 1.

Box 1. Succession Planning Themes Identified in Telephone Interviews (*n* = 8 Respondents)

- Clinical skill and experience of ideal successors was emphasized; commercial or business acumen was de-emphasized
- Hospital pharmacy leadership requires some unique attributes: systems-thinking, ability to manage outside of the profession or areas of expertise (e.g., pharmacist as manager of technicians; clinicians as managers of distribution staff), ability to navigate rapid change (e.g., changing scopes of practice, therapeutic developments)
- Leadership competencies (of candidates) are most critical in selecting a successor
- Leadership experience of the successor is important (in selection process), but not critical; many pharmacists have suitable experience
- Positions conducive to succession planning are not confined to the top positions, such as the department head
- Succession planning is of high importance
- Succession planning is the responsibility of the current pharmacy leaders; human resources' role is to support and provide framework

Table 1. Demographic Characteristics of Survey Respondents

Characteristic	No. (%) of Respondents*
Age, years	*n* = 71
Mean (range)	45 (27–65)
< 36	18 (25)
36–45	20 (28)
46–55	18 (25)
≥ 56	15 (21)
Gender	*n* = 75
Female	50 (67)
Male	23 (31)
Other	1 (1)
Prefer not to say	1 (1)
Location of current employment	*n* = 73
Western Canada and territories	32 (44)
Central Canada	17 (23)
Atlantic Canada	24 (33)
Current job title	*n* = 75
Director or similar (e.g., Chief of Pharmacy, Executive Director)	21 (28)
Manager	17 (23)
Clinical Coordinator/Supervisor or similar title (e.g., Senior Pharmacist)	16 (21)
Staff Pharmacist	18 (24)
Other	3 (4)
Type of facility	*n* = 75
Community hospital	24 (32)
Teaching hospital	39 (52)
Outpatient health system setting (e.g., ambulatory clinic)	1 (1)
Long-term care facility	1 (1)
Other	10 (13)
Hospital size (no. of beds)	*n* = 62
< 50	3 (5)
50–249	17 (27)
250–499	28 (45)
≥ 500	14 (23)

*Except where indicated otherwise.

Succession Planning

Of the 83 respondents, 13 (16%) reported that their organizations had a succession planning program in place, 52 (63%) reported no program, 17 (20%) did not know whether a program existed, and 1 person did not answer the question. With respect to the perceived prevalence of succession plans in hospital pharmacy departments across Canada (*n* = 75 respondents), 64 respondents (85%) were of the opinion that such programs were somewhat rare to never in place, 5 (7%) had a neutral opinion, 6 (8%) thought such programs were somewhat common, and none responded that programs were common or always in place.

Eight respondents (11%) stated that they were currently an identified successor for another position (*n* = 75), 45 (60%) were not identified as a successor, and 22 (29%) did not know their status in this regard. When asked whether they had identified a successor for their current position (*n* = 75), 12 (16%) responded "yes" and 63 (84%) responded "no". Four respondents reported that they had arrived at their current position via a succession plan (*n* = 74), another 66 (89%) reported not being in their current position as a result of a succession plan, and 4 did not know.

Of the 13 respondents who reported that succession planning programs were in place within their respective organizations, the programs were regarded as mandatory in 3 cases; otherwise, 5 reported voluntary programs, 3 did not know whether their program was mandatory, and the remainder did not respond to the question. In all 13 cases (100%), oversight of the existing program was internal to the pharmacy department.

The level of agreement and disagreement with statements about the need for a succession plan for specified positions, such as staff pharmacist and manager, was variable (see Figure 1). When asked whether a successor was needed for the respondent's current position (*n* = 75), 54 (72%) responded "yes", 6 (8%) did not think it was necessary, and 15 (20%) did not know.

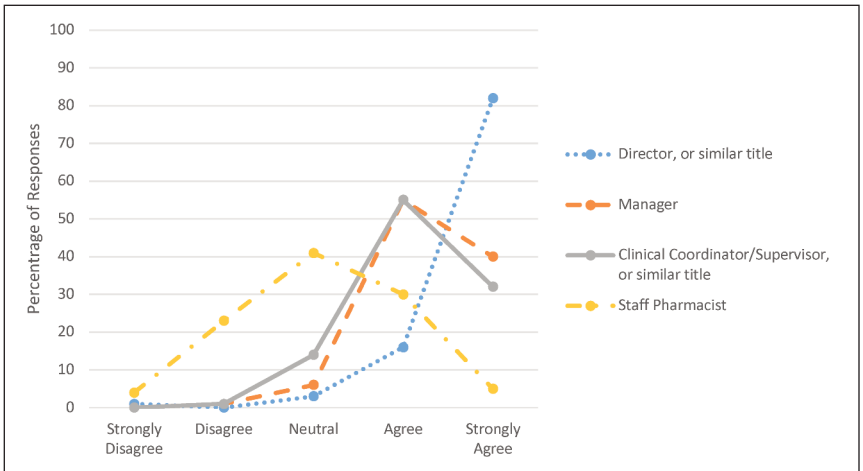

Figure 1. Survey responses regarding respondents' level of agreement with statements about the need for a succession plan for certain types of positions (*n* = 82).

Table 2. Barriers to Succession Planning in Hospital Pharmacy (*n* = 83 Respondents)

Barrier	No. of Responses*
Lack of formal planning structure/tools	63
Unionized environment, whereby seniority is often prioritized over performance	46
Lack of succession plan implementation	45
Lack of career ladder positions	44
Uncertainty of future organizational structure	35
Lack of opportunities to assess or develop competencies (i.e., leadership competencies) in pool of potential successors	32
Cursory approach to formal succession plans	25
Concerns that a developing successor will leave	14
Factors external to the workplace (e.g., family/parental leave)	12
Other†	6

*Respondents were asked to select all that applied.
†Examples of responses: "potential candidates are not interested in leadership and would prefer staying in their current roles", "lack of resources to develop and/or maintain leadership competencies", "lack of time to implement a succession plan".

Box 2. Facilitators of Succession Planning in Hospital Pharmacy (*n* = 51 Respondents)*

- Availability of candidates with desire to lead
- Collective sense of urgency (e.g., early identification of impending retirements) and acceptance of the issue at hand
- Competent existing leadership (e.g., willing to share responsibilities, vision)
- Flexibility in existing roles (to accommodate leadership development opportunities)
- Formal and mandatory succession plans
- Leadership competency assessment (e.g., recognition that leading projects is not equivalent to leading people)
- Mentorship, coaching, in-house and external leadership training and development (e.g., residency programs, PharmD rotations)
- More entry-level, career ladder positions; more mixed positions with leadership and clinical responsibilities
- Opportunities for staff to demonstrate leadership skills (e.g., committee involvement)
- Residency and internship programs for hospital practice
- Techniques for identifying potential candidates
- Top–down (including external to pharmacy) direction and support to implement plans

*Respondents provided answers in free text (no prespecified list).

Regarding oversight of a succession planning program, the majority (69 respondents) felt that the pharmacy department should have primary responsibility, with the human resources department supporting the process.

When asked to assess the value of leadership experience (among potential successors) on a scale from 1 to 6, where 1 = not required and 6 = required (*n* = 82), 41 respondents (50%) gave a score of 5 or 6, 39 respondents (48%) gave a score of 3 or 4, and 2 respondents (2%) gave a score of 1 or 2.

When asked to rank the level of importance of the following factors that may be used in selecting a successor, collated responses were (in order from most to least important) leadership competency, attitude, existing/potential friendship, work ethic, political connection, and clinical competence.

Participants were asked to identify the main barriers to succession planning by selecting from the list developed through telephone interviews. Lack of formal structure or tools for planning was the most frequently identified response (Table 2).

Participants were also asked, by means of an open-ended question, to identify facilitators or enablers of succession planning. Fifty-one respondents provided input on this question, and the aggregated results are presented in Box 2.

DISCUSSION

This study sought to gather data for a contemporary measure of the level of preparedness for leadership succession in Canadian hospital pharmacy departments and to gain related insight from current leaders. The responses showed a scarcity of succession plans, with only 16% of departments having a succession planning program, only 16% of individuals having known successors, and most (85%) reporting their perception that succession plans are rare or nonexistent across Canada. Furthermore, most respondents felt that succession planning is needed, notably demonstrated by 72% stating that their position needed a successor, and most reporting that formal and informal leadership positions were in need of successors. To our knowledge, this is the first time that discordance between the level of preparedness and the perceived need and responsibility for succession planning has been explicitly characterized. Responses broadly conveyed the perception that succession planning for the pharmacy department is the pharmacy profession's responsibility; human resources departments should not lead, but rather should assist and provide support. The most common barriers to succession planning were a lack of formal structure or tools, lack of plan implementation, unionization, and lack of career ladder positions. Facilitators to succession planning were reported as strong existing leadership skills (e.g., good delegation, vision) and an abundant pool of capable successors.

The lack of preparedness for leadership succession has been a known issue in Canadian hospital pharmacy for more than a decade. The 2007 leadership survey found that only 18% of hospital pharmacies had a succession plan.[9] The subsequent CSHP Task Force report, published in 2008, recommended establishment of formal succession plans,[10] but the results of the current survey study suggest that this recommendation has not been heeded in the years since.

The results of the current study also suggest that Canadian hospital pharmacy leaders today believe that the gap in succession planning needs to be addressed; this study may thus serve as a critical starting point in this effort.

Once succession planning programs are in place, a number of positive effects can be realized. Consciously or unconsciously

aspiring leaders may be motivated to become identified as successors, departments and individuals could conduct regular leadership assessments and inventories,[18] and current leaders could "share their load" with leadership aspirants, which would be mutually beneficial to themselves and to the development of their successors.

The limitations of this study are worth noting. First, a French version was not developed and responses were therefore limited to English-speaking participants. Respondents were not asked to confirm that they were indeed Canadian hospital pharmacists, and no strategies were used to prevent multiple responses from the same person. Moreover, the subjective nature of responses, during both the telephone interviews and the survey, may have limited the representativeness. The risk of selection bias cannot be ruled out. Because CSHP members were the only "targets" for direct invitation, responses may have come from those most interested in hospital pharmacy and the preservation of its leadership. Lastly, specific emphasis on sample size and power was not required, because no comparisons were done and the results are reported descriptively. However, this limited our ability to test for saturation of themes. Given the inability to calculate the number of people who received the invitation, it is challenging to determine whether the number of responses was expected and capable of characterizing hospital pharmacy leaders. What is known is that 4.5% of hospital pharmacists and technicians who responded to the 2013/14 Hospital Pharmacy in Canada Survey self-identified as managers.[19] In the context of the approximately 2800 CSHP members at the time of the survey, this proportion would by represented by about 126 potential respondents, and the 83 responses to the survey would equate to a response rate of about 64%. However, a denominator of 126 should be used with caution: it may be an overestimation, given that technician managers were included in the 4.5% value noted above, or it may be an underestimation, given that the survey invitation was extended to anyone who considered their role key to the organization, without necessarily holding a formal leadership title such as "manager". The response rate may be further validated by another CSHP member survey that was completed only a few weeks prior to ours, which was open to all CSHP members and which received 116 responses (C. Lyder, Director of Members and Programs, CSHP, verbal communication, April 5, 2018).

Countering the impact of these limitations were certain elements of the study design; in particular, the survey was based on previously tested questions[12] and was tested in both the interview and pilot phases. In addition, the survey design included a mix of closed-ended and open-ended questions, with space available for free-text comments or expansion of more restricted responses.

The lack of succession planning identified in this study must be addressed with a sense of urgency by individual pharmacists, current leaders, and the profession at large. We therefore recommend a collectively focused effort centred on succession planning. Our approach to recommendations differs from the 2008 Task Force Report,[10] which contained a substantial number of high-level recommendations (n = 23), only a few of which have subsequently been enacted or tracked. Given the barriers and facilitators shared by respondents to the current survey, a worthy endeavour would be development of a national pharmacists' toolkit for succession planning. This toolkit could include fundamental information on how to start succession planning for an individual position. It could also include strategies to overcome barriers, such as gaining control over union-imposed limitations and developing leaders in a context of limited resources. Furthermore, a collective commitment to mandate succession plans within pharmacy departments would ensure that the profession is being proactive, rather than reactive to external forces. Lastly, it is recommended that the level of preparedness for leadership succession be measured regularly, perhaps through the "Human Resources" section of the Hospital Pharmacy in Canada Survey.

CONCLUSION

Most departments and individual leaders represented in this study were not prepared with succession plans, yet most felt that such planning is needed. Furthermore, the general opinion of respondents was that existing pharmacy leadership is responsible for addressing the discordance. A collective effort to proactively enact succession planning programs in Canadian hospital pharmacy departments would offer multiple benefits to existing and aspiring leaders and, ultimately, the profession as a whole.

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ORIGINAL RESEARCH

Survey of Therapeutic Drug Monitoring Practices in Pediatric Health Care Programs across Canada

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ABSTRACT

Background: Therapeutic drug monitoring (TDM) is helpful in situations where a drug has a narrow therapeutic index, a drug dosage does not reliably predict serum concentration, or a serum drug concentration has surrogate value (i.e., is reflective of clinical outcomes). TDM is especially important for the pediatric population, where wide variability in pharmacokinetics and differences in body composition and drug disposition exist. Unfortunately, very little is known about pediatric TDM patterns and the factors that affect the ordering of serum drug measurements.

Objectives: To describe TDM practice for pediatric patients in Canada, to report on the drugs that are monitored and how they are monitored, and to discern factors that influence pediatric TDM patterns.

Methods: An electronic survey was developed with online survey software and was disseminated to 42 pediatric health care centres in Canada over the period January to March 2016.

Results: Of the 42 sites invited to participate in the survey, 20 (48%) responded. All sites reported performing TDM for pediatric patients, and the median number of drugs monitored was 18.5 (range 9–28) per site. The sites differed in terms of TDM practice (e.g., indications for TDM, types of serum drug measurements). Pharmacogenetic testing currently does not play a major role in TDM. Reported barriers to TDM practice include perceived lack of clinical value for certain drugs, limited access to analytical testing, and delayed return of test results.

Conclusions: TDM practice is widespread in Canada. To better utilize TDM for clinical practice, future efforts can be aimed toward increasing awareness of the clinical value of TDM and improving the timeliness of access to TDM results.

Keywords: therapeutic drug monitoring, pediatric, survey, Canada, hospital

RÉSUMÉ

Contexte : Le suivi thérapeutique pharmacologique est utile dans les cas où un médicament possède un indice thérapeutique étroit, si une posologie ne permet pas d'établir de façon fiable les concentrations sériques ou si les concentrations sériques d'un médicament ont une valeur de substitution (c'est-à-dire qu'elles reflètent les résultats cliniques). Le suivi thérapeutique pharmacologique est particulièrement important pour la population pédiatrique, où il existe une grande variabilité pharmacocinétique et des différences quant à la composition corporelle et au devenir des médicaments dans l'organisme. Malheureusement, on ne connaît que peu de choses à propos des habitudes de suivi thérapeutique pharmacologique de l'enfant et des facteurs qui influencent la prescription d'examens mesurant les concentrations sériques des médicaments.

Objectifs : Offrir un portrait des habitudes de suivi thérapeutique pharmacologique de la population pédiatrique au Canada, faire un compte rendu des médicaments qui nécessitent un suivi et la manière dont se déroule cette surveillance et déceler les facteurs qui influencent les habitudes de suivi thérapeutique pharmacologique de l'enfant.

Méthodes : Un sondage électronique a été mis au point à l'aide d'un logiciel de sondage en ligne puis envoyé à 42 centres de soins pédiatriques au Canada de janvier à mars 2016.

Résultats : Vingt (48 %) des 42 établissements interrogés ont répondu au sondage. Tous les établissements ont indiqué réaliser des suivis thérapeutiques pharmacologiques auprès de la population pédiatrique et le nombre médian de médicaments nécessitant une surveillance était de 18,5 (écart de 9 à 28) par établissement. Les établissements présentaient des différences en ce qui a trait aux habitudes de suivi thérapeutique pharmacologique (comme les indications pour les suivis thérapeutiques pharmacologiques et les types de mesures sériques de médicaments). À ce jour, les examens pharmacogénétiques ne jouent pas un rôle important dans le suivi thérapeutique pharmacologique. Selon les répondants, des éléments faisaient obstacle à la réalisation du suivi thérapeutique pharmacologique, notamment la croyance que certains médicaments n'ont pas de valeur clinique, l'accès limité à des tests diagnostiques et les retards dans l'obtention des résultats d'examen.

Conclusions : La réalisation du suivi thérapeutique pharmacologique est répandue au Canada. Afin de l'exercer de façon plus optimale dans le cadre de la pratique clinique, le personnel de la santé doit être davantage sensibilisé à la valeur clinique du suivi thérapeutique pharmacologique et il est nécessaire d'améliorer la rapidité d'accès aux résultats de ce suivi.

Mots clés : suivi thérapeutique pharmacologique, pédiatrie, sondage, Canada, hôpital

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INTRODUCTION

Therapeutic drug monitoring (TDM) is the clinical practice of measuring drug concentrations in the blood to optimize drug dosage regimens. It is helpful in situations where a drug has a narrow therapeutic index, a drug dosage does not reliably predict serum concentration, or a serum drug concentration has surrogate value. It may also be warranted in situations where there is large variation in pharmacokinetic parameters between different patients or within the same patient, because of differences or changes in kidney or liver function, volume status, body composition, or age. For drugs that meet the above-mentioned criteria, TDM is indicated on a clinical basis when a new regimen is started, a dosage is changed, or the serum drug concentrations are changing, either because of changes in a patient's clinical status or because interacting medications have been started or discontinued.[1]

In Canada, TDM is common practice and is recognized as being especially important for the pediatric population, because children's developmental physiology and differences in body composition lead to wide variability in pharmacokinetics, which may in turn affect the relation between dose and serum concentration. In addition to assisting with ensuring appropriate serum concentrations for effectiveness, TDM may be helpful in evaluating drug safety, as children may not be able to communicate effectively when they are experiencing adverse drug effects. However, children (especially neonates) are known to have lower total blood volumes, and blood sampling can contribute to anemia. Moreover, the relation between a drug's serum concentration and its effectiveness and safety is not well established for all medications for which TDM may be done.[2] As such, clinicians should utilize TDM only when it is clinically helpful and only in the context of clinical assessment of the patient. Indeed, there are instances when it may be more appropriate to treat the patient on the basis of clinical status rather than solely on the basis of drug concentration. For example, if a patient who is taking an antiepileptic medication is well and seizure-free, dose changes may not be warranted, even if the serum drug concentration is below or above the standard target therapeutic range for that drug. The benefit of TDM in pediatrics was reported by the Hospital for Sick Children in Toronto, Ontario, where initiation of a TDM consultation service resulted in a reduction in the percentage of supratherapeutic drug concentrations (4.25% before service initiation versus 2.25% after; $p < 0.01$).[3]

Although TDM has been reported to be beneficial in pediatric practice, its use has not been well described. To our knowledge, no study attempting to characterize TDM practice for pediatric patients in general has been published. Moreover, TDM practice in Canada is poorly described, although nationwide surveys from other countries (e.g., United States, Australia, China, Malaysia, and Saudi Arabia[4-8]) exist. In Canada, results from a recent survey aiming to characterize vancomycin TDM practice for pediatric patients revealed significant variations among pediatric hospitals,[3] which raises the possibility of wide variations in general pediatric TDM practice.

