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Adverse Drug Reaction Reporting: Opportunities to Increase Pharmacists' Role

Stephen Shalansky

This issue of the *Canadian Journal of Hospital Pharmacy* (*CJHP*) includes 2 articles that concern adverse drug reactions (ADRs). Roy and Ma[1] report on the impact of a policy change on pharmacists' reporting of ADRs, while Auyeung and Lee[2] provide a case report of Stevens–Johnson syndrome associated with ciprofloxacin use. Over the past several decades, the *CJHP* has published numerous articles describing pharmacists' involvement in ADR reporting and treatment, as well as the incidence of adverse drug events. This long-term, continuing focus on ADR reporting in the *CJHP* is a good prompt for all of us who work as pharmacists to re-evaluate our current perspectives on this topic and to become aware of new opportunities to increase pharmacists' role in this important responsibility.

ADR monitoring is key to drug regulation processes around the world, and pharmacists play an integral role in drug safety in all practice settings.[2,3] The day-to-day role of clinical pharmacists in hospitals is particularly well suited for identifying and reporting ADRs. In the context of its Therapeutics Access Strategy, Health Canada operates the MedEffect Canada program, with the intent of centralizing and simplifying ADR reporting.[4] Faculties of pharmacy across Canada teach students about the goals and importance of ADR reporting, and clinical rotations often include components of the ADR reporting process among their required activities. Despite the emphasis on ADR reporting in pharmacy education and hospital pharmacy practice, the frequency of reporting remains suboptimal, with pharmacists being responsible for only 10% of all ADR reports submitted to Health Canada in 2012.[1,5] What can we, as pharmacy practitioners, do to improve the uptake of this fundamentally important responsibility?

First and foremost, we can become familiar with the current Canadian ADR reporting process, and be role models the next time any of us encounters a reportable ADR. With implementation of entry-to-practice PharmD programs across Canada and the resulting increase in the number of student rotations in hospitals, there is ample opportunity to involve students in the MedEffect Canada program. In a recent study, Wentzell and others[6] showed that the availability of pharmacy students to facilitate ADR reporting helped to offset pharmacists' workload associated with this activity, and increased the frequency of ADR reporting. Furthermore, the students strongly agreed that the responsibility for reporting ADRs should remain with pharmacy students during future rotations.

The proposed amendments to the Food and Drug Regulations that would require hospitals to report serious ADRs, published in June 2018 in the *Canada Gazette, Part I*,[7] create incentive to be more proactive about ADR reporting. Once you have worked through one ADR report for Health Canada, it will be much easier the next time, and you can start to build momentum. Teach your students about ADR reporting when on rotation and even during didactic lectures. Hold a journal club about the MedEffect Canada program, even if you don't have a case example immediately on hand. Also, be sure to educate your patients about medication safety principles, including ADR reporting, particularly for patients who have previously experienced an ADR. It is important to keep in mind that patients can report ADRs directly to Health Canada through the same process as pharmacists use.

Case reports are a constructive mechanism for sharing valuable information about ADRs, and an excellent way to start or build on your publication experience. In my own very first publication (which happens to have appeared in *CJHP*),[8] I reported on an ADR resulting from a drug interaction, and I know several other clinical pharmacists whose first publication

involved a case report of an ADR. Roy and Ma[1] have gone a step further by publishing a description of how they implemented a policy change to reinforce and streamline the ADR reporting requirements at their institution's outpatient clinics. Of course, ADR reporting is the responsibility of all members of the health care team, and it is also a key component of Accreditation Canada's Medication Management Standards—a good reminder that such reporting is not considered optional by the accreditors.[9]

Large-scale studies in both Canada and the United States have demonstrated that adverse drug events are both common and often preventable.[10,11] ADR reporting has resulted in many important changes to drug labelling, the publication of safety alerts, and even the withdrawal of specific products from the Canadian market.[12] ADR reporting does take time, but the impact it can have on patient care and medication safety is clearly worth the small effort it takes up front.

When faced with an ADR in your clinical practice, keep your patients in mind. There is undoubtedly a time when you have made a therapeutic recommendation or performed an intervention in which information about a previously reported ADR played a vital role. Help ensure that pharmacists faced with similar situations in the future have as much information as possible to make the best therapeutic interventions for the unfortunate patients who have experienced an ADR or are at risk of a future ADR. Collectively, we can help improve patient and product safety, as well as enhancing Canadians' knowledge to ensure they can make the best choices possible about their medication regimens.

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La déclaration des réactions indésirables aux médicaments : une occasion d'étendre le rôle des pharmaciens

par Stephen Shalansky

Le présent numéro du *Journal canadien de la pharmacie hospitalière* (JCPH) contient deux articles à propos des réactions indésirables aux médicaments (RIM). Roy et Ma[1] écrivent sur les effets d'un changement de politique concernant la déclaration des RIM par les pharmaciens tandis qu'Auyeung et Lee[2] présentent une observation clinique du syndrome de Stevens-Johnson associé à l'utilisation de la ciprofloxacine. Au cours des dernières décennies, le JCPH a publié bon nombre d'articles décrivant le rôle des pharmaciens dans la déclaration des RIM et le traitement de ces dernières ainsi que sur l'incidence des événements indésirables liés aux médicaments. L'intérêt marqué que porte depuis longtemps le JCPH pour la déclaration des RIM est un bon incitatif pour nous tous qui travaillons comme pharmaciens à réévaluer notre point de vue sur ce sujet et à devenir conscients des nouvelles occasions d'accroître le rôle des pharmaciens dans cet important champ de responsabilité.

La surveillance des RIM est centrale aux processus de réglementation des médicaments dans le monde et les pharmaciens sont indispensables en ce qui touche la sécurité des médicaments dans les différents milieux de pratique[2,3]. Le rôle quotidien des pharmaciens cliniciens dans les hôpitaux est particulièrement idéal pour la détection et la déclaration des RIM. Dans le cadre de sa Stratégie d'accès aux produits thérapeutiques, Santé Canada a élaboré le programme MedEffet Canada afin de centraliser et de simplifier la déclaration des RIM[4]. Les facultés de pharmacie de partout au Canada enseignent aux étudiants les objectifs derrière la déclaration des RIM ainsi que son importance et les stages cliniques comprennent souvent des éléments du processus de déclaration des RIM au sein de leurs activités obligatoires. Malgré l'accent mis sur la déclaration des RIM dans l'enseignement de la pharmacie et dans la pratique de la pharmacie hospitalière, la fréquence des déclarations est sous-optimale, car les pharmaciens n'avaient envoyé à Santé Canada que 10 % de l'ensemble des déclarations de RIM en 2012[1,5]. Que pouvons-nous faire en tant que praticiens de pharmacie pour améliorer la prise en charge de cette responsabilité fondamentale?

Tout d'abord, nous pouvons nous familiariser avec le processus canadien actuel de déclaration des RIM et agir de façon exemplaire la prochaine fois que l'un d'entre nous détectera une RIM pouvant être déclarée. Grâce à la mise en place de programmes de Pharm. D. comme diplôme d'entrée dans la profession partout au pays et au nombre accru de stages en hôpitaux qui en résulte, les occasions de faire participer les étudiants dans le programme MedEffet Canada sont nombreuses. Dans une étude récente, Wentzell et collab.[6] ont montré que la disponibilité des étudiants en pharmacie pour faciliter la déclaration des RIM permettait de réduire la charge de travail des pharmaciens associée à cette activité et d'augmenter la fréquence des déclarations de RIM. De plus, les étudiants étaient tout à fait d'accord pour dire que la responsabilité de la déclaration des RIM devrait demeurer celle des étudiants en pharmacie au cours de stages futurs.

Les modifications au Règlement sur les aliments et drogues qui obligeraient les hôpitaux à signaler les effets indésirables graves, publiées en juin 2018 dans la Partie I de *La Gazette du Canada*, [7] suscitent la motivation à déclarer plus diligemment les RIM. Après avoir fait une première déclaration de RIM à Santé Canada, les suivantes seront beaucoup plus faciles, et vous pourrez continuer sur votre lancée. Enseignez à vos étudiants à produire des déclarations de RIM durant leurs stages et même pendant les cours magistraux. Consacrez une séance d'un club de lecture au programme MedEffet Canada même si vous n'avez pas un exemple à portée de main. Assurez-vous aussi d'informer vos patients, particulièrement ceux qui ont déjà subi une RIM, à propos des principes de sécurité des médicaments, y compris la déclaration des RIM. Il est important de ne pas oublier que les patients peuvent déclarer des RIM directement à Santé Canada selon le même processus que celui utilisé par les pharmaciens.

Les observations cliniques représentent des mécanismes efficaces de diffusion d'information importante à propos des RIM et une excellente façon de commencer ou de continuer à publier. Dans le premier article que j'ai publié (et qui se trouve avoir paru dans le JCPH)[8], j'ai écrit sur une RIM causée par une interaction médicamenteuse et je connais plusieurs autres pharmaciens dont la première publication portait sur une observation clinique concernant une RIM. Roy et Ma[1] sont allés un peu plus loin en publiant une description de la façon dont ils ont mis en place un changement de politique destiné à confirmer et à rationaliser les critères de déclaration des RIM dans les cliniques de consultation externe de leur établissement. Bien sûr, la déclaration des RIM demeure la responsabilité de l'ensemble des membres de l'équipe de soins; elle est aussi un élément central des normes de gestion des médicaments d'Agrément Canada, ce qui nous rappelle que ces déclarations ne sont pas facultatives dans l'esprit des instances d'agrément[9].

Des études à grande échelle réalisées au Canada et aux États-Unis ont montré que les événements indésirables liés aux médicaments sont fréquents et souvent évitables[10,11]. La déclaration des RIM a mené à bon nombre d'importants changements à l'étiquetage des médicaments, à la diffusion d'avis de sécurité et même au retrait de produits précis du marché canadien[12]. La déclaration des RIM exige assurément du temps, mais la portée qu'elle peut avoir sur les soins aux patients et la sécurité des médicaments vaut amplement le petit effort nécessaire en amont.

Lorsque vous êtes en présence d'une RIM au cours de votre pratique clinique, gardez vos patients à l'esprit. Vous avez sûrement déjà fait une recommandation thérapeutique ou réalisé une intervention pour laquelle de l'information concernant une RIM déclarée précédemment par autrui était décisive. Faites en sorte que les pharmaciens devant des situations futures semblables aient accès à autant d'information que possible pour réaliser les meilleures interventions thérapeutiques auprès des pauvres patients qui ont déjà subi une RIM ou qui sont à risque d'en subir une. Ensemble, nous pouvons améliorer la sécurité des patients et des produits tout en enrichissant les connaissances des Canadiens pour nous assurer que ces derniers puissent faire les meilleurs choix possibles quant à leur pharmacothérapie.

[Traduction par l'éditeur]

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Impact of a Policy Change on Pharmacists' Reporting of Adverse Drug Reactions

Renaud Roy and Janice Ma

ABSTRACT

Background: Spontaneous reports of adverse drug reactions (ADRs) form an essential component of both drug safety monitoring and patient safety initiatives. Pharmacists are well positioned to report ADRs, but many barriers exist to their doing so. Over the past decade, substantial changes have occurred with regard to drug regulations and medication safety initiatives, and it is possible that knowledge-based interventions may be needed to enhance ADR reporting by pharmacists.

Objective: To determine whether ADR reporting behaviours of pharmacists improved after release of a revised policy on the reporting of medication incidents.

Methods: A telephone survey was administered to pharmacists practising in the Canadian Forces Health Services Group. Self-reported behaviours and perceived barriers related to ADR reporting were compared before and 3 months after the updated policy was released. Accuracy in participants' self-assessed ADR reporting was evaluated using independently derived workload statistics.

Results: During the second survey phase (after release of the revised policy), a greater proportion of respondents reported awareness of institutional policies on ADR reporting and declared that they were able to complete all necessary ADR reports during their assigned work hours. However, the number of ADR reports submitted did not increase. Participants' recall of their ADR reporting behaviour was corroborated by workload data. During the second survey phase, there was a noticeable reduction in the number of free-form comments mentioning lack of staff as a barrier to ADR reporting.

Conclusions: Release of a more comprehensive policy was not associated with an increase in the number of ADR reports generated by pharmacists in the study setting. Interventions to strengthen the organization's work processes for detection of ADRs and submission of individual ADR reports should be strongly considered, to reinforce and enhance existing ADR reporting behaviours among pharmacists.