The purpose of this study was to describe current pediatric TDM practice in Canada. Specifically, this study aimed to describe what drugs are being monitored and how they are being monitored. Secondarily, this study also aimed to investigate whether other factors (e.g., characteristics of pediatric programs, availability of laboratory testing, training of pharmacists) affected pediatric TDM practice.

METHODS

Distribution List for Survey

Survey participants were clinical coordinators, pharmacy managers, or their delegates, representing Canadian health care centres identified through the Canadian Association of Paediatric Health Centres and investigator contacts. Each health care centre was first contacted by telephone to determine whether it fit the criteria of serving pediatric patients (age 0–18 years) and performing TDM (i.e., ordering measurement of serum drug concentrations). If both criteria were met, an invitation to participate in the survey was sent by e-mail. Participants were asked to disclose the name of the site for which they were responding, to control for instances of multiple responses from a single site (in which case their responses were to be compared and averaged). However, the data were de-identified and aggregated for analysis.

Survey

An English-language survey was developed using the online survey software FluidSurveys (Chide it, Inc) (see Appendix 1, available from https://www.cjhp-online.ca/index.php/cjhp/issue/view/189/showToc). Face validity was determined by a clinical pharmacist who was not involved in the study but who had expertise in both survey methodology and TDM. Following receipt of approval from the institutional ethics review board, the survey was distributed electronically to participants on the distribution list. The online survey was available for completion from January 12 to March 8, 2016. The survey consisted of 2 parts. The first part contained questions relating to general TDM practice, including characteristics of the responding institution, pharmacy involvement in TDM, types of drugs monitored, barriers to TDM, indications for TDM, types of drug levels measured, and genotypic testing for TDM. The questions included in the survey were based on existing literature.[4-8] Specific drugs listed in the survey were based on previous studies[4-8] and TDM lists from our institutional chemistry laboratory. Although genotypic testing is not routinely performed for TDM, the survey included a question about pharmacogenomics, in light of expanding developments in gene research and the increasing availability of genotypic testing that could influence future TDM. The second

part of the survey asked questions about the total number of drug serum measurements ordered per site in a typical month, as well as the location where TDM analytical tests were done. During the 2-month response period, a total of 3 reminders were sent, at 2-week intervals. No incentives were offered for completing this survey.

Participants were not required to complete both parts of the survey, but responses that were less than 50% complete were excluded from data analysis.

Data Analysis

Statistical analysis was performed with the IBM SPSS Statistics Premium GradPack program (version 22.0). Continuous outcomes based on 2 comparators (e.g., stand-alone pediatric hospital versus pediatric ward/service within an adult centre, teaching hospital versus nonteaching hospital, pharmacists able or unable to independently order serum drug measurements) were analyzed using the Student *t* test if parametric or the Mann–Whitney *U* test if nonparametric. For outcomes with multiple (> 2) comparators (e.g., pharmacy model: drug distribution centred, clinical practice centred, separate distribution and clinical practice, integrated distribution and clinical practice), analysis of variance was used when the outcomes were parametric, and the Kruskal–Wallis statistic when the outcomes were nonparametric. Linear regression analysis was performed to investigate whether increasing pharmacy involvement, pharmacist education, number of beds in the hospital, or availability of on-site TDM testing correlated with higher number of drugs monitored per site. Pharmacy involvement was measured as the summative number of all pharmacist-related TDM activities performed at the institution, specifically, ordering measurement of drug levels, interpreting results and modifying drug therapy accordingly, documenting TDM intervention in patient charts, or other. Each activity was weighted equally. Pharmacist education was measured as the summative number of all TDM training opportunities at each site, specifically, entry-to-practice degree curriculum, residency training curriculum, education modules "on the job", on-the-spot learning, or other. Each training opportunity was weighted equally.

RESULTS

Of 45 sites contacted initially, a total of 42 sites met both criteria, and 47 e-mail contacts were received from potential participants. Forty-seven surveys were then distributed to the 42 sites by email. Twenty-two survey responses were received, but 2 of these did not meet the minimum 50% completion criterion and thus were excluded (survey completion rate 91%). No site reported more than once, so averaging of results was not required. Ultimately, 20 responses were used for data analysis (48% of all sites that met the original criteria). Seven (70%) of the 10 Canadian pediatric hospitals and 13 (41%) of the 32 pediatric/ward services in Canada participated in this survey (Table 1).

From a list of 30 drugs for which measurement of serum concentration is commonly ordered, respondents were asked to select those that were monitored at their site. Overall, the median number of drugs monitored per site was 18.5 (range 9–28). For the 7 pediatric hospitals, the median number of drugs monitored was 19 (range 16–28), and for pediatric wards within adult centres the median was 18 (range 9–25). The most commonly monitored drugs (i.e., TDM reported by ≥ 80% of sites) were antibiotics (aminoglycosides, vancomycin), antiepileptics (phenobarbital, phenytoin, carbamazepine, valproic acid), lithium, immunosuppressants (cyclosporine, tacrolimus), digoxin, and theophylline/aminophylline (Table 2). Unfortunately, only 3 sites submitted data for the total number of serum drug measurements ordered at their site in a typical month (for part II of the study), which was insufficient for any meaningful interpretation.

Respondents were asked to select from a list of 6 potential barriers to TDM for the medications not monitored at their sites. The most common reasons for not monitoring certain medications (from the list of 30 medications included in the survey) were perceived lack of clinical value, poor access to analytical tests, and time delay to receipt of test results (Table 3).

For the commonly monitored drugs and drug classes (e.g., aminoglycosides, vancomycin, antiepileptics, and immunosuppressants), the indications for ordering serum drug measurements are listed in Table 4. The most common reasons reported were clinical changes to a patient's status, changes to a patient's renal or hepatic function, or initiation of the medication.

The reported timing of sampling for measurement of serum drug concentrations, relative to dose administration, is presented in Table 5. For a substantial proportion of responses, the timing of sampling was reported as "random" or "other", which included responses such as "8hr post dose using Hartford Nomogram", "3hr and 6hr post dose levels (routine)" for aminoglycosides (extended), "post-load level for patients in status epilepticus" for antiepileptics, and area under the curve (AUC) for immunosuppressants.

Of the factors determining whether TDM was performed (Table 6), availability of on-site analytical testing was the only one that was statistically significant ($R^2 = 0.683$, $p < 0.001$).

Of the 20 sites that responded to the survey, 6 sites (30%) reported performing pharmacogenetic testing, but such testing was not part of TDM at any of these sites. Only 3 of the 6 sites that reported pharmacogenetic testing provided examples of the tests performed. All 3 of these sites performed genetic testing for thiopurine methyltransferase before initiation of a thiopurine drug; in addition, one site reported testing of the HLA-B*1502 allele (for carbamazepine) and HLA-B*5701 (for abacavir). Two sites indicated that they were in the process of improving the availability of these tests for their sites.

Table 1. Characteristics of Canadian Hospitals Responding to a Survey of Therapeutic Drug Monitoring

Characteristic		No. (%) of Respondents* (*n* = 20)
Province		
British Columbia		4 (20)
Alberta		3 (15)
Saskatchewan		1 (5)
Ontario		8 (40)
Quebec		2 (10)
Nova Scotia		1 (5)
Prince Edward Island		1 (5)
Pediatric setting		
Pediatric hospital		7 (35)
Pediatric ward/service		13 (65)
University affiliation		
Yes		18 (90)
No		2 (10)
Hospital size	**Total Beds†**	**Pediatric beds‡**
< 50 beds	0	8
50–200 beds	4	9
201–500 beds	11	3
> 500 beds	4	0
Unknown	1	0
No. of beds (median and IQR)	425 (230–450)	115 (22–161)

IQR = interquartile range.
*Except where indicated otherwise.
†Data in this column represent the number of institutions in each category, based on the total number of beds in each insitution.
‡Data in this column represent the number of insitutions with pediatric beds in each category, whether the institution was a pediatric hospital or a hospital serving patients of any age with some dedicated pediatric beds. For example, there were no hospitals with total number of beds less than 50, but 8 hospitals had dedicated pediatric beds that numbered fewer than 50. Conversely, there were 4 hospitals with more than 500 beds in total, but no hospitals had more than 500 dedicated pediatric beds.

DISCUSSION

In this study, we found that TDM services are widely available for monitoring drug therapy in pediatric patients in health care centres across Canada, a result that is consistent with TDM surveys conducted in other countries.[4-8] All respondents indicated that they provide TDM services for pediatric patients. Our study provides data from 7 provinces across Canada, and captures information for 70% of the 10 Canadian pediatric hospitals. No information was available for Nunavut, Northwest Territories, Yukon, Manitoba, New Brunswick, or Newfoundland and Labrador.

We found that TDM was not widely available for many drugs (with TDM being reported for a median of 18.5 drugs out of 30 listed in the survey); however, those drugs that were commonly monitored were monitored by many sites (e.g., 16 of the frequently monitored drugs were monitored by ≥ 80% of all sites). It appears that the most common reasons for ordering measurement of serum drug levels were the initiation of new medications, changes in a patient's clinical status, or changes to a patient's renal or hepatic function. It is thus interesting to note that the addition or discontinuation of an interacting drug was not a common reason to order measurement of serum drug concentrations, although the effect of an interacting medication on the concentrations of other drugs may be comparable to effects related to changes in a patient's renal or hepatic function. Nevertheless, for medications that are more often used in the management of chronic diseases (e.g., antiepileptics for epilepsy, immunosuppressants for organ transplant or cancer), it does appear that the addition or discontinuation of an interacting medication prompted more frequent ordering of serum drug measurement (about 80% of the time).

The findings for the types of serum drug measurement ordered were interesting. Thirty percent of sites monitored peak concentrations for aminoglycosides (extended-interval dosing), whereas monitoring only the trough or random concentration is considered the norm.[9] We found that only 25% of sites monitored peak vancomycin concentrations, which was not surprising, considering that Delicourt and others[10] found previously that Canadian hospitals monitored peak vancomycin concentrations for only about 10% of their patients. Monitoring peak vancomycin concentration is currently controversial in pediatric pharmacotherapy practice, and there are variations in practice across the country and internationally. Finally, a remarkable proportion of responses regarding the types of serum drug

Table 2. Monitored Drugs and Location of Analytical Testing

Drug	No. (%) of Hospitals Monitoring (*n* = 20)	Test Location; % of Hospitals*				
		On Site	Within Same City	Within Province	Within Country	Outside Country
Antibiotics						
Amikacin, extended-interval dosing	17 (85)	38	31	31	0	0
Amikacin, traditional dosing	19 (95)	38	31	31	0	0
Gentamicin, extended-interval dosing	19 (95)	85	15	0	0	0
Gentamicin, traditional dosing	20 (100)	79	21	0	0	0
Tobramycin, extended-interval dosing	18 (90)	85	15	0	0	0
Tobramycin, traditional dosing	19 (95)	79	21	0	0	0
Vancomycin	20 (100)	93	7	0	0	0
Antiepileptics						
Carbamazapine	19 (95)	85	15	0	0	0
Ethosuximide	8 (40)	29	29	29	0	14
Phenobarbital	20 (100)	77	8	15	0	0
Phenytoin	20 (100)	92	8	0	0	0
Valproic acid	20 (100)	85	15	0	0	0
Antipsychotics, antidepressants						
Clozapine	7 (35)	57	29	14	0	0
Imipramine	2 (10)	20	20	60	0	0
Lithium	18 (90)	67	25	8	0	0
Immunosuppressants						
Cyclosporine	18 (90)	67	25	8	0	0
Sirolimus	11 (55)	50	25	25	0	0
Tacrolimus	16 (80)	60	30	10	0	0
Antiarrhythmics						
Digoxin	19 (95)	75	25	0	0	0
Disopyramide	3 (15)	0	17	50	17	17
Lidocaine	4 (20)	14	14	43	29	0
N-Acetylprocainamide	2 (10)	0	14	57	29	0
Procainamide	3 (15)	0	14	57	29	0
Propranolol	2 (10)	33	33	33	0	0
Quinidine	4 (20)	14	14	43	29	0
Other						
Acetaminophen	2 (10)	90	10	0	0	0
Caffeine	7 (35)	67	0	22	0	11
Methotrexate	12 (60)	80	10	10	0	0
Salicylate (acetylsalicylic acid)	6 (30)	67	33	0	0	0
Theophylline/aminophylline	17 (85)	58	33	8	0	0

*Percentages based on number of hospitals performing monitoring for each particular drug.

Table 3. Reported Barriers to Therapeutic Drug Monitoring (TDM)

Barrier	No. (%) of Hospitals (*n* = 20)
Perceived lack of clinical value	16 (80)
Poor access to analytical tests	10 (50)
Time delay to test results	8 (40)
Limited TDM operating hours	2 (10)
Lack of training	1 (5)
Technical difficulties in retrieving sufficient sample from patient	0 (0)

measurements ordered were described as "other" (e.g., up to 16% for certain drugs/drug categories). This suggests potential unique variations in practice that this survey may not have been able to fully capture.

The main reported barriers to TDM were perceived lack of clinical value for the drugs that were not monitored, followed by poor access to analytical tests and time delay to receiving test results. We were not surprised to learn that perceived lack of

clinical value was the greatest barrier to TDM (reported by 80% of respondents). Although helpful in monitoring drug efficacy and safety, TDM may be considered redundant when there are other objective, overt patient signs and symptoms or laboratory markers that can be used to monitor therapy. Clinicians are often told to treat the patient, not the levels, and this principle is reflected in the survey results. Given the low blood volumes available in children, it appears that TDM tests are not ordered except when deemed to be clinically helpful, examples of which are highlighted in Table 4 for some of the commonly monitored medications. With regard to the barrier of poor access, we also found that drugs were monitored less frequently when sites did not have on-site analytical testing available (R^2 = 0.683, p < 0.001). It is evident, then, that the availability of analytical testing is a barrier to optimal TDM practice. The results of this survey also suggest that TDM might be used more often if the timeliness of receiving test results could be improved, as the results would be more applicable to informed decision-making.

This survey study had several limitations, the main one being that certain adult centres that also serve pediatric patients may have experienced difficulty in answering the survey questions, because TDM practice may be different for pediatric and adult patients, and the survey did not specifically address these differences. However, in our analysis of potential differences between pediatric hospitals and pediatric wards in adult centres (where confounding may exist), we did not detect any significant differences (p = 0.48), although this may have been a result of the small sample size. Also, responses may vary from one pharmacist to another at the same site (depending on past work experiences, work culture, etc.), and the survey sought responses from only one pharmacist at each site. By contacting the clinical coordinator/pharmacy manager at each site, we hoped to minimize this variability and to get a general picture of TDM practices at each specific site. Finally, a majority (40%) of the data came from Ontario sites.

Table 4. Indications for Therapeutic Drug Monitoring (TDM) (n = 20)

Type of Drug	Indication for TDM; No. (%) of Respondents*									
	Initiation of Medication		Clinical Changes		Changes in Renal or Hepatic Function		Adding or Discontinuing an Interacting Medication		Does Not Monitor This Drug		Unknown	
Aminoglycosides, extended-interval dosing	15	(75)	16	(80)	17	(85)	10	(50)	1	(5)	1	(5)
Aminoglycosides, traditional dosing	17	(85)	18	(90)	18	(90)	11	(55)	1	(5)	1	(5)
Antiepileptics	16	(80)	18	(90)	13	(65)	16	(80)	0	(0)	1	(5)
Immunosuppressants	14	(70)	15	(75)	14	(70)	13	(65)	1	(5)	4	(20)
Vancomycin	17	(85)	18	(90)	18	(90)	11	(55)	0	(0)	1	(5)

*For each medication, a given institution responding to the survey could have multiple indications for performance of TDM.

Table 5. Types of Serum Drug Measurements (n = 20)

Type of Drug	Type of Measurement; No. (%) of Respondents									
	Peak		Trough		Random		Other		Unknown	
Aminoglycosides, extended-interval dosing	6	(30)	17	(85)	7	(35)	3	(15)	0	(0)
Aminoglycosides, traditional dosing	17	(85)	19	(95)	4	(20)	0	(0)	0	(0)
Antiepileptics	0	(0)	19	(95)	4	(20)	1	(5)	1	(5)
Immunosuppressants	0	(0)	15	(75)	1	(5)	3	(15)	1	(5)
Vancomycin	5	(25)	20	(100)	7	(35)	0	(0)	0	(0)

*For each medication, a given institution responding to the survey could perform multiple types of serum drug measurements.

Table 6. Factors Potentially Affecting Pediatric Therapeutic Drug Monitoring (TDM)

Factor	Statistical Test	p Value
Stand-alone pediatric hospital versus pediatric ward/ service in adult centre	Mann Whitney U	0.48
University affiliation	Mann Whitney U	0.06
Ability of pharmacist to independently order TDM	Mann Whitney U	0.52
Extent of pharmacist training	Linear regression	0.15
Pharmacy practice model	Kruskal–Wallis	0.57
Extent of pharmacist involvement	Linear regression	0.65
Number of beds	Linear regression	0.06
Availability of on-site analytical test	Linear regression	< 0.001

CONCLUSION

TDM for pediatric patients is accessible and available in many pediatric health care programs in Canada, but differences exist in terms of the types of drugs monitored, when they are monitored, and how they are monitored. Pharmacogenetic testing is not widely available to many sites and is not currently used in TDM; however, efforts to improve the availability of pharmacogenetic testing for TDM are underway at several institutions. Currently, the most important reason for not routinely monitoring certain drugs in pediatrics is perceived lack of clinical value; further investigation into the reasons for this perception may be warranted, given that the current survey was not designed to specifically address this issue. However, it is recognized that barriers to optimal TDM practice also include the availability and timeliness of TDM test results.

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Real-Life Frequency of New-Onset Thrombocytopenia during Linezolid Treatment

Nicole Giunio-Zorkin and Glen Brown

ABSTRACT

Background: Thrombocytopenia is a well-recognized adverse effect of linezolid; however, the frequency of this adverse effect during therapy has been variable across previous studies, and the associated risk factors are unclear.

Objectives: To identify the real-life frequency of new-onset thrombocytopenia due to linezolid and to determine the associated risk factors.

Methods: A retrospective observational cohort study was conducted among consecutive inpatients at a tertiary care hospital who received linezolid for a minimum of 5 days between January 2013 and August 2017. Data were extracted from electronic medical records obtained from a hospital database. Thrombocytopenia was defined as platelet count less than 100×10^9/L or a 50% reduction from baseline (i.e., before linezolid initiation). Risk factors were identified by comparing the characteristics of patients who experienced the adverse effect during linezolid therapy with those of patients who did not experience the adverse effect. Continuous data were analyzed with the *t* test and categorical data with the χ^2 test.