Keywords: adverse reactions, pharmacists, drug monitoring, organization and administration

RÉSUMÉ

Contexte : Les déclarations spontanées des réactions indésirables aux médicaments (RIM) sont essentielles à la pharmacovigilance et aux initiatives au profit de la sécurité des patients. Les pharmaciens sont bien placés pour déclarer des RIM, mais divers éléments y font obstacle. Au cours de la dernière décennie, d'importants changements ont eu lieu en ce qui touche aux règlements sur les médicaments et aux initiatives en sécurité des médicaments, et il est possible que des interventions fondées sur le savoir soient nécessaires pour améliorer dans l'ensemble les déclarations des RIM par les pharmaciens.

Objectif : Déterminer si les habitudes des pharmaciens relatives à la déclaration des RIM se sont améliorées après la mise à jour d'une politique portant sur la déclaration des incidents liés aux médicaments.

Méthodes : Les pharmaciens qui exerçaient dans le Groupe des Services de santé des Forces canadiennes ont été sondés par téléphone. On a comparé les réponses des pharmaciens quant à leurs propres habitudes de déclaration et aux éléments perçus comme des obstacles à la déclaration des RIM, avant la mise à jour de la politique et trois mois après sa mise à jour. L'exactitude des réponses des participants à propos de leurs propres habitudes de déclaration des RIM a été vérifiée à l'aide de statistiques sur la charge de travail obtenues indépendamment.

Résultats : Pendant la deuxième phase de l'enquête (après la mise à jour de la politique), une plus grande proportion de répondants ont indiqué être conscients des politiques institutionnelles sur la déclaration des RIM et ils ont soutenu qu'ils étaient en mesure de remplir tous les rapports de déclaration des RIM nécessaires pendant leurs heures normales de travail. Cependant, le nombre de déclarations de RIM soumises n'a pas crû. Les habitudes de déclaration de RIM que les participants ont affirmé avoir ont été corroborées par les données sur la charge de travail. Dans la deuxième phase de l'enquête, il y a eu une baisse notable du nombre de commentaires libres indiquant le manque de personnel comme obstacle à la déclaration des RIM.

Conclusions : La mise en place d'une politique plus détaillée n'a pas été associée à une augmentation du nombre de déclarations de RIM produites par des pharmaciens dans le contexte de cette étude. Des interventions visant à améliorer, au sein de l'organisme, les méthodes de travail pour la détection des RIM et le dépôt de déclarations de RIM individuelles doivent être fortement envisagées afin de consolider et d'améliorer les habitudes de déclaration des RIM chez les pharmaciens.

Mots clés : réactions indésirables, pharmaciens, suivi pharmacologique, organisation et administration

Can J Hosp Pharm. 2018;71(4):227-33

INTRODUCTION

Over the past 2 decades, there have been calls for greater action to reduce the harms arising from inappropriate medication use. The US Institute of Medicine's landmark report in 1999 was the first to draw widespread attention to the impact of medication errors and adverse drug events,[1] and its findings have been corroborated elsewhere.[2-4] Other publications have further emphasized the extent to which these harms are preventable.[5-7] As a result, several guidance documents now exist that outline practices to prevent harm from medication use. However, pharmacists may encounter challenges and conflicts as they strive to implement these recommendations.[8,9]

Adverse drug reactions (ADRs) are an important subset of adverse drug events. Interest in ADRs—which are considered to reflect the innate safety profile of specific chemical compounds (drug safety)—predates more recent efforts to address the safety of drugs in clinical use (patient safety). Following the thalidomide disaster in 1961, regulatory bodies adopted an international approach to addressing drug safety issues, and the resulting activities were regrouped under the term "pharmacovigilance".[10] ADR monitoring is a key component of the pharmacovigilance activities that are performed both by national drug regulators[11,12] and by the pharmaceutical industry,[13] and it is recognized that spontaneously generated ADR reports play a key role in this regard.[10,14,15] Surveillance of ADRs in medication users outside the hospital setting may be especially helpful, as such individuals may have fewer confounding factors to complicate the assessment of causality. Surveillance in outpatients may also detect ADRs in different drug categories,[16] such as herbal and natural health products.[17,18] ADR reports obtained directly from patients may also provide earlier signals of adverse effects and can capture humanistic outcomes that may be overlooked or downplayed by health professionals.[19] As a result, many drug regulatory bodies now encourage direct reporting of ADRs by consumers.[20]

Pharmacists are clearly well positioned to contribute meaningfully to drug safety through ADR reporting,[21] particularly in hospitals and other organized health care settings.[22-24] Canadian pharmacists have led a number of initiatives to enhance reporting of ADRs, including efforts to investigate natural health products used in community settings.[17,18] to encourage completion of ADR reports when nonformulary drugs are required,[25] and to establish networks for ADR monitoring in high-risk patient populations.[26] The importance of ADR investigation and reporting is also incorporated into the professional practice standards for pharmacy in Canada,[27] and the practice is variably mandated in different Canadian provinces.[28-30] Health Canada is also implementing legislative changes to mandate the reporting of serious ADRs (as well as medical device incidents) through hospitals.[31] Nonetheless, underreporting of ADRs remains common, with pharmacists' reports accounting for just 10.4% of all ADR reports submitted to Health Canada in 2012.[32] Many barriers have been known to contribute to underreporting of ADRs (and adverse drug events more broadly) among pharmacists and other health care professionals,[33] including factual and skill-based knowledge deficits,[33-37] personally held beliefs and attitudes,[33-35,38] and social or environmental pressures.[33,36,37]

The Canadian Forces Health Services Group (CFHSG) currently maintains over 20 distinct outpatient treatment clinics, which have differing levels of pharmacy support for both clinical services and dispensing of medications. In 2015, the existing organizational policy on ADR reporting was revised to reiterate the importance of reporting adverse reactions to all health products. This new version of the policy streamlined the number of references that had to be consulted for reporting purposes, and also enabled the organization to better address requirements for formal accreditation as a health care institution. Under this revised policy, an adverse reaction is defined as any undesirable effect that arises in a patient and is suspected to be associated with the use of a specific health product. Five categories of health products—aligned with the regulatory regime for pharmaceuticals in Canada—are named in the policy. The policy also clearly identifies when reports must be submitted to a monitoring department within the organization, in addition to designated departments of Health Canada.

This study was conducted primarily to determine whether the newly introduced policy was associated with changes in the ADR reporting behaviours of pharmacists working in the outpatient clinics of the CFHSG. Secondary objectives involved verifying the accuracy of pharmacists' recall of their ADR reporting behaviour using workload-based records and assessing perceived barriers to ADR reporting.