Results: A total of 102 patients were included (38 women, 64 men; overall mean age 50 years, standard deviation [SD] 21). The mean duration of linezolid therapy was 14 (SD 10) days. Thrombocytopenia occurred in 18 patients (17.6%). Risk factors for the development of thrombocytopenia included mean duration of therapy (22 [SD 18] days versus 12 [SD 7] days; $p = 0.023$), renal replacement therapy (17% versus 4%; $p = 0.032$), renal impairment (61% versus 32%; $p = 0.021$), and concomitant administration of unfractionated heparin (50% versus 21%; $p = 0.013$).

Conclusions: The real-life frequency of new-onset of thrombocytopenia in patients receiving linezolid for a minimum of 5 days was 17.6%. Risk factors for linezolid-induced thrombocytopenia included prolonged duration of therapy, renal impairment, and concomitant unfractionated heparin.

Keywords: linezolid, thrombocytopenia, frequency, risk factor, renal impairment

RÉSUMÉ

Contexte : La thrombopénie est une réaction indésirable bien connue, induite par le linézolide; cependant, la fréquence de cette réaction indésirable pendant le traitement hvariait d'une étude à l'autre et on ignore quels sont les facteurs de risque associés à cet antibiotique.

Objectifs : Découvrir la fréquence réelle des nouveaux cas de thrombopénie causés par le linézolide et déterminer les facteurs de risque qui lui sont associés.

Méthodes : Une étude de cohorte observationnelle rétrospective a été menée auprès de patients hospitalisés consécutivement dans un hôpital de soins tertiaires, qui ont reçu du linézolide pendant au moins cinq jours entre janvier 2013 et août 2017. Les données ont été tirées des dossiers médicaux électroniques provenant d'une base de données d'un hôpital. La thrombopénie a été définie comme un taux de plaquettes de moins de 100×10^9/L ou comme une réduction de 50 % de leur valeur initiale (c'est-à-dire, avant l'amorce du traitement au linézolide). Les chercheurs ont établi les facteurs de risque en comparant les caractéristiques des patients ayant subi la réaction indésirable pendant leur traitement au linézolide avec les caractéristiques des patients n'ayant pas subi cet effet indésirable. Les données continues ont été analysées à l'aide d'un test *t* et les données catégoriques à l'aide d'un test de χ^2.

Résultats : Au total, 102 patients ont été admis (38 femmes, 64 hommes; âge moyen de 50 ans, écart-type de 21). La durée du traitement au linézolide était de 14 jours (écart-type de 10). Dix-huit patients (17,6 %) ont souffert de thrombopénie. Parmi les facteurs de risque de thrombopénie, on comptait la durée moyenne du traitement (22 jours [écart-type de 18] contre 12 jours [écart-type de 7]; $p = 0{,}023$), le traitement de suppléance rénale (17 % contre 4 %; $p = 0{,}032$), l'insuffisance rénale (61 % contre 32 %; $p = 0{,}021$) et l'administration concomitante d'héparine non fractionnée (50 % contre 21 %; $p = 0{,}013$).

Conclusions : La fréquence réelle de nouveaux cas de thrombopénie parmi les patients recevant du linézolide pendant un minimum de 5 jours était de 17,6 %. Parmi les facteurs de risque de thrombopénie associés au linézolide, on mentionne l'allongement de la durée du traitement, l'insuffisance rénale et l'administration concomitante d'héparine non fractionnée.

Mots clés : linézolide, thrombopénie, fréquence, facteur de risque, insuffisance rénale

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INTRODUCTION

Linezolid is an oxazolidinone antibiotic with activity against drug-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*.[1] Linezolid is not usually a first-line agent because of its adverse effect profile; instead, it is reserved for situations requiring its particular spectrum of activity.[2] The toxic effects of linezolid include peripheral neuropathy, serotonin syndrome, and myelosuppression.[3] Given the landscape of rising antimicrobial resistance rates, linezolid is an important therapeutic option, and understanding the risk of toxicity will help guide clinicians in its use.[4]

The manufacturer has reported that the percentage of patients treated with linezolid who experienced thrombocytopenia in clinical trials was 2.4% (range 0.3% to 10%).[3] Interestingly, postmarketing studies have reported higher rates of linezolid-associated thrombocytopenia, ranging from 15% to 50%.[1,5-9] The onset of the thrombocytopenia has been reported to range from within 7 days of starting the drug until as long as 14 days after discontinuation.[8] The exact mechanism of linezolid-induced thrombocytopenia has not yet been elucidated. Proposed mechanisms include suppression of release of platelets from mature megakaryocytes,[10] oxidative damage of circulating platelets,[11] and immune-mediated platelet destruction.[12]

Possible risk factors for linezolid-induced thrombocytopenia identified in the literature include a higher daily weight-based dose,[1] concurrent renal insufficiency[1,8] concurrent need for hemodialysis,[8] prolonged treatment duration,[6,8,13] elevated baseline leukocyte concentration,[6] chronic liver disease,[13] previous vancomycin use,[14] low baseline leukocyte concentration,[8] and low baseline serum protein concentration.[8] In addition, higher predose (trough) concentration of linezolid in the plasma and higher values for area under the concentration–time curve (AUC) have been suggested as possible risk factors.[15,16] The association of these risk factors with linezolid-induced thrombocytopenia has varied among studies. It is important to identify risk factors for thrombocytopenia, because such risk factors would help in identifying patients at greater risk for development of this adverse effect and thus in need of increased monitoring or consideration of alternative therapy.[8] Fortunately, the thrombocytopenia is reversible upon discontinuation of the drug,[17] but the risk of bleeding may be heightened during the period of low platelet concentration.[18]

There is no consensus on the real-life frequency of new-onset linezolid-induced thrombocytopenia. The safety concerns of this side effect and the potential need for discontinuation of effective drug therapy warrant further exploration of its frequency and associated risk factors. The primary objective of this study was to determine the real-life frequency of new-onset thrombocytopenia in patients receiving linezolid for longer than 5 days. The secondary objective was to evaluate the risk factors potentially associated with linezolid-induced thrombocytopenia.

METHODS

This retrospective observational cohort study involved patients who received linezolid (intravenously or orally) for a minimum of 5 days at St. Paul's Hospital between January 2013 and August 2017. The study protocol was reviewed and approved by the Providence Healthcare Research Ethics Board. For this type of study, individual patient consent was not required.

Patients were identified from the hospital's electronic health care database, and all consecutive patients who took linezolid for a minimum of 5 days during the specified time period were screened for inclusion. Linezolid treatment days were consecutive, and each patient was included only once per admission, regardless of the number of discrete courses of linezolid therapy. Data from repeat admissions of the same patient were included in the analysis. Patients who were discharged on continuing linezolid therapy were evaluated only until the date of discharge. Patients were excluded if they had a platelet count less than 100×10^9/L at the time of linezolid initiation, a hematological disorder causing decreased platelet production or survival, bone marrow–suppressing chemotherapy within 2 weeks before linezolid, diagnosis of disseminated intravascular coagulopathy or below-normal fibrinogen concentration before or during linezolid therapy, or occurrence of hemorrhage at any site that was not caused by thrombocytopenia and that required transfusion of packed red blood cells or platelets. The target was a convenience sample size of about 100 patients.

Data were collected from patients' electronic health care records. The information collected included age; sex; weight; dose and route of administration of linezolid; duration of treatment; vancomycin therapy within the 2 weeks preceding linezolid therapy; concurrent administration of low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), or piperacillin; renal replacement therapy; and indication for linezolid. Laboratory data extracted included serum creatinine, platelet count, total protein concentration, albumin concentration, C-reactive protein (CRP) concentration, total bilirubin concentration, and international normalized ratio. The values collected for these variables included baseline values (closest to and preceding initiation of linezolid) and the most aberrant values during linezolid treatment. Patients were identified as having renal impairment if they required renal replacement therapy or had elevated serum creatinine (> 90 µmol/L for females; > 100 µmol/L for males), either at baseline or during linezolid treatment. In addition, the first platelet value that satisfied the definition of thrombocytopenia was collected, along with information about whether linezolid was stopped or the patient received a platelet transfusion. For patients with thrombocytopenia, the first normal platelet count after discontinuation of linezolid was recorded, if available. The number of days to the first thrombocytopenic platelet value, the lowest platelet value, and first normal platelet value were also recorded.

Thrombocytopenia was defined as platelet count less than 100 × 10^9/L cells or a 50% reduction from baseline. In the previous literature, definitions of thrombocytopenia have varied from a decrease in platelet count of at least 25% from baseline[19] to a decrease of greater than 75% from baseline.[20] The definition of thrombocytopenia used in this study balances the risk of missing patients with clinically relevant thrombocytopenia with the risk of including patients who had non–clinically relevant thrombocytopenia.

Results are presented as mean values (with standard deviations [SDs]) or percentages. Continuous data were analyzed with the unpaired 2-tailed t test and categorical data with the χ^2 test; *p* values less than 0.05 were considered significant.

RESULTS

A total of 102 patients (38 women and 64 men; overall mean age 50 [SD 21] years) were included in the study. The mean duration of linezolid therapy was 14 (SD 10) days. The platelet count declined from baseline sufficiently to meet the definition of thrombocytopenia in 18 patients. In 64 of the remaining 84 patients, the platelet count declined from baseline, but the reduction was insufficient to fulfill the definition of thrombocytopenia. The mean decreases in platelet concentration from baseline were 179 (SD 87) × 10^9/L (mean percentage decline 60% [SD 10%]) among patients with thrombocytopenia and 60 (SD 59) × 10^9/L (mean percentage decline 17% [SD 15%]) among patients without thrombocytopenia.

The frequency of thrombocytopenia was 17.6% (18/102). For patients with thrombocytopenia, the mean lag time to the first thrombocytopenic platelet value (relative to initiation of linezolid) was 16 (SD 12) days. The mean time to the lowest thrombocytopenic platelet value was 21 (SD 15) days. The first thrombocytopenic platelet value occurred within 14 days of initiation in 50% (9/18) of the patients. Linezolid was stopped for 61% (11/18) of the patients with thrombocytopenia, and 1 patient received a platelet transfusion. The mean time to the first normal platelet value after discontinuation of linezolid was 6 (SD 5) days, based on data for 9 patients (data were unavailable for the other 9 patients).

The characteristics of patients with and without thrombocytopenia were compared. Patients with thrombocytopenia had a significantly longer duration of treatment, and significantly higher frequencies of renal impairment, renal replacement therapy, osteomyelitis, and concurrent UFH (Table 1). In addition, the presence of elevated serum creatinine during linezolid therapy was found significantly more frequently among patients with thrombocytopenia (Table 2).

DISCUSSION

In this study, the frequency of thrombocytopenia was 17.6%, and risk factors for linezolid-induced thrombocytopenia included renal impairment, renal replacement therapy, osteomyelitis, longer duration of therapy, and concomitant UFH. Previous studies have identified renal impairment as a risk factor.[1,5,7,8,15,20-23] About 30% of linezolid administered is cleared unchanged through the kidneys, and the drug is otherwise metabolized by oxidation of the morpholine ring.[3] Metabolism of linezolid forms 2 inactive metabolites that are renally cleared.[3] In practice, the dose of linezolid is not adjusted on the basis of renal function, because the product monograph states that similar plasma concentrations of linezolid are achieved regardless of renal function.[3] However, this statement in the monograph was based on data for a single 600-mg oral dose of linezolid, and Matsumoto and others[22] have shown that patients with renal impairment have increases in linezolid trough concentrations and AUC. Higher plasma concentrations of linezolid have been identified as a risk factor for linezolid-induced thrombocytopenia.[15,22] Furthermore, Brier and others[24] showed that patients with renal impairment have higher concentrations of the 2 metabolites of linezolid. Although the mechanism of linezolid-induced thrombocytopenia is poorly understood, the accumulation of linezolid or its metabolites in patients with renal impairment might explain the higher frequency of thrombocytopenia in association with renal insufficiency.

Prolonged duration of linezolid therapy has been associated with linezolid-induced thrombocytopenia[5-8,13] Consistent with these findings, our study identified longer duration of therapy as a risk factor. Interestingly, the first thrombocytopenic platelet value occurred within 14 days of initiation in 50% of the patients. This outcome has been noted previously: in a study by Nukui and others,[15] one-half of the patients in whom thrombocytopenia occurred experienced this adverse effect within 11 days of starting linezolid. We do not feel that the thrombocytopenia in our study population was due to the initial infection that warranted linezolid therapy, because the onset of the decline in platelets occurred after a minimum of 5 days of therapy (according to the study's inclusion criteria), by which time the infection should have started resolving. We did not stratify patients in terms of early- and late-onset thrombocytopenia and were therefore unable to assess risk factors for early-onset thrombocytopenia. Notably, the platelet count declined from baseline in most of the patients in this study. It appears that linezolid is likely to cause a drop in platelets; however, the significance and timing of the drop may depend on certain risk factors. Although prolonged duration of linezolid therapy is a risk factor, thrombocytopenia may occur earlier than 14 days after initiation. Health care professionals should remain vigilant in monitoring for thrombocytopenia for the entire duration of linezolid treatment.

Thrombocytopenia occurred more frequently among patients who were receiving concomitant UFH. We included in this study patients receiving concomitant LMWH and UFH study because many hospital inpatients receive one of these agents for prophylaxis of venous thromboembolism. If we had excluded

Table 1. Characteristics of Patients with and without Thrombocytopenia

Characteristic	No. (%) of Patients*		*p* Value
	With Thrombocytopenia (*n* = 18)	Without Thrombocytopenia (*n* = 84)	
Sex, female	5 (28)	33 (39)	0.36
Age (years) (mean ± SD)	58 ± 17	49 ± 22	0.07
Weight (kg) (mean ± SD)	69 ± 16	65 ± 21	0.32
Linezolid route			
Oral	11 (61)	56 (67)	0.65
IV	2 (11)	10 (12)	0.92
Both oral and IV	5 (28)	18 (21)	0.56
Linezolid dose (mg/kg) (mean ± SD)	9.1 ± 2.1	10.1 ± 2.8	0.10
Linezolid dosage			
600 mg BID	17 (94)	82 (98)	0.47
600 mg BID to once daily	1 (6)	2 (2)	0.47
Duration of linezolid therapy (days) (mean ± SD)	22 ± 18	12 ± 7	0.023
Vancomycin within preceding 2 weeks	7 (39)	31 (37)	0.87
Concurrent medications			
LMWH	8 (44)	33 (39)	0.69
UFH	9 (50)	18 (21)	0.013
Piperacillin	3 (17)	10 (12)	0.58
Renal replacement therapy	3 (17)	3 (4)	0.032
Renal impairment	11 (61)	27 (32)	0.021
Indication for linezolid			
Intra-abdominal infection	5 (28)	9 (11)	0.056
Cystic fibrosis exacerbation	3 (17)	23 (27)	0.34
Urinary tract infection	2 (11)	19 (23)	0.27
Bacteremia of unknown origin	2 (11)	13 (15)	0.64
Pneumonia	2 (11)	5 (6)	0.43
Osteomyelitis	3 (17)	2 (2)	0.011
Skin and soft-tissue infection	1 (6)	7 (8)	0.69
Meningitis	0 (0)	1 (1)	0.64
Other	0 (0)	5 (6)	0.29

LMWH = low-molecular-weight heparin, SD = standard deviation, UFH = unfractionated heparin.
*Except where indicated otherwise.

Table 2. Laboratory Data for Patients with and without Thrombocytopenia

Variable	Group; No. (%) of Patients		*p* Value
	With Thrombocytopenia (*n* = 18)	Without Thrombocytopenia (*n* = 84)	
Abnormal value at baseline			
SCr elevated*	9/18 (50)	23/84 (27)	0.061
Platelets < 150 × 10^9/L	3/18 (17)	5/84 (6)	0.12
Albumin < 35 g/L	12/12 (100)	43/56 (77)	0.063
CRP > 3.1 mg/L	5/6 (83)	52/53 (98)	0.058
Total bilirubin > 20 µmol/L	0/15 (0)	5/65 (8)	0.27
Most aberrant value			
SCr elevated*	11/18 (61)	27/84 (32)	0.021
Platelets < 150 × 10^9/L	15/18 (83)	10/84 (12)	< 0.001
CRP > 3.1 mg/L	9/10 (90)	31/33 (94)	0.67
Total bilirubin > 20 µmol/L	2/10 (20)	2/28 (7)	0.26

CRP = C-reactive protein, SCr = serum creatinine.
*For women, elevation of SCr was defined as > 90 µmol/L; for men, elevation of SCr was defined as > 100 µmol/L.

these patients, our sample size would have been too small to allow analysis of any contributing risk factors. Previous studies assessing risk factors for linezolid-induced thrombocytopenia did not record information about concomitant use of LMWH and UFH.[1,5-9,15,20-22] It is possible that concomitant UFH is a risk factor for linezolid-induced thrombocytopenia. Conversely, this finding may be related to other factors. We cannot exclude the possibility that patients experienced heparin-induced thrombocytopenia. However, the rates of this form of thrombocytopenia would likely have been low in our study, given that previously reported rates are only up to 5% of patients receiving UFH and less than 1% of those receiving LMWH.[25] In addition, it is notable that one of the patients with thrombocytopenia had received only 2 doses of UFH. A third possibility is that this finding is related to renal impairment. UFH is used in place of LMWH for prophylaxis of venous thromboembolism in patients with renal impairment. The higher frequency of thrombocytopenia among patients receiving concomitant UFH may relate to these patients having renal impairment, which would place them at higher risk of linezolid-induced thrombocytopenia.

The frequency of thrombocytopenia was also higher among patients with osteomyelitis. This outcome may have been related to the longer duration of linezolid treatment required for this type of infection. Only 5 of the 102 patients had osteomyelitis, and it has not been noted as a risk factor in previous studies. This result is likely a chance finding.

Other reported risk factors for linezolid-induced thrombocytopenia identified by previous investigators have included elevated baseline leukocyte concentration,[6] low baseline leukocyte concentration,[8] low baseline serum protein concentration,[8] higher daily weight-based dose,[1] chronic liver disease,[13] and previous vancomycin use.[14] Because of the impact of infection on leukocyte count, changes in leukocyte concentrations were not evaluated. Data for serum protein concentration were not available for most of our patients. No difference in weight-based dose (milligrams per kilogram of body weight) was noted between the groups. Similarly, there was no difference in total bilirubin between the groups, but we did not assess patients' histories for chronic liver disease. As a result, chronic liver disease as a potential risk factor was not sufficiently assessed. The groups did not differ in terms of previous vancomycin use.

Several limitations should be considered when interpreting our results. First, the sample size was small (102 patients). Our extensive exclusion criteria limited the sample size, but were necessary to help rule out other causes of thrombocytopenia. Second, data were not available for all risk factors for all patients; for example, we were unable to analyze serum protein as a risk factor. Finally, plasma linezolid concentrations were not investigated. This study did not address the risk for further decrease in platelet concentration among patients who had thrombocytopenia at the time of linezolid initiation, nor did it consider the contribution of other potential mechanisms for a decrease in platelet concentration.