METHODS

Review and Approval of the Study Protocol

This study involved administration of a telephone survey to individual pharmacists and review of administrative workload records for clinical teams. Institutional approval of the study concept was first obtained through the Surgeon General's Health Research Program, whereas the study protocol itself was approved independently by the Human Research Ethics Committee of Defence Research and Development Canada on April 3, 2014 (Protocol Number 2014-012). This research was conducted in accordance with the ethical standards of these organizations and the Helsinki Declaration.

Study Participants

Individuals who were provincially licensed and directly employed as pharmacists within the CFHSG (i.e., occupying a designated position, either on a short-term contractual basis or as an ongoing member of staff) were eligible to participate in the study. Persons who were not registered as pharmacists—including

pharmacy students, pharmacy assistants, and pharmacy technicians—were excluded from the survey. Similarly, any licensed pharmacists working in positions that were not officially classified as requiring licensure as a pharmacist (e.g., health care administrators, project officers) were not eligible to participate. All eligible personnel were advised of the study via email before being contacted by the research nurse. Informed consent was sought verbally from individual participants at the beginning of each telephone survey.

Data Collection

A standardized telephone survey (Appendix 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/177/showToc) was administered to all eligible personnel (in English or French, as appropriate) by a single research nurse at 2 separate time points: once before the revised policy was formally introduced ("pre") and once 3 months afterward ("post"). The survey contained a total of 25 questions, divided across 5 separate domains: respondent characteristics, awareness of current policy, technical expertise related to ADR reporting, personal ADR reporting behaviours, and perceived barriers to ADR reporting. Seventeen of the survey questions were formulated to generate yes/no responses, and the remaining 8 questions were open-ended. During each sampling period (i.e., pre– and post–policy change), 3 attempts were made to contact each eligible individual. At any point in the survey, participants could decline to answer any specific survey questions without further elaboration. All submitted responses were analyzed.

Analysis

The McNemar test was applied to determine whether there were any significant changes in the proportion of respondents answering yes/no questions in the affirmative in the post–policy change survey. For determining whether changes in pharmacists' ADR reporting behaviour occurred after release of the revised policy (based on the numbers of ADRs reported), the analysis was restricted to individuals who reported providing patient care during at least 15% of their work time in the previous 3 months. (This proportion is consistent with practice requirements established for direct patient care in one Canadian province,[39] and ensured that full-time clinical pharmacists who were absent due to extended leave or work assignments during the preceding 3 months would be appropriately distinguished from those in nonclinical positions.) All responses to open-ended questions were further collated, anonymized, and reviewed to identify recurring themes.

To assess the accuracy of pharmacists' recall of their ADR reporting behaviours (a secondary objective), 2 different measures of ADR reports were generated and compared to determine the level of agreement. Pharmacists were first grouped according to the clinic to which they were assigned, and their individual responses to question 14 of the survey—asking whether the pharmacist had reported an ADR during the preceding 3 months—were pooled. This allowed each clinic to be categorized as either having reported an ADR or not. A separate categorization was then made of the same clinics (i.e., as either reporting or nonreporting) using counts of ADR reports previously logged in the organization's pharmacy workload measurement system. This particular workload measurement system forms an integral part of the software that patient care pharmacists use regularly throughout their work day, and enables key clinical interventions, including ADR reports, to be recorded in real time, e.g., immediately before or after making a change to a patient's drug therapy. The kappa statistic was then used to assess the level of agreement between these 2 categorizations.

RESULTS

According to records in the CFHSG central database, a total of 87 discrete positions for study-eligible pharmacists were identified across the organization for each of the study's sampling periods. Attempts were made to contact the individuals who officially occupied each of these positions during the 2 sampling periods (June 2014 for the pre–policy change survey and November 2014 for the post–policy change survey). Because of staff absences and rotation/cross-coverage between clinics, not all individuals who responded in the first survey period were available to reply during the second survey period. In total, 63 individuals completed the survey in the period before the policy change (72% response rate) and 58 after (67% response rate). Completion rates for individual survey questions were generally high, with only 4 questions that were not answered by all respondents. Further description of the respondents is provided in Table 1.

Changes in Pharmacist ADR Reporting Behaviours

ADR reporting behaviour was assessed for those individuals who reported spending at least 15% of their work time providing patient care. This restriction limited the responses to 48 (76%) of the 63 respondents to the pre–policy change survey, and 44 (76%) of the 58 respondents to the post–policy change survey (Table 1). The absolute number of these "patient care" pharmacists who were aware of an ADR was lower in the period following introduction of the new policy (19 in the pre–policy change survey versus 11 in the post–policy change survey), but the proportion of pharmacists who reported the ADRs they identified did not change (9 of 19 [47%] versus 5 of 11 [45%], respectively).

Accuracy of Pharmacist Recall of ADR Reporting

For this part of the analysis, ADR reporting metrics were generated for all sites that provided a response to the survey during either the pre– or post–policy change sampling period. This

Table 1. Characteristics of Survey Respondents and ADR Reporting Behaviours*

Characteristic	Survey Timing; No. (%) of Respondents†	
	Pre–Policy Change	Post–Policy Change
Total no. of pharmacist positions identified	87	
Total no. of respondents	63 (72)	58 (67)
Time practising as a pharmacist (years) (mean ± SD)	15.4 ± 10.9	13.8 ± 9.9
Data related to ADR reporting behaviours		
No. (%) of pharmacists with patient care > 15% of work time	48/63 (76)	44/58 (76)
No. (%) of pharmacists with substantial patient care who had awareness of an ADR	19/48 (40)	11/44 (25)
No. (%) with ADR awareness who reported identified ADRs	9/19 (47)	5/11 (45)

ADR = adverse drug reaction, SD = standard deviation.
*No significant difference was identified for any of the characteristics reported in this table.
†Except where indicated otherwise.

yielded a total of 31 observation periods for comparison (17 and 14, respectively). When the pooled survey responses and submitted workload reports were compared, there was agreement in terms of reporting and nonreporting status for all but 4 of the observation periods, which resulted in good agreement overall (kappa = 0.7647). In 3 of the discordant cases, the survey respondent(s) did not recall submitting an ADR report, although such a report had been recorded for their clinic within the workload measurement system.

Other Aspects of Pharmacovigilance among Pharmacists

There was a significant change from baseline for only 2 questions (Table 2). Overall, participants who responded after the policy change were significantly more likely to indicate that they were familiar with current organizational policies on ADR reporting (54 of 58 [93%] post–policy change versus 48 of 63 [76%] pre–policy change; $p = 0.013$). The second question asked respondents whether they felt they could complete all necessary ADR reports during their assigned work hours; for this question, fewer survey participants declined to respond in the survey period following introduction of the revised policy (i.e., 55 of 63 participants responded at baseline, compared with 57 of 58 participants after the revised policy was released). This improved response rate was associated with a significant improvement in this measure of ADR reporting capability (53 of 57 [93%] responding in the affirmative post–policy change versus 41 of 55 [75%] pre–policy change; $p = 0.006$).

Responses to other survey questions did not differ significantly between the surveys done before and after the policy change (Table 2). Nonsignificant increases were noted in the proportions of respondents attesting to awareness of different types of ADRS, assessing causality before submitting an ADR report, and subscribing to receive notifications from the MedEffect Canada program. A majority of respondents to both surveys stated that they would be comfortable exercising a lead role in the reporting of ADRs (46 of 63 respondents [73%] in the first versus 49 of 58 respondents [84%] in the second survey period). In the associated free-form comments, many respondents stated that they were "already doing this", with several noting that it was considered a "duty" or employment requirement. Smaller proportions of respondents (68% and 64%) agreed that creating a single point of contact for all drug-related adverse effects would increase the likelihood that they would report ADRs specifically.

With regard to barriers to ADR reporting, comments provided voluntarily before the policy change repeatedly cited the need for more staff (9 of 15 responses). Fewer comments were made about the need for dedicated time ($n = 4$) and tangible resources ($n = 3$), such as more computers in the pharmacy, to support ADR reporting. In contrast, after the policy change, comments on the need for additional staff were not predominant (i.e., cited in only 2 of 6 comments submitted).

DISCUSSION

Following release of a comprehensive revised policy on medication incident reporting, pharmacists in the CFHSG reported both greater awareness of ADR-related policies and an enhanced ability to report ADRs during their assigned work hours. Enhanced policy awareness was to be expected, as additional communications related to this study may have prompted participants to familiarize themselves with existing policies in preparation for the survey. However, the detected increase in self-reported ability to report ADRs—a finding supported by dramatically fewer free-form comments regarding a need for additional staff—was surprising to us. Because no direct changes were made in the practice environment to address barriers cited in the initial survey responses (such as increasing the number of work hours, staff, or computers for the pharmacy), it appears that the revised policy altered the perception of "necessary" ADR reports, such that these now appeared to be eminently do-able in respondents' existing practice sites.

Unfortunately, despite the observed improvement in pharmacists' confidence in reporting ADRs, there was no detectable increase in the actual number of ADR reports

Table 2. Responses to Other Survey Questions

Question Topic	Survey Timing; No. (%) of Respondents*	
	Pre–Policy Change (*n* = 63)†	Post–Policy Change (*n* = 58)†
Is aware of current policies on ADR reporting‡	48 (76)	54 (93)
Is required to report *within* the organization	46 (73)	50 (86)
Is required to report *externally*	46 (73)	42 (72)
Uses different forms for reporting adverse effects	20/62 (32)	18 (31)
Is aware of different types of adverse effects	49 (78)	52 (90)
Mechanisms used to submit ADR reports		
Phone	1 (2)	2 (3)
Mail	2 (3)	1 (2)
Fax	38 (60)	27 (47)
Online	22 (35)	27 (47)
Reports ADRs that are well known or in monograph	16 (25)	14 (24)
Assesses causality before submitting a report	48 (76)	50 (86)
Has read the latest edition of *CARN*	22 (35)	16 (28)
Subscribes to receive MedEffect notices	41 (65)	47 (81)
Is able to complete all ADR reports during work hours§	41/55 (75)	53/57 (93)
Is able to access all information needed to report ADRs	53/54 (98)	55/57 (96)
Is comfortable exercising a lead role on ADR reporting	46 (73)	49 (84)
Feels that a single point of contact is likely to increase reporting	43 (68)	37 (64)
Has received feedback following ADR report	22 (35)	15 (26)
Was satisfied with the feedback received	20/22 (91)	14/15 (93)

ADR = adverse drug reaction, *CARN* = *Canadian Adverse Reaction Newsletter* (now renamed as *Health Product InfoWatch*).
*Unless indicated otherwise, there was no significant change in response following adoption of the new policy.
†Each percentage is based on the number of respondents to that question. Where the number of respondents was less than the total number of respondents, the denominator is stated.
‡Significant difference: $p = 0.013$.
§Significant difference: $p = 0.006$.

generated. Following release of the new policy, both a lower number of identified ADRs and an unchanged rate of reporting for identified ADRs were noted. There is no reason to believe that the incidence of ADRs would have changed substantially during the study's timeframe; therefore, the lack of an observable effect on the primary outcome measure can best be attributed to a lower rate of ADR detection by pharmacists. Previous studies have noted that altering the working definition of an ADR, either alone or in concert with modifications to reporting infrastructures, can significantly change the rates at which ADRs are both detected and subsequently reported.[16,40-42]

The pharmacists' self-identified ADR reporting rate remained consistent at about 45% in both survey periods, and accuracy of respondents' recall was supported by independently generated workload data. Given the substantial number of considerations that must be taken into account when deciding to report suspected ADRs,[43] this rate appears reasonable. Therefore, if a greater number of ADR reports is desired (i.e., to increase the power to detect safety issues affecting this patient population), new mechanisms will be needed to make ADR detection more sensitive and ADR reporting less cumbersome. Such system modifications should be carefully designed to capture data against the full range of medication-related monitoring that needs to occur, with recognition that the number of reports required may vary depending on whether the system aims to investigate *drug* safety or *patient* safety.

It must also be recognized that systems designed to detect ADRs in other settings may not be ideally suited for implementation in this specific outpatient environment. As an example, although the presence of dedicated ADR personnel (supplemental to the existing pharmacy teams) can increase the detection of ADRs,[17,18,44] adoption of a single point of contact for incident reporting does not appear to be strongly supported by the outpatient pharmacists surveyed in this study, many of whom clearly felt compelled, professionally, to exercise a leading role in this area. Instead, given the encouraging improvements reported here (following an extremely low-intensity educational intervention), more formalized training interventions should be investigated preferentially for pharmacists in these practice sites.