CONCLUSION

The real-life frequency of new-onset thrombocytopenia among patients receiving linezolid for a minimum of 5 days was 17.6%. Notable risk factors for linezolid-induced thrombocytopenia included renal impairment, renal replacement therapy, and prolonged duration of therapy (although some patients experienced thrombocytopenia within 14 days of treatment). Clinicians should monitor patients for linezolid-induced thrombocytopenia throughout therapy. Particular attention should be paid to patients with renal impairment.

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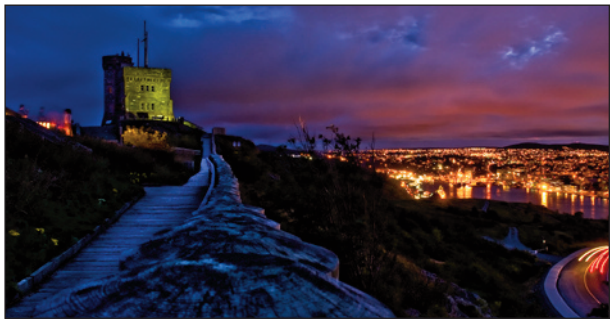
ON THE FRONT COVER



Signal Hill
St John's, Newfoundland and Labrador

Signal Hill, positioned strategically at the mouth of St John's Harbour, has been the site of many fortifications since the 17th century. On December 12, 1901, the first transatlantic wireless transmission was received at Signal Hill by Guglielmo Marconi. Today, it is a National Historic Site of Canada. Joshua Bryant took the cover photograph with a Nikon d5100 in late summer, 2013. Joshua is a Clinical Pharmacist with Northwest Telepharmacy Solutions.

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

Antiemetics for Postoperative Nausea and Vomiting in Patients Undergoing Elective Arthroplasty: Scheduled or As Needed?

Ouida Antle, Ashley Kenny, Julie Meyer, and Luciana G Macedo

ABSTRACT

Background: Postoperative nausea and vomiting (PONV) is one of the most commonly reported adverse experiences after surgery. PONV is a major risk factor for delayed patient mobilization and consequently increased length of hospital stay.

Objectives: The primary objective was to compare the effectiveness of scheduled versus as-needed administration of antiemetic for the prevention and treatment of PONV in the first 48 h after elective hip or knee arthroplasty. The secondary objective was to determine whether PONV affected mobilization on either postoperative day 0 or postoperative day 1 in each study group.

Methods: This retrospective cohort study used chart reviews for collection of patient data. PONV and mobilization were compared for patients who received antiemetics on a scheduled or as-needed basis following elective hip or knee arthroplasty performed between January and September 2016.

Results: Of the 132 patients included in the study, 65 received antiemetics on an as-needed basis and 67 had scheduled antiemetic therapy. Thirty-one (46%) of the patients in the "scheduled" group received antiemetics as intended; the others missed one or more of the scheduled doses. There was no statistical difference in PONV between treatment groups with either intention-to-treat or as-treated analysis. Furthermore, there was no statistically significant difference in mobilization, on either POD 0 or POD 1, between patients who received scheduled antiemetic and those who received antiemetic on an as-needed basis.

Conclusions: Scheduled use of antiemetics did not significantly affect PONV, nor did it positively influence mobilization in the postoperative period for patients undergoing elective arthroplasty. Further high-quality prospective studies are needed to confirm these results.

Keywords: postoperative nausea and vomiting, ondansetron, antiemetic, arthroplasty, scheduled versus as-needed therapy

RÉSUMÉ

Contexte : Les nausées et vomissements postopératoires sont parmi les réactions indésirables les plus fréquentes après une intervention chirurgicale. Elles représentent un facteur de risque important de retard de mobilisation et par conséquent de prolongation du séjour à l'hôpital.

Objectifs : L'objectif principal visait la comparaison de l'efficacité d'une administration régulière d'antiémétiques à une administration au besoin pour la prévention et le traitement des nausées et vomissements postopératoires au cours des 48 heures suivant une arthroplastie non-urgente de la hanche ou du genou. L'objectif secondaire était de déterminer si les nausées et vomissements postopératoires avaient des répercussions sur la mobilisation des patients durant la journée postopératoire 0 ou 1 dans chaque groupe à l'étude.

Méthodes : Les données de la présente étude de cohorte rétrospective proviennent des analyses de dossiers des patients. La comparaison portait sur les nausées et vomissements postopératoires et la mobilisation de patients ayant reçu des antiémétiques prescrits régulièrement ou au besoin après avoir subi une arthroplastie non-urgente de la hanche ou du genou, réalisée entre janvier et septembre 2016.

Résultats : Parmi les 132 patients admis à l'étude, 65 ont reçu des antiémétiques au besoin et 67 en ont pris régulièrement. Trente et un (46 %) patients du groupe auquel on avait prescrit une prise régulière ont reçu des antiémétiques comme prévu, les autres ont sauté une ou plusieurs doses prévues. Aucune différence statistique n'a été relevée quant aux nausées et vomissements postopératoires entre les groupes, que ce soit à l'aide d'une analyse selon l'intention de traiter ou selon le traitement reçu. De plus, il n'y avait aucune différence statistiquement significative du point de vue de la mobilisation, pour les jours postopératoires 0 et 1 entre les patients ayant pris régulièrement des antiémétiques et ceux en ayant pris au besoin.

Conclusions : L'administration régulière d'antiémétiques n'a pas eu d'effet significatif sur les nausées et vomissements postopératoires tout comme elle n'a pas influencé positivement la mobilisation au cours de la période postopératoire des patients ayant subi une arthroplastie non-urgente. De plus amples études prospectives de grande qualité sont nécessaires pour confirmer ces résultats.

Mots clés : nausées et vomissements postopératoires, ondansétron, antiémétique, arthroplastie, comparaison entre traitement régulier et traitement au besoin

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INTRODUCTION

Postoperative nausea and vomiting (PONV) is one of the most commonly reported adverse experiences after surgery. It occurs in about 30% of the general surgical population and in up to 80% of high-risk surgical patients.[1,2] PONV is a major risk factor for delayed patient mobilization and consequently increased length of hospital stay and prolonged overall recovery in hospital; it may therefore be indirectly associated with increased health care costs.

The 2014 consensus guidelines for the management of PONV,[3] compiled under the auspices of the Society for Ambulatory Anesthesia, proposed that establishing the baseline risk of PONV is of value when determining ways to reduce the risk for this adverse effect, identifying effective regimens for prophylaxis, and recommending strategies for treatment when PONV occurs.[3] The use of risk stratification for PONV is supported by the literature.[1,2,4]

The consensus guidelines suggest use of the simplified Apfel score[1] to predict a patient's risk of PONV. The Apfel score ranges from 0 to 4, with 1 point assigned to each of the following 4 independent risk factors: female sex, nonsmoker status, history of PONV or motion sickness, and use of postoperative opioids. The risk of PONV increases with increasing number of risk factors and has been reported to be about 10% with no risk factors, about 20% with 1 risk factor, about 40% with 2 risk factors, about 60% with 3 risk factors, and about 80% with 4 risk factors.[3]

The Apfel score was prospectively validated in patients undergoing surgery with general anesthesia and was found to have good predictive accuracy.[1] However, it has not been specifically validated in patients undergoing regional anesthesia, nor has it been specifically examined in patients undergoing orthopedic surgery.

The consensus guidelines[3] recommend considering PONV prophylaxis using 1 or 2 interventions in adults at moderate risk for PONV and 2 or more interventions in adults at high risk for PONV. The recommended interventions include nonpharmacological, anesthesia-specific, and pharmacological options. The guidelines do not support giving prophylactic antiemetics to all patients undergoing surgical procedures. In addition, there is little guidance in these guidelines concerning the treatment of PONV occurring in the period immediately after an elective surgical procedure but before the patient has been discharged from the hospital.

Many different strategies have been trialled to facilitate patients' early mobilization and discharge from hospital. Over the years at our own institution, we have observed utilization of new surgical approaches (e.g., direct anterior versus lateral approach for hip replacements), changes to pain management regimens (e.g., IV versus oral administration of opioids), and use of spinal anesthesia instead of general anesthesia. Recently, the orthopedic surgeons have started using scheduled antiemetic therapy for patients undergoing hip and knee replacement surgery, regardless of each individual's risk factors. The purpose of this intervention is to decrease the incidence of PONV. Although antiemetic medications are generally well tolerated, adverse events may still occur, and scheduled use of these medications may be associated with significant issues, such as increased side effects or concerns about drug–drug interactions. We found no previous studies suggesting that implementation of this protocol in clinical practice can significantly reduce PONV or the length of hospital stay in this patient population. The typical length of stay for elective hip and knee arthroplasty at the study institution, based on the Alberta Bone and Joint Health Institute knee and hip replacement patient care plans (commonly referred to as the "pathways"), is a total of 4 days in hospital (i.e., POD 0 to POD 3).[5,6] On the study unit, we aim to discharge patients as soon as possible after their surgery. A desire to shorten the length of stay in hospital is a primary driver for changing how antiemetic medications are ordered and administered in this patient group.

The current study was undertaken, in a spirit of inquiry, following the local practice change to use of scheduled antiemetics. The primary objective was to compare the effectiveness of scheduled versus as-needed antiemetic therapy in the first 48 h after surgery (i.e., on POD 0 and POD 1) for the prevention and treatment of PONV in patients undergoing elective hip or knee arthroplasty. Although a variety of antiemetics may be appropriate for treating PONV in this population, ondansetron is the drug most widely used for this indication and is the first-line antiemetic used for PONV at the study institution; it was therefore the focus of our study. Clinical observations at our institution indicate that patients typically require an antiemetic only within the first 48 h after surgery, and it is rare for an antiemetic to be administered beyond the first 48 h. Therefore, for the purposes of this study, antiemetic use was evaluated on POD 0 and POD 1.

The secondary objective was to determine, within each study group, whether PONV was associated with mobilization on POD 0 or POD 1. The exploratory objective was to evaluate whether Apfel scores (independent of the intervention) predicted PONV in this population of patients undergoing elective arthroplasty.

METHODS

Study Design and Timeline

A retrospective chart review was used to collect data for this pilot study. Notes and documentation by physicians, nurses, and allied health professionals were reviewed within the electronic medical record and in the paper chart for each included patient. Data were obtained for consecutive adult patients admitted to an acute orthopedic surgery inpatient unit at Foothills Medical Centre in Calgary, Alberta, from January 1 to September 30, 2016. Data collection for consecutive patient charts continued until we attained convenience samples (groups of nearly equal size) of patients receiving scheduled or as-needed antiemetic

therapy. The start date for data collection was based on when surgeons began ordering ondansetron for "scheduled" postoperative use. Some surgeons were slower to adopt this practice change than others, which allowed for a comparator group (receiving antiemetics on an as-needed basis) within the same timeframe.

Ethics Approval

Ethics approval was obtained from the Health Research Ethics Board of Alberta (Community Health Committee) (approval #HREBA.CHC-16-0044). A waiver of consent was granted because of the retrospective nature of the study.

Data Sources

Patients were identified through the hospital's electronic medical record software Allscripts Sunrise Clinical Manager (SCM) (Eclipsys), which contains detailed clinical information about all patients and their hospital stay, including demographic information, diagnostic imaging results, laboratory values, procedures and treatments received, progress notes, and discharge summaries. SCM records and supplementary paper charts were used to obtain all of the data for the study. The information about PONV and mobilization was taken from documentation by both nursing and physiotherapy staff. More specifically, PONV was documented as present or absent with a yes/no question in the nursing flowsheets. PONV was documented by physiotherapy staff (in the electronic progress notes) if it occurred during mobilization. Documentation of PONV and mobilization is part of standard nursing assessment and practice on the unit.

Inclusion and Exclusion Criteria

Patients 18 years of age or older who had been admitted for elective total knee or total hip arthroplasty and who remained on the study unit after their surgery were included in the study. Patients were excluded if they had undergone bilateral joint arthroplasty, unicompartmental (partial) knee arthroplasty, revision of previously performed surgery, resurfacing surgery, or trauma and fracture surgery of the hip or knee. Also excluded were patients taking any type of chemotherapeutic agent for cancer treatment (oral or IV) and patients who were pregnant or breastfeeding.

Patient Characteristics and Data Collection

Demographic data were collected from review of each patient's electronic health record to determine age, sex, type of surgery, date of surgery, and date of discharge. The following data concerning administration of antiemetics were also collected: dose, frequency, and number of doses administered.

Intervention

This study did not itself involve any interventions, but instead evaluated the intervention (antiemetic therapy) ordered by the surgeons. Patients for whom a scheduled dose of ondansetron was prescribed were compared with those for whom any other antiemetic regimen was prescribed. The "scheduled" antiemetic regimen was ondansetron 4–8 mg IV every 6–8 h (q6–8h) for 48 h after surgery. For patients within this group, a prescriber could order other antiemetics to be used on an as-needed basis, in addition to the scheduled ondansetron, for example, metoclopramide 10 mg PO or IV q6–8h as needed or dimenhydrinate 25–50 mg PO or IV q6–8h as needed. The "as-needed" antiemetic regimen involved orders for a medication to be administered at the patient's request to treat acute symptoms of PONV. The as-needed antiemetic regimen always included ondansetron 4–8 mg PO or IV q6–8h as needed (the first-choice antiemetic for this population); patients could also have additional orders for either or both of the following: metoclopramide 10 mg PO or IV q6–8h as needed or dimenhydrinate 25–50 mg PO or IV q6–8h as needed. If any patient experienced intractable nausea or vomiting, the prescriber was contacted and, upon appropriate clinical assessment, could order a one-time dose of dexamethasone or methylprednisolone sodium succinate IV. These options are not part of the regular arthroplasty pathway, and their use was assessed on a case-by-case basis. The choice of antiemetic or antiemetics ordered and whether the drugs were ordered on a scheduled or as-needed basis was at the surgeon's discretion. Most antiemetic prescribing in this patient population is driven by an electronic order set listing ondansetron and metoclopramide; however, physicians may order different antiemetics (outside of the electronic order set) as deemed clinically appropriate.

Outcomes

The primary outcome was the occurrence of PONV on POD 0 and POD 1 (i.e., within 2 timeframes: 0–24 h after surgery and 24–48 h after surgery).

The secondary outcome was whether the patient was able or unable to mobilize on POD 0 or POD 1. As set out in the unit's care pathway, a patient was considered to have met the criteria for mobilization, from a physiotherapy standpoint, on POD 0 if the patient could stand at the bedside and do bed exercises (ankle pumping, static quadriceps, and buttock exercises). The minimum requirement for mobilization on POD 1 was considered to have been met if the patient walked a minimum of 10 m twice during the day, progressing to an eventual distance goal of 15–20 m, as well as repeating the bed exercises performed on POD 0.

Adherence to the protocol was assessed for patients in the "scheduled" group by considering the number of doses administered within the first 24 h. In this group, adherence was defined as receiving at least 3 doses in the first 24 h.

Statistical Analysis

Demographic characteristics are reported with means and standard deviations (for normally distributed variables) or with

medians and interquartile ranges (for variables not normally distributed and for ordinal variables).

Logistic regression was conducted to evaluate the relation between intervention groups and the primary and secondary outcomes. Given previous literature[3] reporting that higher Apfel scores are associated with occurrence of PONV, Apfel score was included in the model as a potential effect modifier (treatment × Apfel score interaction). The inclusion of the Apfel score in the model also controlled for age, sex, and smoking status. Both intention-to-treat (a priori) and as-treated (post hoc) analyses were conducted. The as-treated analysis was conducted because a large number of those for whom scheduled administration was prescribed did not receive all of their scheduled doses, and we wanted to explore potential trends in effects.

Chi-square tests were used to investigate whether Apfel score was associated with the primary and secondary outcomes.

One of the main reasons for using antiemetics is to decrease PONV and thus to facilitate earlier mobilization, potentially reducing the time to hospital discharge. We therefore used logistic regression to investigate the association between PONV and mobilization, controlling for the intervention.

All data analyses were conducted using Stat version 14.1 (StataCorp LP). The level of significance was set at 0.05 for all statistical analyses.

RESULTS

A total of 132 patient charts were reviewed, with 65 of the patients receiving "as-needed" antiemetic treatment, and 67 receiving "scheduled" antiemetic treatment. Demographic characteristics are presented in Table 1. Overall, there were more women than men in both groups (48 women in the "as-needed" group and 47 women in the "scheduled" group), and there were few smokers in either group (3 and 8, respectively). There were no statistically significant differences between groups in terms of baseline measures.

About half of the patients in both groups (36 [55%] in the "as-needed" group and 31 [46%] in the "scheduled" group) had PONV on POD 0; the proportions decreased to 20 (31%) and 14 (21%), respectively, by POD 1. Most patients were able to mobilize on POD 0 (57 [88%] in the "as-needed" group and 62 [93%] in the "scheduled" group). Of patients who were unable to mobilize on POD 0, the reason was PONV for 3 patients in the "as-needed" group and 2 patients in the "scheduled" group. There were no statistically significant differences between groups in terms of these measures.

Thirty-one (46%) of the patients in the "scheduled" group received antiemetics as intended (i.e., therapy was adherent with the physician's orders); the others missed one or more of the scheduled doses.

Table 1. Characteristics of Sample and Primary Outcomes

Characteristic or Outcome	Group; No. (%) of Patients*	
	As-Needed Therapy (*n* = 65)	Scheduled Therapy (*n* = 67)
Age (years) (mean ± SD)	65.6 ± 9.6	63.5 ± 9.9
Sex, female	48 (74)	47 (70)
Duration of hospital stay (days) (mean ± SD)	3.19 ± 1.51†	3.88 ± 4.24
Apfel score (median and IQR)	3 (3–3)	3 (2–3)
No. of doses of antiemetic		
Total	1 (2)	3 (4)
Within 24 h	Not measured	2.21 (1.21)
No. (%) who received > 3 doses (scheduled therapy only)	Not measured	31 (46)
Surgical location		
Hip	29 (45)	36 (54)
Knee	36 (55)	31 (46)
Smoker	3 (5)	8 (12)
Postoperative nausea and vomiting		
On POD 0	36 (55)	31 (46)
On POD 1	20 (31)	14 (21)
Mobility		
Able to mobilize on POD 0	57 (88)	62 (93)
Able to mobilize on POD 1	57 (88)	54 (81)
Unable to mobilize on POD 0 because of PONV	3 (5)	2 (3)
Unable to mobilize on POD 1 because of PONV	1 (2)	1 (1)
Breakthrough medications required	18 (28)	23 (34)

IQR = interquartile range, POD = postoperative day, PONV = postoperative nausea and vomiting, SD = standard deviation.
*Except where indicated otherwise.
†One outlier was omitted because the stay was complicated for reasons unrelated to the initial surgery.

Apfel Score and Outcomes

The Apfel score was associated with PONV on POD 0 ($\chi^2 = 30.52$, df = 3; $p < 0.001$) but not with PONV on POD 1 ($\chi^2 = 3.91$, df = 3; $p = 0.27$), mobilization on POD 0 ($\chi^2 = 3.39$, df = 3; $p = 0.34$), or mobilization on POD 1 ($\chi^2 = 0.29$, df = 3; $p = 0.96$).