It is clear that training interventions should incorporate mechanisms to provide meaningful feedback that can reinforce health professionals' learned behaviours over time.[45] In particular, standardized procedures to electronically acknowledge receipt of ADR-related information are likely be well received among CFHSG pharmacists, most of whom already subscribe to receive electronic notifications from Health Canada's MedEffect Canada program. Standardization of procedures to transmit ADR reports is also expected to be highly appreciated, particularly among

military pharmacists, who are highly mobile (Pharmacy Officers can expect to be posted to a different base or work unit every 2–3 years.). Electronic modes of communication could also be used to address persistent knowledge deficits, which may lower the numbers or the quality of submitted reports.

Limitations

The study design unfortunately did not allow us to conclusively determine the degree to which the observed increase in self-reported ADR reporting ability was directly attributable to the policy change itself. The study population may have evolved in 2 key respects over the course of the study period, either of which would independently alter collective confidence in ability to report ADRs during work time. First, pharmacy managers may have made staffing decisions (either consciously or unconsciously) that preferentially assigned pharmacists with greater ADR experience and training to patient care positions during the later survey period. However, if that were the case, these "higher-capability" pharmacists would have had multiple opportunities to detect new and existing ADRs, and both the proportion of pharmacists detecting ADRs and the overall number of ADR reports ought to have increased over time. Alternatively, this finding could be explained if hiring processes over the study period introduced a greater number of recent graduates into the population of outpatient pharmacists. In at least one previous North American report, younger pharmacists were more likely to hold attitudes conducive to ADR reporting,[38] and certainly pharmacists licensed more recently could be assumed to be more familiar with current ADR reporting requirements and drug categorizations established by the federal regulator over the past decade. While not a statistically significant difference, the average number of years worked as a pharmacist was lower among those who responded after the policy change (15.4 versus 13.8 years, $p = 0.70$; see Table 1), which supports the second theory. The latter explanation is also consistent with the finding of a greater awareness of existing policies after the policy change, since review of such policies would normally be completed during "onboarding" processes for new hires. Despite this limitation, it remains reasonable to assume that additional work to enhance ADR reporting would be appropriate, particularly to create mechanisms and tools that would make completion of ADR reports less time consuming and ADR detection more thorough.

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ORIGINAL RESEARCH

Antimicrobial Use at Acute Care Hospitals in Nova Scotia: A Point Prevalence Survey

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ABSTRACT

Background: Point prevalence surveys are used to monitor antimicrobial use and identify targets for improvement through antimicrobial stewardship activities. Few studies have evaluated antimicrobial use in Nova Scotia acute care institutions.

Objectives: To determine the prevalence and characteristics of antimicrobial use in Nova Scotia hospitals.

Methods: A point prevalence survey was conducted between June and November 2015 for patients admitted to hospitals with at least 30 acute care beds. On each survey day, charts were reviewed to identify patients receiving antimicrobial agents on that day. Data were gathered on the type of antimicrobial agent prescribed, route of administration, intended duration of use, and indication. Adherence to regional and local treatment guidelines was assessed. Results were summarized descriptively. Findings were compared using the Fisher exact test or the Cochran–Armitage trend test.

Results: Twelve of the 13 eligible hospitals participated, and a total of 1499 patient charts were examined. The overall prevalence of antimicrobial use was 30.6% (458/1499). The prevalence of antimicrobial use differed significantly according to area of specialty, with the highest prevalence occurring in intensive care wards (47.2%, 50/106) and surgical wards (43.4%, 179/412), as compared with medical wards (27.9%, 192/687) and "other" specialty wards (11.1%, 32/289) ($p < 0.001$). Among the 520 indications for antimicrobial use, the most common was respiratory tract infection (81 or 15.6%). In total, 660 antimicrobial agents were prescribed to the 458 patients; a third of these patients (152 or 33.2%) received more than 1 antimicrobial agent. The class of antimicrobials most frequently prescribed was "other beta-lactam antimicrobials" (31.2%, 206/660). The majority of antimicrobials (62.0%, 409/660) were prescribed for administration via the parenteral route. Adherence to regional treatment guidelines was 29.9% (26 of 87 indications analyzed). Documentation of indication was lacking for 104 (20.0%) of the 520 indications, and documentation of the intended duration of antimicrobial use was lacking for 326 (62.7%) of the 520 indications.

Conclusions: Antimicrobial agents were prescribed for about one-third of acute care patients in Nova Scotia. Specific targets for improvement in antimicrobial use include decreases in prescribing of broad-spectrum and parenteral antimicrobials, better adherence to guidelines, and improved documentation. In developing initiatives, antimicrobial stewardship programs in Nova Scotia should focus on identified targets for improvement.

Keywords: antimicrobial utilization, antimicrobial stewardship, antimicrobial agent, antibiotic

RÉSUMÉ

Contexte: Les enquêtes de prévalence ponctuelle sont employées pour surveiller l'utilisation des antimicrobiens et cibler des points à améliorer grâce aux activités de gestion responsable des antimicrobiens. Peu d'études se sont penchées sur l'utilisation des antimicrobiens dans les établissements de soins de courte durée en Nouvelle-Écosse.

Objectifs : Déterminer quelle est la prévalence de l'utilisation des antimicrobiens dans les hôpitaux de la Nouvelle-Écosse et offrir un portrait de cette utilisation.

Méthodes : Une enquête de prévalence ponctuelle a été menée entre juin et novembre 2015 pour les patients admis aux hôpitaux dotés d'au moins 30 lits de soins de courte durée. À chaque jour d'enquête, des dossiers médicaux ont été examinés afin de repérer les patients ayant reçu des agents antimicrobiens cette journée-là. On a recueilli des données sur le type d'agent antimicrobien prescrit, la voie d'administration, la durée attendue d'utilisation et l'indication. Le respect des lignes directrices thérapeutiques régionales et locales a aussi été évalué. Les résultats ont été résumés de façon descriptive. Les comparaisons ont été vérifiées à l'aide du test exact de Fisher ou du test de tendance de Cochran-Armitage.