Effect of Interventions

There were no differences in results between the intention-to-treat and the as-treated analyses; therefore, only results from the intention-to-treat analysis are presented below.

Apfel score did not act as an effect modifier for any of the primary or secondary outcomes, and thus interaction effects were not included in the final model. However, the Apfel score was a predictor of the association between intervention and PONV in the first 24 h after surgery. The intervention was not significantly associated with the primary outcome of PONV on either POD 0 or POD 1, nor was it associated with the secondary outcome of mobilization on either POD 0 or POD 1 (Tables 2 and 3).

Eighteen patients in the "as-needed" group and 23 patients in the "scheduled" group had intractable PONV and required additional rescue medication (defined as "breakthrough medication") for PONV (Table 1). A χ^2 test showed no significant difference in the use of rescue medication for PONV between the treatment groups ($\chi^2 = 0.5$, df = 1; $p = 0.48$).

Table 2. Logistic Regression for Association of Intervention with Primary and Secondary Outcomes (Intention-to-Treat Analysis)*

Outcome	OR (95% CI)	*p* Value
PONV		
On POD 0	0.85 (0.39–1.85)	0.68
On POD 1	0.64 (0.29–1.40)	0.28
Mobilization		
On POD 0	2.07 (0.62–6.97)	0.24
On POD 1	0.59 (0.22–1.54)	0.28

CI = confidence interval, OR = odds ratio, POD = postoperative day, PONV = postoperative nausea and vomiting.
*Analysis controlled for Apfel score.

Table 3. Logistic Regression for Association between PONV and Mobilization*

Outcome	OR (95% CI)	*p* Value
PONV POD 0 and mobilization POD 0	1.85 (0.57–6.04)	0.31
PONV POD 0 and mobilization POD 1	1.77 (0.68–4.64)	0.24
PONV POD 1 and mobilization POD 1	0.81 (0.23–2.85)	0.74

CI = confidence interval, OR = odds ratio, POD = postoperative day, PONV = postoperative nausea and vomiting.
*Analysis controlled for intervention.

DISCUSSION

The notion that scheduled ondansetron treatment in the immediate postoperative period would decrease nausea and vomiting and therefore encourage earlier mobilization and reduce the length of stay in the hospital is elegant in theory. However, in this study, the scheduled administration of antiemetic, specifically ondansetron, did not result in a statistically significant difference in either PONV or mobilization. Notably, Apfel score did indeed predict PONV outcomes in patients undergoing elective arthroplasty, who at the study facility largely undergo regional anesthesia.

The routine use of scheduled administration of antiemetics for all patients undergoing surgery is not supported by the most recent consensus guidelines[3] or by a number of independent researchers.[4,7] This is based on a lack of evidence for the use of scheduled antiemetics, the possibility of rare but unwanted side effects, and economic reasons. The results of this study support the current clinical guidelines. However, some clinicians have argued for a more liberal use of postoperative antiemetics, to reduce the risk of PONV and to facilitate early hospital discharge.[8] Further research is needed to confirm or refute this benefit.

To the best of our knowledge, this is the first study to explore the question of whether scheduled administration of ondansetron in the postoperative period results in less PONV among adult patients undergoing elective knee or hip replacement. Our results do not support the hypothesis that administering ondansetron postoperatively to all patients undergoing this type of surgical procedure will lessen the occurrence of PONV or improve early mobilization for patients undergoing hip or knee replacement. We acknowledge that we examined postoperative antiemetic use only while the patient was on the inpatient unit. We did not look at intraoperative use of antiemetics or administration in the Post Anesthesia Care Unit, as this information would have been difficult to retrieve. However, it is possible that patients received a dose of ondansetron at the end of the surgical procedure, since ondansetron is prescribed at the anesthesiologist's discretion.

The limitations of this study include the small sample size (132 participants), which limited the statistical power, and the retrospective nature of the study design. The small sample limits considerably any conclusions that can be drawn from the results. Another limitation was poor adherence to the regimen for scheduled use of ondansetron after surgery. Poor adherence was likely due to the lack of education provided to members of the health care team before implementation of this new regimen for around-the-clock medication. Our data collection demonstrated a lack of consistency within the physician group as to how ondansetron was ordered, as well as a lack of consistency within the nursing group as to how ondansetron was administered. Furthermore, although we were able to control for known factors that contribute to a patient's risk of PONV, such as the Apfel score, larger studies are needed to identify other currently unknown confounders. The strengths of this study included

collection of retrospective data from consecutive patients undergoing care within one hospital unit, which had a standardized protocol for patient care and mobilization after surgery; this limited potential confounders in patients' outcomes.

This study has provided initial data on the effectiveness of "scheduled" versus "as-needed" ondansetron and allows for further research to be conducted in this patient population related to PONV, mobilization, and length of stay. Specifically, one area of further research could be to examine more closely patients with known higher Apfel scores (3 or 4 out of 4) who are undergoing elective orthopedic arthroplasty to determine the effectiveness of "scheduled" versus "as-needed" antiemetics in this population. Although we did not find an interaction effect in our study, a prospective clinical trial with a larger sample might be useful to evaluate this intervention in a higher-risk population. This study also contributes to the scarce data about the use of specific antiemetics in patients undergoing orthopedic surgery, particularly elective arthroplasty.

CONCLUSION

In this study, scheduled use of antiemetics in the immediate postoperative period did not significantly affect the occurrence of PONV in patients undergoing elective arthroplasty. Further high-quality prospective clinical trials are needed to confirm these results.

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Biosimilar Drugs and the Hospital Formulary: A Canadian Experience

Jennifer Fenna, Kathy Watkins, and Micheal Guirguis

INTRODUCTION

Biologics, a class of large, complex drugs that are derived from living organisms rather than chemical synthesis,[1,2] represent an emerging area of drug therapy. Biologic drugs are important treatment options often used in chronic diseases and cancer. From a health care system perspective, they are a major contributor to rising drug expenditures.[3,4] However, as patents for branded products expire, there is an opportunity to develop biosimilar drugs in Canada.[1,5] Biosimilars are highly similar versions of biologics already authorized for market,[5] which are comparably efficacious and safe, but potentially less expensive.[6]

As the market for biosimilars grows, their inclusion in hospital formularies can benefit the health care system and improve quality of care by increasing patients' access to treatment options and reducing expenditures.[3] However, biosimilars have class- and product-specific characteristics that differ from those of traditional small-molecule drugs,[7] and a formulary evaluation to determine efficacy, safety, and cost-effectiveness requires additional considerations. Drugs and therapeutics committees (DTCs) play a critical role in evaluating biosimilars and improving their uptake in acute care. Ultimately, a DTC serves to establish and maintain a formulary that best meets the needs of prescribers, patients, and the health care organization.[8]

The purpose of this article is to describe one provincial health authority's practice in adding biosimilars to its acute care formulary. A summary of the available literature on considerations when adding biosimilars to formulary is provided. This information is then applied to the experience of the authors' health authority, to identify the strengths and challenges of its formulary review and decision process for biosimilar drugs. The article is intended to educate Canadian hospital pharmacists about formulary and practice management tools and principles, as well as educational strategies, to support the safe and effective use of biosimilars.

BACKGROUND

Regulatory Pathway

In order to be marketed, a biosimilar must be demonstrated to be sufficiently similar to the reference product, meaning there is no clinically meaningful difference in safety, purity, or efficacy.[1,9,10] In Canada, biosimilars are approved via an abbreviated pathway. Using a totality-of-evidence approach, stepwise development begins with structural and functional studies and continues with human clinical studies.[2] Relative to the originator biologics, biosimilars require fewer patients to be studied, and less clinical data to support their efficacy and safety, but must have more analytical information (e.g., structure and function).[11] Additionally, biosimilars may be authorized for use for more than one indication (through extrapolation of therapeutic similarity from one indication to another), even if clinical studies have not been conducted for each indication.[1]

Formulary Tools and Biosimilars

Biosimilars are not the same as generic versions of a drug,[2] in that they are highly similar to, but not exact copies of, the originator product.[12] Traditional small-molecule generics can be chemically synthesized and are identical with their respective reference products.[12] In contrast, biologics are large proteins developed from living sources (e.g., bacteria), with manufacturing steps that are numerous and complex.[12] As such, there is potential for differences among batches of the same biologic.[1,11] Because the manufacturing process for any biologic is proprietary, it is impossible for a competitor to replicate all aspects of it.[1]

The strong similarity between a biosimilar and its corresponding biologic has implications for the types of formulary tools that can be used for evaluation.[12,13] The concepts of substitution, interchangeability, and switching must be understood in this regard

(Table 1). Substitution is "the act of dispensing one product in place of another."[1] Interchangeability occurs when one drug can be substituted for another at the time of dispensing, with the substituted product being so like its originator that it is expected to achieve the same clinical effect in any given patient.[1,5,13] In Canada, interchangeability decisions are made at the provincial/territorial level[1,13]; there are also some differences in how provinces define these concepts.[5] Therapeutic interchange, also known as therapeutic substitution,[1,13] is a formulary management tool that allows substitution of a different medication from the same class of drugs with similar therapeutic efficacy and safety.[1,12] Therapeutic interchange is done at the pharmacy level and involves collaboration between the prescriber and the pharmacist.[13,14] Therapeutic interchanges done by hospital pharmacists are based on a medical directive from the organization's DTC or from an individual physician.[1] This type of interchange differs from switching to a biosimilar, which involves changing a specific patient's medication after therapy with a biologic has already been established for that patient.[1] Decisions about switching are generally made by individual patients and their practitioners, on a case-by-case basis.[1,13] At this time, Canadian guidance does not support the application to biosimilars of routine drug interchange or substitution practices that are commonly used for generic drugs.[1,5,10]

Evaluation of Biosimilars for Formulary Inclusion

Key elements of formulary review of biosimilars include evaluation of clinical parameters (indications, clinical data, immunogenicity), product characteristics (nomenclature, supply management, packaging and labelling), and institutional considerations (substitution, pharmacovigilance, costs and reimbursement, patient and provider education, tracking and information system implications).[3] Griffith and others[11] developed a checklist of considerations to be taken into account when evaluating biosimilars for formulary inclusion. Although this checklist is based on the US health system perspective, the process can be applied to Canadian settings to ensure that all important elements are considered in formulary review of a biosimilar.

Little has been published on Canadian efforts in this area, although experiences from other parts of the world show that uptake has not reached its full potential, and many barriers exist to inclusion of biosimilars on formulary.[11] Factors that limit the uptake of biosimilar products include limited prescriber awareness, lack of interchangeability between biosimilars and originator products, a need for more pharmacovigilance data to supplement clinical trial data, and differences in value-added elements such as manufacturer support programs, which can lead to practical and logistical issues.[5,7] Health care systems and hospitals must proactively develop policies regarding the use of biosimilars.[3] Further to the considerations of efficacy, safety, and cost-effectiveness that are standard in formulary reviews, the evaluation of biosimilars should include consideration of clinical, product, and institutional factors.[3]

Table 1. Comparison of Generic and Biosimilar Drugs with Corresponding Brand

Concept	Category; Comparison with Brand	
	Small-Molecule Generic	Biosimilar
Bioequivalence	Yes	No
Interchangeability	Yes	No
Therapeutic equivalence	Yes	Yes
Therapeutic substitution	Yes	Yes
Switching	Yes	No

Decision Framework

An understanding of the theoretical decision framework used by prescribers when incorporating an innovation into practice can be helpful in understanding and improving the uptake of biosimilars.[15] Previous research has indicated that 5 key criteria influence a clinician's choice to implement an innovation: relative advantage (the degree to which the innovation is perceived as being better than its predecessor), compatibility (how consistent the innovation is with the existing values, past experiences, and needs of potential adopters), complexity (perception of difficulty of use), trialability (ability to experiment with the innovation on a limited basis before adoption), and observability (how observable the results are to others).[15] Meeting these adoption criteria could positively influence the future success of biosimilars within an organization, and these criteria can also be used to evaluate an existing situation to determine steps needed for improvement.

DESCRIPTION OF THE PRACTICE

The DTC of the authors' organization is a multidisciplinary committee that makes decisions about medication listings in the drug formulary, as well as policies and procedures related to formulary processes. Drug utilization evaluation and stewardship pharmacists, who are part of the DTC, are responsible for conducting the formulary reviews.

To prepare for the addition of biosimilar drugs to the acute care formulary, steps were taken to educate pharmacy staff. This staff education took the form of a "backgrounder" document, a concise reference document designed to facilitate discussions between front-line pharmacy staff and the prescribers with whom they work on drug-use issues within the organization. The biosimilars backgrounder provided information about the development of biosimilars in Canada and related concepts, and discussed the non-interchangeability of biosimilars with reference biologics.

In 2016, the DTC decided that biosimilars listed on the provincial benefit list (for ambulatory drugs) would be provided to patients receiving care within the organization, for the purpose

of continuity of care. This decision took into consideration the regulatory prohibition against interchanging a biosimilar with its originator product and was intended to prevent any disruptions in therapy for patients already stabilized on a branded product before admission to hospital. Further decisions about each biosimilar's formulary status were then to be made through the usual review process.

To date, 3 biosimilar drugs have been added to the formulary, each with different approaches and considerations, as detailed in Table 2. All had undergone the Common Drug Review process, a national approach to reviewing drugs newly approved in Canada in order to make a recommendation on eligibility for public reimbursement,[16] and were listed on the provincial drug benefit list before being considered for addition to the acute care formulary.

Biosimilar 1

The first biosimilar was initially brought to market without approval for the full breadth of indications given for the originator brand. This situation arose from regulatory concerns about extrapolating data from one disease state to another because of differences in disease mechanisms and the safety profile of the biologic in different diseases. The indications not originally approved were added later, on the basis of additional data and rationales addressing concerns about mechanisms of action. Upon review of this biosimilar for formulary inclusion in the authors' organization, the recommendation to the DTC and the subsequent decision by the DTC were that it be added with restrictions aligning it with the originator biologic on the formulary and with the criteria of the provincial drug benefit list for coverage. Stakeholder feedback was gathered from relevant clinicians within the organization. Through this process it was discovered that some prescribers were hesitant to use the biosimilar product because of questions about the regulatory process and a perceived lack of transparency concerning the scientific rationale used for approval of all indications through extrapolation. There was also uncertainty about patients' access to infusion clinics for administration of the biologic. Although the brand had a well-established system of supports for administration of doses to patients, it was unclear how many administration sites the manufacturer of the biosimilar had confirmed.

Information about the formulary decision was disseminated via an electronic newsletter circulated to clinical staff, supplemented with live presentations (through online conference). A document of frequently asked questions (FAQs) was developed and linked to the formulary record. Uptake of the biosimilar was measured 6 months after its addition to the formulary. Results showed limited use, with unequal utilization patterns in various geographic areas of the province. Although the organization had listed the biosimilar on equal footing with the originator product, the added support services offered by the manufacturer of the originator brand made it difficult for the biosimilar to gain uptake. The auditing process also uncovered limitations with data capture in some pharmacy systems due to problems with drug nomenclature.

Table 2. Characteristics of 3 Biosimilars Introduced to a Health Authority's Formulary

Drug	Status of Drug in Acute Care Formulary	Prescriber Feedback	Interchangeability Data	Communication	Uptake Results	Unit Cost/ Volume of Use
Biosimilar 1	• Formulary with restrictions • Aligned with external drug benefit coverage	• Concerns about extrapolation of indications • Questions about infusion clinics and patient support services	No	• Live web conference sessions • FAQ document • Formulary newsletter	• Limited uptake after 6 months; 12-month audit planned • Challenges with data retrieval because of drug naming in pharmacy systems	High/low
Biosimilar 2	• Formulary with restrictions (biosimilar positioned as product of choice) • Listed on 2 different formularies on basis of indication • Aligned with external drug benefit coverage	• Generally positive • Concerns about use for sensitive patient populations • Improved comfort if local data could confirm efficacy and safety while transitioning to use of biosimilar	No	• Live web conference and in-person sessions (targeted discussions with clinicians) • FAQ document • Formulary newsletter	• Audits planned for 6 and 12 months • QI project in progress	Medium/ medium
Biosimilar 3	• Open-listed • Aligned with external drug benefit coverage	• Feedback not requested	Yes	• Formulary newsletter	• Audits planned for 6 and 12 months	Low/high

FAQ = frequently asked questions, QI = quality improvement.

Biosimilar 2

The situation for the second biosimilar was more complex because different indications had separate coverage sources, with the drug being listed on both the provincial acute care formulary and the formulary for a high-cost drug program. Additions to the formulary for the high-cost drug program follow a separate process for review and final decision.

Relevant prescribers were consulted about the proposed status of the biosimilar on the acute care formulary and the formulary for the high-cost drug program. Clinicians were generally receptive to using the biosimilar product for one indication; however, they expressed concerns about sensitive patient populations (i.e., patients in critical condition), in which no direct clinical studies had been done. There were also questions about potentially increased adverse effects of the biosimilar relative to the originator product, as reported in published studies. Prescribers noted that their confidence in using the biosimilar for sensitive patient populations would increase if local data (from within the organization) could be collected to assess efficacy and safety. In response to this request, a future quality improvement project was planned, with support from the drug utilization evaluation and stewardship pharmacist.

With a desire for stronger uptake of biosimilars, the DTC aimed to maximize use by positioning this biosimilar as the product of choice for the specified indications. This preference was communicated directly to stakeholders, who were consulted before broader communications to other clinical staff. An FAQ document was also developed for reference purposes. To determine uptake, utilization audits are planned for 6 and 12 months after implementation.

Biosimilar 3

Supporting information for the third biosimilar included data from studies in which patients were switched from the originator product to the biosimilar, which provided a level of evidence not seen with the other 2 biosimilars. This third biosimilar was recommended by the Common Drug Review for reimbursement with conditions, and was added to the provincial drug benefit list as a regular benefit ("open listed"). Although the DTC wanted to increase uptake of the biosimilar, it took a cautious approach with this formulary listing, because there had been stakeholder disagreement with a previous DTC decision regarding the same class of drugs. With this biosimilar, the DTC recommended that it be listed with unrestricted formulary status, meaning that either the brand or the biosimilar product could be used in new starts, as well as for continuing therapy. Because the listing was at parity with the originator brand already on formulary, a broad stakeholder survey was not conducted; the same is often done for formulary decisions that represent line extensions (e.g., addition of new strengths of a drug that is already listed on the formulary) or changes to product listings that do not affect clinical practice. The decision was communicated to clinical staff through the electronic newsletter and live presentations. Utilization audits are planned for 6 and 12 months after implementation to measure uptake of the biosimilar.

EVALUATION OF THE PRACTICE

In relation to the checklist proposed by Griffith and others,[11] the organization's process adequately addressed most considerations for formulary review of biosimilars. The areas of greatest challenge and focus were safety and efficacy, hospital and patient considerations, and economic considerations. In general, clinicians had some reservations about the available clinical data and questions about the sufficiency of data for the indications being considered for formulary inclusion. These reservations and questions were not surprising, given that the regulatory pathway and authorization of biosimilars for indications without supporting clinical studies represent a newer concept for prescribers.

Product naming was also identified as an important issue to be addressed. Having the ability to distinguish biosimilars from the corresponding originator products at order entry, for utilization reports, and for tracking of safety events (pharmacovigilance) is essential. In February 2019 (after this article had been accepted for publication), Health Canada issued formal guidance on how current and future biosimilars should be named,[17] based on results from a joint public consultation conducted by Health Canada and the Institute for Safe Medication Practices Canada on this topic in 2018.[18] In brief, Health Canada recommends that "biologic drugs, including biosimilars, will be identified by their unique brand name and non-proprietary (common) name, without the addition of a product-specific suffix."[17]

Although the organization faced some challenges with the addition of biosimilars to the formulary, there were also positive aspects. For example, a process was put into place regarding the provision of biosimilars not yet added to formulary; such processes have been noted to support the entry of biosimilars into practice.[3] The process included stakeholder feedback through targeted engagement of specific clinical groups, helping to ensure that key contacts were included in the discussion. Having active and direct involvement of the appropriate clinicians has been noted as an important component of formulary review of biosimilars.[7] Also, efforts to support the education of pharmacy and clinical staff about DTC decisions were beneficial for disseminating knowledge about the rationale for biosimilar decisions.

A major consideration was non-interchangeability between biosimilars and their corresponding biologics, and the recognition that automatic interchange or substitution to another formulary item is not supported for biosimilars. However, as studies continue to evolve, with the inclusion of more trials with designs involving multiple switches between a biosimilar and its reference product, the immunogenicity effects of such practices will come to be better

understood.[4] Additionally, monitoring patient outcomes for efficacy and adverse events will be essential to confirm the effects of longer-term use of these agents.[13] As learned during the formulary addition process, clinicians' level of comfort with biosimilar products may be improved by collecting local data to confirm scientific data gathered in clinical trials of the biosimilar.

With respect to sustainability of the health care system, biosimilars have significant potential to reduce the costs associated with the biologics class of drugs.[2,3,6,7] The cost savings associated with using biosimilars were a factor in their listing on formulary, but the overall impact for the organization is yet to be determined. The biosimilar examples described in this article had list prices ranging from 17% to 45% lower than the corresponding originator products. In the current economic climate, there is motivation to optimize drug expenditures and improve drug stewardship.

IMPLICATIONS FOR PRACTICE

As drug experts, hospital pharmacists are ideally positioned to support the use of biosimilars.[6] Pharmacist-led education initiatives can improve prescribers' awareness of and comfort with biosimilars[3] by decreasing knowledge gaps and misconceptions.[19] A strong knowledge base of biosimilar concepts is necessary, and educational strategies to ensure that pharmacists have the necessary competency to select and recommend biosimilars should be in place early on. This requirement implies integration of biosimilars into pharmacy curriculums,[19] as well as into continuing education for pharmacists in practice.

Our observations indicate that the uptake of biosimilars often begins in the acute care setting, as these agents may be started in hospital to stabilize a patient's condition. As such, one vital consideration is alignment of the acute care formulary with public drug plans to ensure continuity of therapy for patients when they are moved from one care setting to another. Coordinating formulary listings for biosimilars in acute care and in the ambulatory setting will help to ensure that patients have timely access to these agents.

Our organization's experience can be examined using the theoretical framework of 5 criteria that influence a prescriber's decision to adopt innovations.[15] Initially, the relative advantage of biosimilars was unclear. Compatibility was low, because of a lack of previous experience with biosimilars, whereas complexity was high, because the concepts surrounding biosimilars were new. The trialability and observability of biosimilars were also low, because the products could be used only after they had been added to the formulary. Uncertainty about biosimilars and a pre-existing affinity for the reference products yielded low motivation for clinicians to change their prescribing behaviour.[15] However, involving clinicians in the review process and addressing knowledge gaps in the areas of clinical safety and efficacy were positive steps providing extra support for change.

The most salient issue was a lack of comfort and confidence on the part of prescribers, mainly related to the regulatory approval process allowing extrapolation of data from one disease condition to another. Some experts had the view that extrapolation should be guided only by appropriate clinical trial evidence. This uncertainty seemed to affect the acceptance of biosimilar 1 more than biosimilars 2 and 3. However, it was unclear whether other factors, such as it being the first biosimilar evaluated and the chronic nature of the disease state being treated, also contributed to slow and limited uptake. Biosimilar 2, which is typically used for shorter treatment periods, seems to have been better received. The approach with that biosimilar was structured to facilitate collection of local data, which enabled trialability and observability of the product's effects in sensitive patient populations. Similar projects could be considered in the future, if capacity exists, as this support helps to address the compatibility of prescriber behaviour with the use of biosimilars.

Finally, it was observed that the approach to formulary review and inclusion may differ among various biosimilars, according to certain product-specific factors. A tailored approach that takes into account provincially based factors related to the sustainability, quality, and supporting infrastructure available for biologics is necessary for their success.[20] To improve the availability of biosimilar drugs in the future, pharmacists and the DTC must apply appropriate formulary tools for practice management.[7]

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Departmental Initiative to Improve Documentation in the Medical Record by Acute Care Pharmacists

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INTRODUCTION

Documentation in a patient's medical record is an integral component of quality health care and as such is a legal requirement for health care providers. It is an avenue to communicate professional judgment, critical thinking, and plans for care among health care professionals; it also provides data to allow better understanding of care issues. Documentation in the medical record by pharmacists has the potential to minimize medication discrepancies and subsequent patient harm while forming a record of the level of care provided by the health care team.[1] The importance of documentation by pharmacists is emphasized by the National Association of Pharmacy Regulatory Authorities (NAPRA) and the Canadian Society of Hospital Pharmacists (CSHP), which both include documentation as a professional practice standard in Canada.[1,2]

Although the importance of documentation is well known,[3] pharmacists have reported that they often do not document in the medical record.[4] Pullinger and Franklin[4] surveyed 39 pharmacists and conducted a focus group with 32 clinical hospital pharmacists in London, England. Common barriers to adequate and complete documentation by pharmacists in the medical record included a preference for verbal communication, fear of criticism from prescribers, lack of belief in the significance of the intervention, and lack of ownership of the medical record. These authors suggested that hospitals develop a formal policy regarding pharmacist documentation and offer suitable training, including what and when to document. Herritt and others[5] reported that the clinical activities most commonly documented by pharmacists were clarifications, order sets, clinical progress notes, and pharmacist suggestions. In contrast, in a more recent study, Baranski and others[6] found that common topics for documentation included resolution of drug-related problems, pharmacokinetic consultation and recommendations, and patient education sessions.

Documentation of patient care issues by pharmacists was an expectation within the Regina Qu'Appelle Health Region, now known as the Saskatchewan Health Authority – Regina area (SHA–Regina). To better understand the quality and frequency of documentation within the local institutions, as well as alignment with CSHP guidelines, a residency project was conducted in 2015. The purpose of the project was to assess the competency of pharmacists in 18 elements of chart note documentation and to quantify the number of instances of documentation by pharmacists.[6] The results showed that although pharmacists documented concisely, clearly, and in a diplomatic tone, there was room for improvement in the frequency and elements of chart note documentation in the medical record.

Further work to improve the frequency of documentation by pharmacists in SHA–Regina followed Kotter's process for creating major change.[7] With implementation of a collaborative prescribing agreement between pharmacists and physicians, the legal requirement for documentation was brought to the forefront of leaders' minds. Legal counsel for the health region spoke to all staff pharmacists regarding the importance of complete and adequate documentation when prescribing medications. The urgency of the need to improve documentation led the clinical leadership team in SHA–Regina to establish a 3-year goal to increase both the quantity and quality of pharmacist documentation in the medical record.

To establish a baseline for documentation frequency, a survey of acute care clinical pharmacists was conducted at 2 tertiary care centres in Regina in September 2016. This group consisted of 35 pharmacists, of whom 40% had postbaccalaureate clinical training and 60% had more than 5 years of work experience. Of the 28 pharmacists who responded to the survey, 23 (82%) reported documenting fewer than half of their interventions in the progress notes. When asked why they did not document certain interventions, the majority of respondents (68% [19/28])

gave timing of the intervention as a reason (i.e., intervention performed during discussion on rounds or with the physician); a secondary reason was lack of time for documentation.

These survey results were compared with local metrics pertaining to documentation. Pharmacists are required to record their interventions on a daily basis using AIM-HIGH, a locally developed, Google Survey–based tracking tool. Tracking covers clinical pharmacy key performance indicators,[8] as well as other key factors prioritized by the clinical leadership team, including documentation in the medical record. Data from the AIM-HIGH tool indicated that 18.96% of all interventions were documented in the progress notes between February and August 2016, which aligned with the self-reported results from the survey.

To gain a better understanding of documentation practices within the Canadian hospital pharmacy community, an environmental scan was conducted through the CSHP Pharmacy Specialty Networks (posted December 2016) and through e-mail contact with Saskatchewan hospital pharmacy managers. Six responses (from separate sites) were received. Respondents from 4 of the sites indicated that their pharmacists used a paper-based charting process as the primary means of documentation, whereas pharmacists at the other 2 sites used electronic medical records. At sites using paper-based charts, the progress note section was most commonly used (by 3 of the 4 sites). Training modules, templates, and policies and procedures were infrequently employed. These responses indicated a wide variety of documentation practices. In the SHA–Regina area, the medical record consists of a mixed paper and electronic system; pharmacists document in the progress note section of the paper chart, because they do not yet have access for documentation in the electronic record. A general SHA–Regina policy outlining the legal importance and logistics of documentation exists; however, activities that require documentation are left to the individual pharmacist's discretion, and although educational certification regarding documentation exists, it is not mandated.

DESCRIPTION OF INITIATIVE

The Documentation Working Group (DWG) was formed in November 2016, with the specified goal of increasing, by 10 percentage points annually for 3 consecutive years, written documentation of acute care pharmacists' interventions in progress notes, both at the individual pharmacist level and departmentally. The DWG also aimed to assess pharmacists' satisfaction with the process used for improving documentation. Following a call for volunteers, initial DWG membership consisted of 5 clinical practice leaders (including C.G., C.R., W.M.S.) and 7 clinical acute care pharmacists from various specialties, which provided a representative sample of the staff pharmacists. The composition of the working group has been fluid, to account for departmental changes and to allow participation by a variety of staff members. The inclusion of front-line pharmacists was intended as a way to develop shared leadership and ownership of the project and to aid in implementation of interventions applicable to practice.

The DWG initially sought to identify local barriers that might be limiting documentation by pharmacists. These barriers were identified through brainstorming sessions within the DWG and informal feedback from other pharmacists. Proposed barriers included perceived lack of time, lack of clarity about what to document, and the perception that notes are not read by other health care professionals, especially physicians. Because the organization uses a paper-based medical record, further barriers included limited access to the medical record, such as during multidisciplinary rounds or when not present on the ward.

The DWG developed enablers to specifically overcome these identified barriers. To improve clarity about what was to be documented by pharmacists, the work standard "Pharmacist Documentation in Patient Progress Notes" (Appendix 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/189/showToc) was developed, outlining medication interventions that require documentation. A second work standard, "Medication Education Provided by Pharmacists" (Appendix 2, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/189/showToc), was developed to reduce repetitive documentation and improve efficiency. This work standard lists topics typically discussed with a patient during medication education counselling. When documenting an educational intervention, the pharmacist cites the standard, with the remainder of the documentation focused on identifying any components that were not addressed, any other relevant information that was discussed, and any patient concerns identified. This work standard was developed to address the barrier of lack of time, by reducing the extent of repetitive, non–patient-specific documentation required. Pharmacy leaders shared these work standards with care providers, and the standards themselves are available for reference by all health care professionals in SHA–Regina. Finally, a quality improvement assessment tool (Appendix 3, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/189/showToc) was developed using a template created during the previously noted residency project, to encourage pharmacists' self-assessment of their notes, to improve the clarity of expected content for notes, and to increase confidence. As each enabler was developed, all pharmacists were educated on its use and were given the opportunity to provide feedback before departmental implementation.

To facilitate ongoing improvement and awareness, the clinical pharmacists in the DWG acted as liaisons with their respective teams. They educated their colleagues on the tools and progress of the DWG, and provided regular feedback to the DWG. These processes reinforced the involvement of all front-line staff to ensure the documentation interventions were relevant and realistic.

EVALUATION OF THE INITIATIVE

Achievement of the DWG's goals was evaluated using data collected through the AIM-HIGH system and a satisfaction survey of front-line pharmacists.

AIM-HIGH data from September 2016 to August 2017 showed an increase in documentation of 9.45 percentage points (from 18.96% to 28.41%) at the departmental level, or a 49.8% improvement in the rate of documentation. All pharmacists had exposure to the interventions, and the 29 pharmacists who were practising at both baseline and the 1-year point were also assessed individually; 16 (55%) of these pharmacists achieved an increase of at least 10 percentage points in documentation rate (Figure 1). Individual assessments were completed to provide auditing and feedback for motivation. These results demonstrated an improvement by both individual pharmacists and the department as a whole and represent the first results of a 3-year, ongoing strategy. Documentation results were shared with all acute care pharmacists on a quarterly basis to ensure engagement in meeting the targeted goals for documentation.

The acute care pharmacist team was surveyed in March 2018 to determine the level of satisfaction with the process used by the DWG to improve documentation rates. All respondents indicated that the working group provided an opportunity for the pharmacist team to somewhat or fully have ownership of decisions and the direction of practice change. They felt that the working group allowed members to feel included in determining direction for the department, and reported that they would support a similar process in the future. All agreed that they had been able to make a meaningful contribution and that the outcomes of the group were valid; none of the respondents stated that they would not participate in a similar process again.

This initiative had some limitations. The data collection tool, AIM-HIGH, required pharmacists to input their own interventions and activities, and the data may therefore have been an incomplete representation of activities performed. Also, individual comparative data were collected only for pharmacists who were practising during the baseline period, which excluded pharmacists new to the department or returning from leave.

IMPLICATIONS AND SIGNIFICANCE FOR PRACTICE

The DWG initiative within SHA–Regina was able to increase the quantity and emphasize the importance of documentation of interventions by pharmacists. Although the department did not quite achieve the initial, arbitrarily selected goal of a 10 percentage point increase, documentation by pharmacists improved by almost 50%. The benefits of increasing documentation include the potential for improved communication between pharmacists and other health care providers, as was anecdotally reported by front-line staff. Greater documentation of activities in the progress notes can reduce duplication of work by pharmacists providing subsequent care and can lead to timely implementation of care plans. Improved satisfaction and confidence were reported by staff through standardization of what needed to be documented in the medical record and how best to document it.

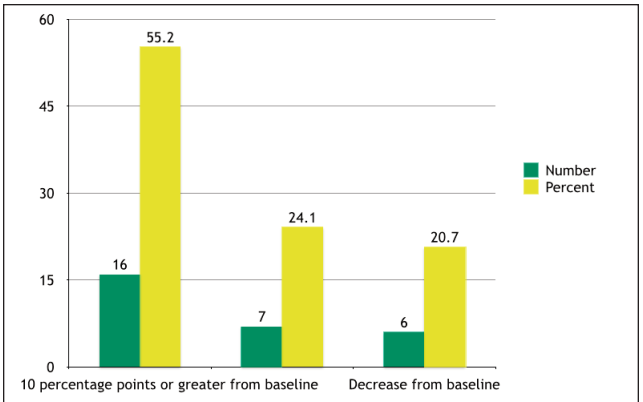

Figure 1. Changes in documentation by individual pharmacists, September 2016 to August 2017.

The activities chosen to improve documentation stemmed from identifying barriers that pharmacists encounter when performing documentation in practice. The barriers identified by our team were similar to those identified by Pullinger and Franklin[4] and included a perceived lack of time, uncertainty about how to document in certain situations, and the perception that notes are not read by other health care professionals, especially physicians. SHA–Regina pharmacists also identified that the shared, paper-based medical record used within the organization was a barrier to timely access for documentation. Although the barriers identified in SHA–Regina were not unique, a process to overcome these barriers for pharmacists has not been documented in the literature, to the best of our knowledge. The tools and knowledge translation initiatives that were implemented here focused on overcoming these site-specific barriers, and the resulting improvement in quantity of documentation highlights the benefits of using these techniques to change practice.

Although some of the barriers have been addressed, there remains room for improvement. A transition to complete electronic medical records is anticipated, which will improve access to the chart and reduce the time required for documentation. To continue improving the quantity of documentation to meet clinical and legal requirements, clinical leadership has set further goals for the DWG, which include prioritizing documentation of all activities relating to level II prescriptive authority in the progress note and working toward documentation of all pharmacists' patient care activities in the medical record (electronic or paper chart). As defined by the Saskatchewan College of Pharmacy Professionals, level II prescriptive authority describes the ability of a pharmacist to prescribe select medications on the basis of a collaborative agreement between pharmacists and practitioners in a public health care institution.[9] The quality and legibility of notes continue to improve through use of the self-assessment tool and education.

We have highlighted the process that we used to improve documentation rates within our acute care pharmacist group.

However, there is a paucity of research describing the effect of pharmacist documentation on patient outcomes. Future research should assess the impact of increased pharmacist documentation on patient outcomes.

CONCLUSION

Both CSHP and NAPRA stress the importance of documentation in the medical record.[1,2] A process based in change management, with front-line staff engagement, to improve documentation of interventions in the progress notes section of a patient chart in SHA–Regina was associated with an increase in documentation (by 9.45 percentage points) over 1 year. Additional stakeholder engagement strategies are being applied to continue efforts toward achieving the 3-year goal.

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Medication Reimbursement Model and Cost Savings in a Canadian Ambulatory Hemodialysis Program

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INTRODUCTION

Hemodialysis (HD) units in Canada provide dialysis treatment and medication therapy to patients with advanced chronic kidney disease. IV iron is commonly indicated for iron deficiency anemia in patients with chronic kidney disease, and is often administered to patients while they receive dialysis in an outpatient clinic.[1] Each provincial government allocates funding to its renal program to operate outpatient HD clinics. The provincial renal program is responsible for its own staffing and drug budgets but has experienced an increase in demand to treat more patients requiring HD.[2] Drugs administered in outpatient clinics are not defined as medically necessary services within the *Canada Health Act*; instead, patients use a variety of sources to fully or partially cover prescription drug costs, which may include private or public insurance plans.[3,4] In the authors' province, public drug coverage is offered through the Nova Scotia Pharmacare Programs, which are available for seniors, families with no or limited private drug insurance, and residents receiving community services.[5] IV iron is a benefit within the Pharmacare drug programs, provided the prescriber completes an exception status form indicating that the patient requires IV iron for management of anemia associated with chronic kidney disease.