Résultats : Douze des 13 hôpitaux admissibles ont été inclus et un total de 1 499 dossiers médicaux de patients ont été examinés. Le taux de prévalence globale d'utilisation d'antimicrobiens était de 30,6 % (458/1499). La prévalence d'utilisation d'antimicrobiens variait significativement selon les unités de soins : en tête de liste, les unités de soins intensifs (47,2 %, 50/106) et les unités de chirurgie (43,4 %, 179/412) comparativement aux unités de médecine (27,9 %, 192/687) et aux « autres » unités de soins (11,1 %, 32/289) ($p < 0.001$). Parmi les 520 indications pour l'utilisation des antimicrobiens, la plus fréquente était l'infection des voies respiratoires (81 ou 15,6 %). Au total, 660 agents antimicrobiens ont été prescrits aux 458 patients et le tiers de ces patients (152 ou 33,2 %) ont reçu plus d'un agent antimicrobien. La classe d'antimicrobien la plus souvent prescrite était les « autres bêtalactamines » (31,2 %, 206/660). La voie parentérale était prescrite pour l'administration de la majorité des antimicrobiens (62,0 %, 409/660). Le respect des lignes directrices régionales de traitement était de 29,9 % (26 des 87 indications analysées). Parmi les 520 indications, 104 (20,0 %) n'étaient pas mentionnées au dossier et 326 (62,7 %) étaient dépourvues de mention de la durée du traitement antimicrobien au dossier.

Conclusions : Des agents antimicrobiens ont été prescrits à environ un tiers des patients recevant des soins de courte durée en Nouvelle-Écosse. L'amélioration de l'utilisation des antimicrobiens devrait cibler précisément les réductions de la prescription d'antibiotiques à large spectre et du

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recours à la voie parentérale, un plus grand respect des lignes directrices et une meilleure consignation. Les programmes de gestion responsable des antimicrobiens en Nouvelle-Écosse devraient être axés sur des objectifs d'amélioration définis afin de mettre au point des stratégies.

Mots clés : utilisation des antimicrobiens, gestion responsable des antimicrobiens, agent antimicrobien, antibiotiquee

INTRODUCTION

International surveillance has shown that antimicrobial resistance is increasing.[1,2] In 2016, the Director-General of the World Health Organization (WHO) warned that "antimicrobial resistance poses a fundamental threat to human health, development, and security".[3] Inappropriate antimicrobial use, occurring in more than one-quarter of all antimicrobial courses prescribed,[4] increases the risk of resistance. In addition, antimicrobial resistance leads to negative health consequences, including a statistically significant increase in mortality.[5]

Because of antimicrobial resistance, Canadians have been encouraged to work collaboratively to identify solutions through surveillance, stewardship, infection prevention and control, and innovation.[6] Several strategies to reduce the risk of resistance can be considered.[7,8] However, to identify solutions and tailor strategies to improve antimicrobial use, an evaluation of antimicrobial utilization is needed.

Point prevalence surveys are a suggested strategy to evaluate antimicrobial use. They have been used nationally and internationally to determine the prevalence of antimicrobial use and to identify areas for quality improvement.[9-18] According to previously published transnational and Canadian point prevalence surveys of antimicrobial use, about one-third of patients admitted to hospital are receiving antimicrobial agents at any given time.[12,13,15,16]

Recent statistics on antimicrobial use based on individual patient-level prescribing data at acute care hospitals in Nova Scotia have not been published. A study that utilized purchasing data for this province suggested an increase in use of fluoroquinolones, from 47.2 defined daily doses (DDD) per 1000 bed-days per year in 1997/98 to 163.8 DDD/1000 bed-days per year in 2002/03.[19] In addition, the *Canadian Antimicrobial Resistance Surveillance System Report 2016* highlighted that in 2014, Nova Scotia had the second highest number of DDD per patient discharge for antimicrobials purchased by hospitals across the country.[20] A current assessment of antimicrobial prescribing in Nova Scotia, with consideration of regional variation in utilization, prescribing indication, and adherence to guidelines, was therefore needed.

The purpose of this study was to determine the prevalence of antimicrobial use in Nova Scotia hospitals; to characterize antimicrobial use in terms of drug selection, route of administration, and indication for prescribing; to compare antimicrobial use by population size, age, and area of specialty; to determine adherence to regional and local guidelines (where they exist); and to determine targets for quality improvement in antimicrobial use.

METHODS

This study was a point prevalence survey of antimicrobial use by patients admitted to acute care hospitals in Nova Scotia, Canada. This study was approved by the research ethics boards of the Nova Scotia Health Authority on April 15, 2015 (File No. 100287), and the IWK Health Centre on September 8, 2015 (File No. 1020269). Both research ethics boards waived the need for informed consent.

Study Setting and Patient Population

This study was completed in Nova Scotia. At the time of this study, Nova Scotia had a population of 941 545.[21] In 2015, just before data collection, 9 health authorities in the province were merged into a single health authority (the Nova Scotia Health Authority), in addition to the IWK Health Centre. The Nova Scotia Health Authority has 1 tertiary specialty hospital (the Queen Elizabeth II Health Sciences Centre), 8 regional hospitals, and about 135 other facilities.[22] In addition to hospitals in the Nova Scotia Health Authority, the province has 1 specialized hospital (the IWK Health Centre), which provides primary, secondary, and tertiary care to women, children, youth, and families.[23]

All hospitals in Nova Scotia with at least 30 inpatient acute care beds at the time of the survey were invited to participate. Smaller hospitals were excluded because available funding was insufficient to collect data at all hospitals throughout the province. Participating hospitals were asked to complete a questionnaire summarizing institution characteristics (hospital type, number of beds) and on-site availability of antimicrobial stewardship or infectious disease expertise. Teaching hospitals were defined as institutions providing highly complex patient care, having a formal partnership with a medical or health sciences school, and having substantial research activity and postgraduate training.[24,25] All other hospitals were defined as community hospitals. Although these institutions constituted a single health authority (excluding the IWK Health Centre) at the time of data collection, differences in formulary restrictions and antimicrobial policies existed throughout the province.

Within each participating hospital, all patients who had been admitted to an acute care bed for at least 24 h at 0800 on the particular institution's survey date(s) were screened for eligibility. Admitted patients in the emergency department, long-term care, restorative care, transitional care, and rehabilitation beds were excluded. Among eligible patients, those for whom a systemic antimicrobial agent had been prescribed were identified and included in the survey.

Data Collection

Data on antimicrobial use were collected by members of the research team over the period June 22 to November 2, 2015. On each survey day, a census of admitted patients was electronically generated for a particular hospital ward. Pharmacists, pharmacy students (who had completed second or third year), and a pharmacy technician used the electronic patient census to identify patients and collect data from paper-based charts. As a quality control measure, to ensure accuracy of data collection, data extraction was assessed by a second individual for 10% of the charts at each site. Any discrepancies in data collection were identified, discussed, and resolved the same day. All eligible patients admitted to the same hospital ward within a given institution were surveyed on the same day. All acute care hospital wards within a participating institution were surveyed within the same 3- to 4-week period.