In 2013, our hospital developed and approved a policy for drugs used in ambulatory care to help address resource issues and provide consistent and equitable funding of drugs and drug administration in outpatient clinics.[6] A policy working group, whose members consisted of a pharmacist, a social worker, a lawyer, a bioethicist, and senior managers, clarified the organization's ethical and legal principles and values regarding drug funding. The policy provided a consistent approach to promote fairness and equity, while reducing drug costs to address sustainability issues within the health care system. The hospital became the payer of last resort, which ensured that patients who could not afford to pay for their medications would still be able to receive the needed medications. Accessing patients' existing public or private insurance was for cost-recovery purposes only (not revenue generation) and was not to unduly affect the time to treatment.[6] Medications that fell under the policy were drugs that might be administered in an outpatient setting but were not required to be given in hospital (e.g., administration in private infusion clinics),[7] excluding specific medications required to perform procedures or treatments, medications included in the province's high-cost drug program, and insured systemic therapies for cancer.[6]

There are limited data in Canada on approaches to changing drug reimbursement for medications administered in outpatient settings from a hospital-funded model to public or private insurance. Our organization published a pilot study that tested and further informed the hospital's policy by exploring drug coverage options for outpatient therapy with rituximab in 39 patients with rheumatoid arthritis.[7] The pilot study showed that 87% of patients had public or private insurance, and making use of that insurance resulted in savings of $304 700 for the ambulatory care program. Most patients reported that they felt supported by the hospital throughout the pilot and were confident in having their doses administered at a private infusion clinic. However, concerns about the infusion facility were identified, and clinically significant delays occurred, which were attributable to the insurance coverage process. These unintended effects were addressed to mitigate harms and maintain a patient-centred approach.[7] In Saskatchewan, the Saskatoon Cancer Centre explored sharing the costs of supportive cancer medications with private insurance to restrict public insurance coverage to patients who had no insurance.[8] Pharmacy students were employed to interview patients waiting for chemotherapy; these interviews showed that 40% of the patients had private drug insurance that could be utilized for supportive cancer medications.[8]

We sought to implement our hospital's payer-of-last-resort drug policy for ambulatory care and to evaluate a reimbursement model for IV iron in several dialysis units in our region.

DESCRIPTION OF PROGRAM

The Nova Scotia Central Zone's renal program provides HD to about 400 patients per year. The program consists of 3 hospital in-centre HD units (300 patients) and 4 satellite HD units (100 patients). Over the past 2 years, the number of patients requiring HD in this region has increased by nearly 7% per year (unpublished data). To manage the increasing costs of delivering dialysis medications, a new reimbursement model was developed, applying the principles of the institution's policy for funding medications used in ambulatory care.

IV iron was the target medication selected for this initiative because it is one of the medications most commonly prescribed and administered during dialysis. In addition, IV iron is a benefit under the publicly funded provincial Pharmacare Programs. Our renal program uses a nurse- and pharmacist-led anemia management protocol for IV iron and erythropoietin-stimulating agents, which is based on standards of care for anemia in patients with chronic kidney disease.[9,10] Engagement and support from renal program managers, pharmacists, nursing staff, physicians, and social workers were obtained for this initiative. Starting in March 2015, a 6-month feasibility pilot was conducted at one of the smaller in-centre HD units (50 patients) to identify and resolve any perceived or actual barriers before full implementation throughout the renal program. Standardized education was provided to all renal program staff to ensure that patients would receive a consistent message regarding the change in coverage for dialysis medication. All dialysis patients received a letter outlining how medications used in the renal program are funded. Drug coverage information was collected from each patient, drug plan coverage forms were completed as required, and prescriptions for IV iron were faxed to a single community pharmacy (designated through the hospital procurement process). The community pharmacy billed the patient's public or private insurance, and any copayments or deductibles remaining were billed to the renal program. A patient-specific supply of IV iron was delivered by the community pharmacy to the dialysis unit for storage and administration by staff. Feedback from patients and staff was key in shaping the medication reimbursement model.

In September 2015, two larger in-centre HD units began implementing this medication initiative; however, without dedicated staff to interview patients and conduct follow-up with the community pharmacy, implementation was successful in only 60% of patients. It was realized that it would be helpful to have a dedicated resource person, with knowledge of drug access navigation, to lead the dialysis medication reimbursement program across all dialysis units, to ensure consistent medication refills and ongoing patient enrollment, and thus to realize the potential cost savings. A funding proposal for a pharmacy practice assistant (PPA) to serve as the drug access navigator was submitted and approved by senior management. The analysis supporting this proposal showed that the cost of the PPA could potentially be offset by efficient and effective application of the existing ambulatory drug funding policy to dialysis medications; the PPA would also be available to support other core areas of the renal program (i.e., conducting medication reconciliation, managing inventory, preparing medications, and navigating coverage for other medications).

In April 2017, the renal program hired a PPA (A.V.) to support drug access navigation and to lead implementation of the funding program for ambulatory dialysis medication for about 400 patients receiving hemodialysis in the 7 HD units. The PPA worked closely with all stakeholders involved in the project to adapt procedures to meet the specific needs of each dialysis unit. Figure 1 outlines the steps in the ambulatory dialysis medication reimbursement model. The PPA oversees the management and reimbursement components of the funding model for the 7 HD units. For the 2 larger in-centre dialysis units, the PPA obtains new or refill prescriptions for IV iron, completes any necessary drug coverage forms with prescribers, receives delivery of the IV iron from the community pharmacy daily (or as needed), and organizes the patient-specific supply in the various dialysis units. The PPA maintains inventory records using an index card system. A card is affixed to each patient's own supply of IV iron; when the balance declines to 2 vials, nursing staff place the card in the PPA's bin, which prompts the PPA to obtain a refill from the community pharmacy. In addition, the PPA receives and reviews a copy of the prescription receipts, which detail the amount billed to private or public insurance as well as the copayments or deductibles that are billed to the renal program. The community pharmacy maintains a database of the billing information, and reports are generated monthly and reviewed with the team.

To expedite collection of drug coverage information and the patient's supply of IV iron before the patient starts dialysis, nurses in the outpatient nephrology clinic give to patients the letter explaining how medications in the renal program are funded; the nurses also obtain information about private or public drug insurance from the patient. If a patient requires IV iron and the prescription has not yet been obtained from the community pharmacy, each dialysis unit has a small ward stock supply (5–10 vials) of IV iron that can be "borrowed" until the patient's own prescription is available. In the satellite dialysis units and one smaller in-centre HD unit, the PPA's role is to support the charge nurse, who is responsible for obtaining new or refill IV iron prescriptions, completing drug coverage forms with the prescribers, and receiving and organizing the weekly delivery of the patient-specific IV iron from the community pharmacy.

EVALUATION OF PROGRAM

From April 2017 to March 2018, data were collected from the community pharmacy and the databases maintained by the

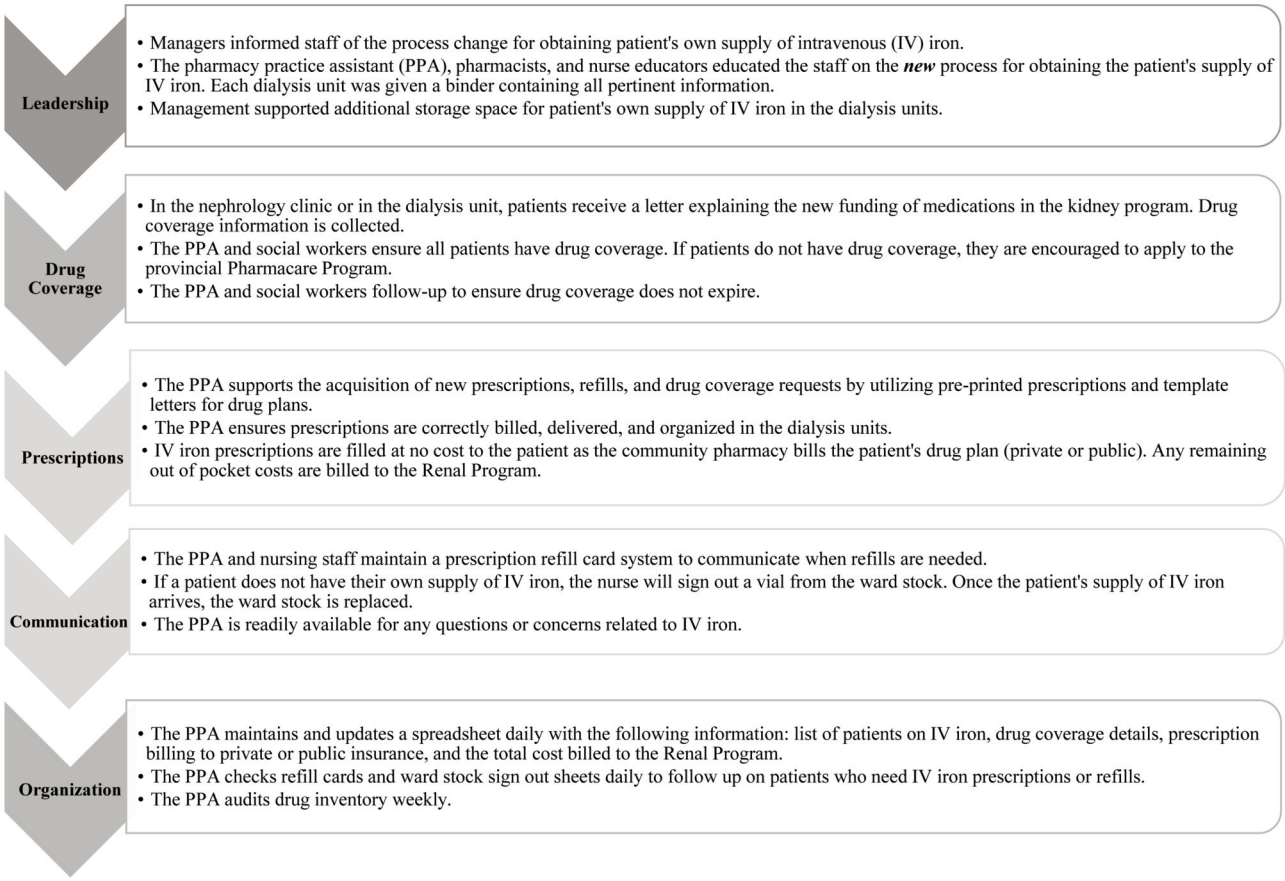

Figure 1. Reimbursement model for ambulatory dialysis medications.

PPA to determine the number of patients who needed IV iron, the number of vials of IV iron dispensed, the type of insurance coverage (private or public) available for each patient's medication, the total costs billed and covered by private and public drug insurance, and the total cost billed to the renal program (including copayments and deductibles for patients with insurance coverage). For patients with no drug insurance, we negotiated with the community pharmacy to pay the same price for IV iron as the hospital was paying for iron sucrose. Because implementation of the program occurred earlier in the in-centre HD units than in the satellite HD units, we used cost data from April 2017 to March 2018 for the in-centre units and from July 2017 to March 2018 for the satellite units. We also determined that the cost of a PPA maintaining the hospital ward stock system for the 7 HD units (including ordering, receiving, storing, and managing IV iron) was equivalent to the cost of having a PPA lead the payer-of-last-resort model for reimbursement for dialysis medication.

A total of 408 patients were enrolled in the ambulatory HD medication reimbursement program: 330 patients in the in-centre units and 78 patients in the satellite units (Table 1). Of these, 253 (62%) were men and 155 (38%) were women. A total of 396 patients (97%) had medication insurance, and 12 (3%) had no medication insurance. Of those with medication insurance, 260 had public insurance and 136 had private medication coverage (Table 1).

Table 2 outlines the total costs billed to and covered by drug insurance, as well as the total cost billed to the renal program for patient copayments, deductibles, and those with no drug insurance coverage ($90 204.79). If the renal program had paid for all vials dispensed during the evaluation period, the hypothetical ward stock drug cost would have been $360 562.50. The overall cost savings to the renal program could thus be calculated as $270 357.71. However, the renal program is itself a provincially funded program, and 64% of the patients enrolled in the HD medication reimbursement program had public drug insurance. Therefore, we determined that the net cost to the provincial system was $236 689.13 (including all costs billed to the Pharmacare Programs and the cost of the renal program). The resulting overall cost saving to the provincial system was $123 873.37. These costs and savings are summarized in Table 3.

Table 1. Baseline Drug Coverage for Patients Receiving Hemodialysis

Type of Insurance	Setting for Hemodialysis; No. (%) of Patients		
	Satellite Units* (*n* = 78)	In-Centre Units† (*n* = 330)	Total (*n* = 408)
Public drug insurance	54 (69)	206 (62)	260 (64)
Private drug insurance	17 (22)	119 (36)	136 (33)
No drug insurance	7 (9)	5 (2)	12 (3)

*From July 2017 to March 2018.
†From April 2017 to March 2018.

Table 2. Costs Associated with the Hemodialysis Medication Reimbursement Model

Patient Group, by Type of Insurance	No. of Vials Dispensed	Amount Billed to Insurance ($)	Cost Covered by Insurance ($)	Cost to Renal Program ($)*
Patients with public drug insurance	4270	185 484.21	146 484.34	38 999.87
Patients with private drug insurance	4775	211 224.88	181 394.96	29 829.92
Patients with no drug insurance	570	NA	NA	21 375.00
Total	9615	396 709.09	327 879.30	90 204.79

NA = not applicable.
*For patients with insurance, the cost to the renal program was calculated as the total billed to insurance minus the cost covered by insurance. For patients with no insurance, the full cost was covered by the renal program.

Table 3. Renal Program versus Provincial System Costs with the Hemodialysis Medication Reimbursement Model

Variable	Cost ($)
Hypothetical cost for renal program to supply IV iron as ward stock*	360 562.50
Actual cost to renal program†	90 204.79
Savings to renal program‡	270 357.71
Actual cost to provincial system§	236 689.13
Savings to provincial system¶	123 873.37

*Calculated as total number of vials × hospital's cost/vial.
†Total cost billed to the renal program (see Table 2).
‡Calculated as the hypothetical cost minus the actual cost to the renal program.
§Calculated as the sum of the cost covered by public drug insurance plus the total cost to the renal program (see Table 2).
¶Calculated as the hypothetical cost minus the actual cost to the provincial system.

IMPLICATIONS AND SIGNIFICANCE FOR PRACTICE

With the ever-growing number of patients requiring dialysis, and the need for programs to manage drug expenditures, application of the hospital's policy for funding drugs used in ambulatory care shifts and aligns HD medication coverage with patients' insurance providers. The policy was developed to provide an equitable, consistent process that hospital staff and physicians could use in determining how drugs and their administration are to be funded in outpatient settings. According to this policy, the renal program was designated as the payer of last resort, balancing the need for financial sustainability with societal responsibility to provide options for patients who cannot afford to pay for their own medications. The payer of last resort is defined as the last payer once all other sources of payment, such as patient assistance programs and private and/or public insurance have been billed.[6] Patients not eligible for coverage by private insurance were encouraged to enroll in the provincial Family Pharmacare Program, which has income-dependent deductibles.[5] Based on patients' deductibles, the renal program determines whether or not it is in the program's best financial interest to assist with the deductible or to pay the cost of the medication each month. For publicly funded plans, the cost saving is greatest in the months leading up to each patient's yearly renewal month (i.e., April), because patients must satisfy the plan deductible or premium, and a certain percentage (20%–30%) of each prescription cost is applied until the maximum copayment is reached. Once both the deductible and the maximum copayment have been reached, there is no charge for additional prescriptions. A significant benefit to patients with this reimbursement program is that the renal program pays down the deductibles and copayments associated with IV iron prescriptions. This reduces patients' out-of-pocket costs for the year and allows them to receive other prescriptions that they otherwise might not be able to afford.

Several limitations are associated with this type of reimbursement model. First, for patients with no drug insurance, we were able to negotiate with the community pharmacy a cost for IV iron that was the same as the hospital's cost for iron sucrose. As a result, for those patients without insurance, prescription costs would have been higher if IV iron had been supplied using the community pharmacy's standard pricing. In addition, changes frequently occur with medication coverage for dialysis patients, and overall cost savings therefore tend to decrease or increase proportionally to the number of patients with private insurance. Although staff input informed implementation of the program, staff members' and patients' satisfaction with the process was not evaluated. Furthermore, patients' clinical status was not assessed; however,

there were no changes to the anemia management protocol or delays in access to IV iron during the implementation, so it is unlikely that any patients were adversely affected by the change in reimbursement of IV iron. Additionally, for larger HD units without a PPA, it would be important to have a dedicated person leading this type of program to realize the cost savings. We are currently expanding this reimbursement model to include other dialysis medications. Hiring a PPA to lead the HD medication reimbursement model allowed our renal program to maximize cost savings during initial implementation. Since then, however, there has been a shift in responsibilities, with the charge nurse in most HD units now managing the program, with support from the PPA, which in turn allows the PPA to focus on medication reconciliation, inventory control and record keeping, special authorization for high-cost medications, and preparation of medications.

CONCLUSION

The authors' renal team successfully developed, implemented, and evaluated an innovative and sustainable reimbursement model for a common medication used in ambulatory dialysis. The HD medication reimbursement model promotes cost savings for both the provincially funded renal program and the public drug program, which ultimately contributes to a more sustainable health care system.

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Has the Time Come to Abandon Routine Use of Unfractionated Heparin in the Hospital Setting?

THE "PRO" SIDE

The first generation of iPhones represented a fundamental shift in communication, and follow-up versions quickly took on the functionality of "smartphones". But what happened to the old flip cell phones? Is anyone still using them? Just as mobile phone users shifted to smartphones, their service providers switched to new and improved practices, because supporting the old way of doing things became too costly. In health care, adaptation of new technology is inconsistent at best, and health care systems are often required to support a variety of platforms, simply because challenging prescriber preferences and engagement in change management is seen as too cumbersome. Much like the old flip phones, unfractionated heparin (UFH) continues to be used by some prescribers who "perceive" comfort, reliability, and cost-effectiveness with its use, but I will argue here that it's time to adopt newer therapies for treatment and prophylaxis of venous thromboembolism (VTE).

Isn't UFH old and cheap?

Well, UFH is certainly old, having been discovered in 1916 and undergoing its first clinical trails in 1935. UFH was originally manufactured from the mucosal tissues of slaughtered meat animals, such as porcine intestines and bovine lungs, with later advances in manufacturing occurring in the face of a contamination crisis. Recently, UFH manufacturing has undergone significant enhancements to ensure production according to the Current Good Manufacturing Practices of the US Food and Drug Administration, but this has resulted in substantially higher costs, with only a limited number of manufacturers now making this product.[1] Along with the increasing cost of UFH itself come various infrastructure costs that act as a drain on health care systems. For example, UFH infusions for VTE treatment require costly nursing time and monitoring by means of activated partial thromboplastin time (a test that is often inaccurate) or the increasingly expensive anti-Xa assay[2]; there are also costs associated with treating heparin-induced thrombocytopenia/thrombosis (HIT/T). The perceived cost-effectiveness of UFH has also been increasingly questioned. In this context, low-molecular-weight heparins (LMWHs) are seen as a safe, effective, and cost-effective alternative in the prevention and treatment of VTE.[3-5]

The LMWHs allow for home-based VTE therapy and prophylaxis with only limited monitoring requirements.[6,7] In a meta-analysis involving treatment of patients with VTE, there was no significant difference in risk between UFH and LMWH in terms of recurrent VTE (relative risk [RR] 0.85, 95% confidence interval [CI] 0.65–1.12), pulmonary embolism (RR 1.02, 95% CI 0.64–1.62), major bleeding (RR 0.63, 95% CI 0.37–1.05), and minor bleeding (RR 1.18, 95% CI 0.87–1.61).[6] Among medical patients, VTE prophylaxis with LMWH reduced the risk of VTE and deep vein thrombosis, with no increased risk of bleeding or death, relative to UFH.[7]

We know UFH is safe, so we should continue to use it, right?

Actually, UFH is associated with a higher risk of HIT/T relative to LMWHs.[5] At one Canadian site, introduction of a UFH-free HIT/T prevention policy dramatically reduced rates of HIT/T and resulted in significant system-wide savings. More specifically, following introduction of the policy, the annual rate of positive HIT/T assay results decreased by 63% and the rate of HIT/T decreased by 91%. Hospital HIT/T-related expenditures decreased by $266 938 per year in the avoid-heparin phase.[8,9] Broader implementation of UFH reduction by Alberta Health Services has also shown promising results, with investigators now finalizing results for publication.

Isn't there always a place for a good "burner phone"?

UFH does have a place in therapy, though only in very specific situations. For example, the use of UFH for coagulation management during cardiopulmonary bypass is likely to continue for some time to come, although the use of LMWH in this setting has been piloted.[10] The perception that UFH administration and its effects can be quickly stopped means there is continued reliance on UFH for planning surgical interventions that involve maintenance of anticoagulation. Greater understanding of the pharmacokinetics and pharmacodynamics of LMWHs will ultimately expand use of these agents, but for the time being UFH use is likely to continue.

Much like our embrace of the smartphone and the consequent demise of the flip phone, the time has come to say goodbye to

the use of UFH for mainstream VTE treatment and prophylaxis and to look to the LMWHs and the new oral agents (though granted, the latter is another topic altogether).

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THE "CON" SIDE

At times, old remains more functional than new, with the advantages of new being offset by certain shortcomings. For example, I still prefer reading a book or a newspaper over an electronic interface—both formats have their place, but I'm not ready to get rid of paper yet. Similarly, although the use of low-molecular-weight heparins (LMWHs) is expanding in Canadian hospitals, a role continues to exist for unfractionated heparin (UFH) in the prevention and treatment of venous thromboembolism (VTE).

Both UFH and LMWH have been studied extensively in the prevention and treatment of VTE, and both are recommended in current guidelines. More recently, the cost differential between UFH and LMWH has decreased, resulting in more frequent utilization of LMWH.

Which agent is selected for use in any given clinical scenario depends upon many factors, including efficacy, safety, and cost. In medical patients for whom thromboprophylaxis is required, the 2012 *Chest* guidelines recommend use of LMWH, low-dose UFH, or fondaparinux strategies, with the choice based on patient preference, compliance, ease of administration, and cost (grade 1B recommendation).[1] Among non-orthopedic surgical patients, the 2012 guidelines delineate the choice by risk of VTE but acknowledge that the risks of fatal pulmonary embolism, symptomatic VTE, and major bleeding are similar between LMWH and UFH.[2] For the acute treatment of deep vein thrombosis or pulmonary embolism in the absence of cancer, the updated 2016 *Chest* guidelines recommend long-term therapy with a direct oral anticoagulant (grade 2B recommendation) over vitamin K antagonists, and also suggest vitamin K antagonists over LMWH (grade 2C recommendation).[3] Little mention is made of initial parenteral anticoagulants in the 2016 report, but the 2012 guidelines recommended LMWH or fondaparinux (grade 1B recommendation) over UFH (grade 2C recommendation).[4]

Patients are diverse and at times are at extremes of weight or suffer from compromised end organ function. On the basis of current population trends, these demographic characteristics are expected to continue evolving. Although both LMWH and UFH can be used in most patients, LMWH may provide the advantages of fixed weight-based dosing and less laboratory assessment to ensure therapeutic levels. However, these advantages may actually serve as limitations in these subpopulations because of altered pharmacokinetics. For example, LMWH may accumulate in patients with impaired renal function, which increases the risk of major bleeding, resulting in the need for costly assessments of anti-Xa levels to examine the extent of anticoagulation. The Canadian product monographs for enoxaparin, dalteparin, and tinzaparin suggest that the safety and efficacy of these LMWHs have not been fully established for patients over 120 kg or below 45 kg.[5-7] The product monograph for enoxaparin suggests a dosage adjustment for patients with severe renal impairment (creatinine clearance < 30 mL/min), with a recommended dosage of 1 mg/kg once daily in this population.[5] The product monographs for dalteparin and tinzaparin provide no clear guidance for patients whose creatinine clearance is below 30 mL/min and suggest that risks for accumulation and bleeding exist; as such, individualized clinical and laboratory monitoring is recommended.[6,7] In the case of tinzaparin, further recommendations are provided for close monitoring of elderly patients with low body weight (e.g., < 45 kg) and those predisposed to decreased renal function.[7]

The ability to easily adjust UFH dosing with well-established laboratory tests and validated dosing nomograms may provide a critical advantage for UFH in patients with renal dysfunction and those at extremes of weight—populations commonly seen in Canadian hospitals. Data from cycle 1 of the Canadian Health Measures Survey (2007–2009) for the presence of chronic kidney disease indicated that the prevalence was 12.5% of the cohort studied, with 3.1% having stage 3–5 disease.[8] Acute kidney injury is common, representing 8%–16% of hospital admissions.[9] As common as renal dysfunction may be, attempting to dose LMWH at the extremes of body weight may become even more of an issue over time. According to Statistics Canada, 61.3% of adult Canadians were overweight or obese in 2015.[10] In Canada between 1985 and 2011, the prevalence of class II obesity (body mass index [BMI] 35.0–39.9) increased from 0.8% to 3.6%, and the prevalence of class III obesity (BMI ≥ 40) increased from 0.3% to 1.6%.[11] In the United States in 2014, the prevalence of morbid obesity (class III) was approximately 8% (or about 1 in every 12 people).[12] Limited data are available to guide dosing of LMWH in patients with morbid obesity, and dosing on the basis of total body weight may result in accumulation of these agents. Data for enoxaparin in this population suggests that a reduced weight-based dose (less than 1 mg/kg) is warranted and that full dosing may result in accumulation and increased risk of bleeding over time.[13,14]

In conclusion, the advantages of LMWH, which include ease of use and fixed dosing with minimal need for laboratory testing, may actually prove to be limitations in certain select populations that are seen clinically. Conversely, the acknowledged limitations of UFH may serve as advantages in these populations. As a result, UFH continues to play an important role in the management of patients who have or are at risk of VTE. Like your favourite book, older technology may at times be preferred to the new.

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The Pharmacist Guide to Implementing Pharmaceutical Care

Alves da Costa F, van Mil JWF, Alvarez-Risco A, editors. Springer International Publishing, 2019. ISBN-13: 9783319925752. Hardcover, 506 pages. $248.50 ($211.23 for CSHP members; see below).

The Pharmacist Guide to Implementing Pharmaceutical Care is intended as a comprehensive reference for pharmacists who want to incorporate pharmaceutical care into their practice. The book's 3 editors are all pharmacists with extensive experience in clinical practice and research. In addition, 67 authors contributed to the various chapters within each of the 8 parts.

Part I (chapters 1 and 2) seeks to establish a standardized definition of pharmaceutical care. Part II (chapters 3–12) addresses aspects of the pharmaceutical care process that are directly related to the patient, such as conducting medication reviews and adherence. Part III (chapters 13–17) describes pharmaceutical care in different regions of the world. Part IV (chapters 18–21) outlines implementation strategies in different settings, such as the community, nursing homes, and hospitals. Part V (chapters 22–25) describes the role of pharmaceutical care in the dispensing of medications. Part VI (chapters 26–33) examines the provision of pharmaceutical care to patients with specific conditions. The remuneration of pharmaceutical care is described in Part VII (chapters 34–38), and part VIII (chapters 39 and 40) looks at teaching pharmaceutical care in both the university and health care settings.

The book starts off strongly as it tries to establish a standardized definition of pharmaceutical care that could be used anywhere in the world. However, although the book seeks to be a comprehensive guide to all aspects of pharmaceutical care, the editors could have streamlined some of the content. For example, readers interested in methods for guideline development have other sources for this information, and the content in chapter 9 could therefore have been less detailed. Chapters 10, 11, and 12 discuss quality indicators, the Economic, Clinical, and Humanistic Outcomes (ECHO) Model, and the development of core outcome sets, respectively. However, the information in these chapters would have been better placed in chapter 18, which ends with only a brief mention of assessing the success of implementation of pharmaceutical care. The current state of pharmaceutical care around the world is discussed in part III. Chapter 16, concerning Latin America, is one of the most interesting: that practice environment is quite different from the other geographic areas mentioned, and the chapter's authors describe their deep exploration of the root cause of these differences. It is unclear why part III makes no mention of Africa. Furthermore, the other chapters in part III have considerable overlap and could have been reframed to focus on the similarities and differences in the various geographic areas described. Part V describes pharmaceutical care in the dispensing of prescription and nonprescription medications, information that could have been presented more briefly in part II, as an aspect of the pharmaceutical care process. In part VI, which separately addresses the management of various conditions, much of the therapeutic content could have been eliminated, as this is available from other sources that evaluate new evidence and update their recommendations annually, such as GOLD (the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, Global Initiative for Chronic Obstructive Lung Disease; https://goldcopd.org) for chronic obstructive pulmonary disease and GINA (the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma; https://ginasthma.org) for asthma. The remaining material describing important disease-specific outcomes that have been identified in the literature, such as the excellent description at the end of the chapter on pharmaceutical care and cardiovascular disease, is likely to be of more relevance to readers.

Overall, the editors and authors of this book should be commended for taking on such an ambitious project. The book provides readers with a snapshot of where pharmaceutical care is internationally and offers multiple examples of practices and initiatives. Pharmacists who practise in areas where pharmaceutical care is not very advanced or who wish to further their practice of pharmaceutical care may find specific parts of the book useful as a starting point for their own learning. For example, pharmacists who have been tasked with implementing a new program at their practice site may find the information about program evaluation and quality indicators useful.

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The Pharmacist Guide to Implementing Pharmaceutical Care and other products and publications are available to CSHP members at a reduced rate through CSHP's website, https://www.cshp.ca/bookstore-members. Members will be asked to log in before being allowed to proceed to CSHP's virtual bookstore.

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Facility: University of Alberta

Laura Murphy

Pharmacy Clinical Leader, Toronto Rehabilitation Institute, University Health Network, Toronto, Ontario

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Clinical Pharmacist, Orthopaedics/Neurology and Multiple Sclerosis Clinic, St. Michael's Hospital, Toronto, Ontario

Traineeship: Advanced training in multiple sclerosis treatment

Education Grant: $6,400

Facility: Multiple Sclerosis Clinic, University of Colorado Hospital

Megan Riordon

Pharmacy Manager, Clinical Practice, Kingston Health Sciences Centre, Kingston, Ontario

Scholarship: ASHP Pharmacy Leadership Academy

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Education Scholarship: US $6,650

Communication : s'adapter à une nouvelle époque, à de nouveaux besoins

par Tania Mysak

Lors d'une rencontre récente, une femme nous a raconté son rétablissement après une blessure à la tête. Une chute en apparence banale lui a occasionné une aphasie suffisamment grave pour compliquer les communications même les plus simples. Sa vie, tant familiale que professionnelle, s'en est trouvée altérée pour toujours. Même si son discours visait à dévoiler l'importance de la « perspective du patient », il m'a poussée à réfléchir à mes années de pratique, principalement aux cas des patients souffrant de troubles neurologiques. Combien de vies ai-je vues être profondément bouleversées par des blessures minant la compréhension ou la production du langage?

Ces moments nous font réaliser à quel point nous tenons la capacité de communiquer pour acquise jusqu'à ce qu'elle fasse défaut. Toutefois, il nous arrive de ne pas tout comprendre ou d'être incompris même lorsque nos phrases sont correctement construites et distinctement prononcées. Ainsi, il se peut qu'un patient ne saisisse pas entièrement l'information ou les choix que lui communique un prestataire de soin. Dans un autre ordre d'idées, un courriel bien intentionné, mais mal compris, peut conduire à une succession de courriels qui nécessiteront une rencontre pour clarifier les positions. Ou encore, un leader de pharmacie peut ressentir de la frustration de voir des collègues qui ne sont pas au courant des nouvelles politiques néanmoins maintes fois répétées.

L'Association nationale des organismes de réglementation de la pharmacie évalue la compétence communicationnelle des pharmaciens, mais se concentre surtout sur leurs compétences langagières à l'écrit et à l'oral et sur l'empathie démontrée lors d'entrevues avec les patients; des aptitudes nécessaires, mais qui ne sont peut-être pas suffisantes aujourd'hui, étant donné la complexité des défis communicationnels et des différentes façons d'accéder à l'information.

Les cibles du programme Excellence de la Société canadienne des pharmaciens d'hôpitaux (SCPH) visent aussi les compétences communicationnelles. Notre sondage (https://www.cshp.ca/what-we-heard) révèle qu'à peine deux tiers des patients (68 %) se disaient satisfaits de leur communication avec l'équipe de la pharmacie. Une proportion semblable de patients considérait que la communication avec leurs fournisseurs de soins de santé n'était pas bonne. Si vous réfléchissez à votre pratique ou à la gestion de votre équipe, que faudrait-il faire pour que la communication avec vos patients ou collègues soit efficace? En tant que professionnels, pouvons-nous exprimer clairement notre valeur et nos besoins aux parties prenantes externes? Ou parlons-nous un jargon de pharmacien qui nous empêche de communiquer efficacement à divers auditoires.

Il en est de même à la SCPH, nous devons réfléchir aux échanges avec nos membres et avec les parties prenantes externes. Notre équipe et des volontaires ont consacré de nombreuses heuresà la création de produits de haute qualité : nos activités éducatives, des ressources pour la pratique, le programme Excellence et même ce journal. Nos membres connaissent-ils ces produits? La SCPH a travaillé d'arrache-pied pour mettre en place des plans faisant progresser la profession, mais la communication entre la direction et les membres est-elle assez efficace pour qu'elle sache si ces plans répondent aux besoins des membres? Un regard honnête sur les compétences communicationnelles de la SCPH révèle que nous pouvons nous améliorer.

Les outils de communications modernes sont sophistiqués, puissants et complexes, à l'image de nos médicaments en pharmacie. L'exploration de données, les médias sociaux interactifs et la surveillance avancée sont maintenant choses communes. Mais lesquels choisir? Comment les exploiter? Comment entrent-ils en interaction avec nos membres? Ils nécessitent un ensemble de compétences que nous devons acquérir pour établir une réelle discussion avec nos membres et entre les membres. À cet effet, la direction de la SCPH a mis sur pied une équipe de marketing et de communication qui sera à la hauteur de l'excellence déployée au sein de notre pratique professionnelle et de nos équipes de services commerciaux. La première étape sera la création d'un poste de Directeur du marketing et de la communication qui sera pourvu dès ce printemps. Cette nouvelle position nous fournira les compétences communicationnelles nécessaires à la reconnaissance et à la satisfaction des besoins des membres de la SCPH, de nos partenaires et de la profession.

Comme disait George Bernard Shaw : « Le plus grand problème en communication, c'est d'avoir l'illusion qu'elle a eu lieu. » C'est ce que la SCPH cherche à éviter! Restez à l'affût!

[Traduction par l'éditeur]

Tania Mysak, BSP, Pharm. D., est présidente désignée et agente de liaison de la Société canadienne des pharmaciens d'hôpitaux.

Communication: Adapting to Changing Times and Needs

Tania Mysak

At a recent meeting, a speaker related her experiences recovering from a head injury. Her relatively minor fall had led to a form of aphasia serious enough to make basic communication difficult. Her work and family life were forever altered. Although the objective of the talk was to provide that all-important "patient perspective", I began to reflect on all my years of practice, primarily with neurology patients. How many times had I witnessed similar scenarios in which someone's life had been profoundly affected because an injury had left them with an inability to understand or express language?

Moments like these make us acutely aware of how we take communication for granted until something goes awry. However, even when our sentences are properly structured or spoken, we can still find ourselves not understanding or being understood. Maybe a patient leaves an encounter with a care provider confused by information and choices not fully understood. Perhaps a well-intentioned e-mail is misinterpreted, which leads to several more e-mails and finally an in-person meeting to resolve the issue. Maybe a pharmacy leader becomes frustrated with colleagues who are unaware of a new department policy, despite its having been communicated multiple times.

The National Association of Pharmacy Regulatory Authorities outcomes for graduating pharmacists include communication skills, yet they largely focus on proficiency in written or verbal language, or on empathetic interview skills with patients—all valuable competencies, but are they sufficient for today's complex communications challenges and modes of consuming information?

The Canadian Society of Hospital Pharmacy (CSHP) Excellence targets consider communication skills as well. Our survey (https://www.cshp.ca/what-we-heard) indicated that only about two-thirds of patients (68%) were satisfied with their conversations with the pharmacy team. The same proportion felt that communication between health care providers wasn't good. Reflecting on your own practice or the management of your team, what will it take to achieve good communication with both patients and colleagues? As a profession, can we articulate our value and needs to external stakeholders, or do we suffer from too much "pharmacist-speak" and an inability to convey our messages to diverse audiences?

Similarly, CSHP must collectively reflect upon our own communication with our members and external stakeholders.

Countless volunteer and staff hours are devoted to creating high-quality products such as our educational events, tools for practice, the Excellence Program, and even this journal. Are our members aware of these products? CSHP has worked diligently on successive strategic plans to advance the profession, but are the channels of communication between the leadership and the membership open enough to know whether these plans are aligned with what our members need and want? A clear-eyed look at CSHP's own communications competencies will undoubtedly show there is room for improvement.

Modern tools of communication are as sophisticated, powerful, and complex as the medicines we have in our pharmacies. Data mining, interactive social media, and advanced surveying are common now. But which ones we select, when we use them, how they interact with our individual members … these represent a skill set we must acquire to start a real conversation with and among our membership. To that end, CSHP's leadership is creating a marketing and communications team, which will complement the excellence we now have in our professional practice and corporate services teams. As a first step, a new Director of Marketing and Communications position will be created and filled this spring. This new position will give us the communications competencies we need to discover and meet the needs of CSHP members, our external partners, and the profession at large.

George Bernard Shaw once said, "The single biggest problem in communication is the illusion that it has taken place." It's a problem that CSHP plans not to have! Stay tuned.

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

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- proposent des occasions supplémentaires aux membres d'agir à titre de leaders d'opinion et de ressources clés pour le Conseil de la SCPH sur des questions de pratique spécialisée, dont la rédaction de déclarations de principes, de lignes directrices et des documents d'information pertinents

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