The European Surveillance of Antimicrobial Consumption Network (ESAC-Net) is a European surveillance network that has developed a standardized methodology for assessing antimicrobial utilization through point prevalence surveys. With permission, a standardized data collection form for the current study was developed on the basis of the network's 2009 form. The European Centre for Disease Prevention and Control (ECDC) has adopted the point prevalence survey methodology of ESAC-Net to monitor antimicrobial use and has published a technical document that provided guidance in completing data collection.[26]

Information was gathered on the type of clinical ward, patient demographic characteristics, antimicrobial utilization, and indication for prescribing. Information collected on the clinical ward included the name of the ward, area of specialty (if applicable), and total number of patients who had been admitted to the ward for at least 24 h at 0800 on the day of the survey. The type of antimicrobial agent was coded according to the WHO's classification index for the Anatomical Therapeutic Chemical (ATC) system, 2015 edition.[27] Included systemic antimicrobials were antibacterials, antimycotics, antimycobacterials, antivirals, intestinal anti-infectives, and antiprotozoals. Information collected on indication for antimicrobial prescribing was based on anatomic site.

Guideline Adherence

Data collectors (pharmacists and pharmacy students) assessed antimicrobial use against existing regional and locally approved evidence-based guidelines. Adherence to guidelines for antimicrobial selection, dose, and duration was assessed for community-acquired pneumonia, acute exacerbation of chronic obstructive pulmonary disease (COPD), urinary tract infections (UTIs), and nonpurulent cellulitis. Adherence to guidelines for surgical site prophylaxis was assessed at the IWK Health Centre. These indications were selected on the basis of availability of regional guidelines and their frequency of occurrence in this patient population. The Capital Health *Antimicrobial Handbook – 2012*,[28] which is the source of the regionally developed guidelines for community-acquired pneumonia, UTIs, and cellulitis, was used to assess adherence to guidelines in the adult population at all hospitals within the Nova Scotia Health Authority. Adherence to guidelines in a regional preprinted order for management of acute exacerbation of COPD, developed by the Queen Elizabeth II Health Sciences Centre, was also assessed. In addition, adherence to local guidelines developed between 2008 and 2015 by individual community hospitals for the specified indications (where available) and the IWK Health Centre was evaluated. In the event that a data collector was uncertain about adherence to guidelines, a member of the research team was consulted. If adherence remained unclear, 2 additional members of the research team (infectious disease physician and/or clinical pharmacist) independently reviewed the case and provided a recommendation. If disagreement occurred at this stage, the case was reviewed by a third member of the research team (infectious disease physician or clinical pharmacist), whose recommendation prevailed.

Data Analysis

Prevalence and type of antimicrobial agent used, route of administration, indication for antimicrobial prescribing, documentation, and adherence to guidelines were summarized descriptively. Prevalence of antimicrobial use was reported at the patient level. Type of antimicrobial used, route of administration, and documentation of intended duration were reported at the prescription level. Indication for antimicrobial use, adherence to guidelines, and documentation of indication were reported as proportions of total indications in the study population. In calculating prevalence, the number of acute care patients admitted for at least 24 h and having an active prescription for 1 or more systemic antimicrobial agents at 0800 on the day of the survey represented the numerator, and the number of acute care patients admitted for at least 24 hours at 0800 on the day of the survey represented the denominator.[9] Findings for prevalence and antimicrobial use by age (17–65 years, > 65 years), population size (small versus large population centre), and area of specialty (medicine versus surgery) were compared using the Fisher exact test. Findings for route of administration (oral, parenteral, inhalation) by population size (small versus large population centre) and age (0–16 years, 17–65 years, > 65 years of age) were compared using the Cochran–Armitage trend test. The analysis did not control for type I error.

RESULTS

Hospital Characteristics

Twelve of 13 hospitals meeting the inclusion criteria participated in the survey. Two of the hospitals were categorized as teaching hospitals located in large population centres (population ≥ 100 000), and the other 10 hospitals were community hospitals located in small or medium population centres (population between 1000 and 99 999).[29] Both of the teaching hospitals employed infectious disease physicians certified by the Royal College of Physicians and Surgeons of Canada and dedicated infectious disease or antimicrobial stewardship pharmacists. Only 1 community hospital had a certified infectious disease physician, and another had an antimicrobial stewardship pharmacist; however, many of the community hospitals indicated that they were able to interact in a timely manner, via telephone consult, with an infectious disease physician from a larger teaching hospital or regional community hospital. At the time of data collection, antimicrobial stewardship committees had been established at 7 of the 12 participating study sites. Of the 5 sites that did not have stand-alone antimicrobial stewardship committees, 3 had an antimicrobial agent committee that reviewed stewardship policies.

Table 1. Baseline Characteristics of Patients Receiving Antimicrobial Agents at Acute Care Hospitals in Nova Scotia

Characteristic	No. (%) of Patients (*n* = 458)	
Sex		
Male	221	(48.2)
Female	233	(50.9)
Unknown	4	(0.9)
Age		
≤ 16 years	34	(7.4)
17–65 years	193	(42.1)
> 65 years	229	(50.0)
Unknown	2	(0.4)
Type of hospital		
Teaching	225	(49.1)
Small or community	233	(50.9)
Specialty		
Medical	192	(41.9)
Surgical	179	(39.1)
Intensive care	50	(10.9)
Other	32	(7.0)
Unknown	5	(1.1)

Antimicrobial Use

The charts for a total of 1499 eligible hospital inpatients were reviewed; for 458 (30.6%) of these patients, at least 1 antimicrobial agent was prescribed. Approximately one-third of the patients who were taking antimicrobial agents (33.2%, 152/458) were receiving combination therapy. The baseline characteristics of the patient population are summarized in Table 1. A total of 660 antimicrobial agents were prescribed for 520 indications. The most common indications were respiratory tract infections (15.6%, 81/520), prophylaxis for surgical site infections (12.7%, 66/520), and UTIs (10.8%, 56/520). Indications for antimicrobial prescribing are summarized in Figure 1.

The prevalence of antimicrobial use differed significantly according to area of specialty, with the highest prevalence occurring in intensive care wards (47.2% [50 of 106 intensive care patients had at least 1 antimicrobial prescription]) and surgical wards (43.4%, 179/412), as compared with medical wards

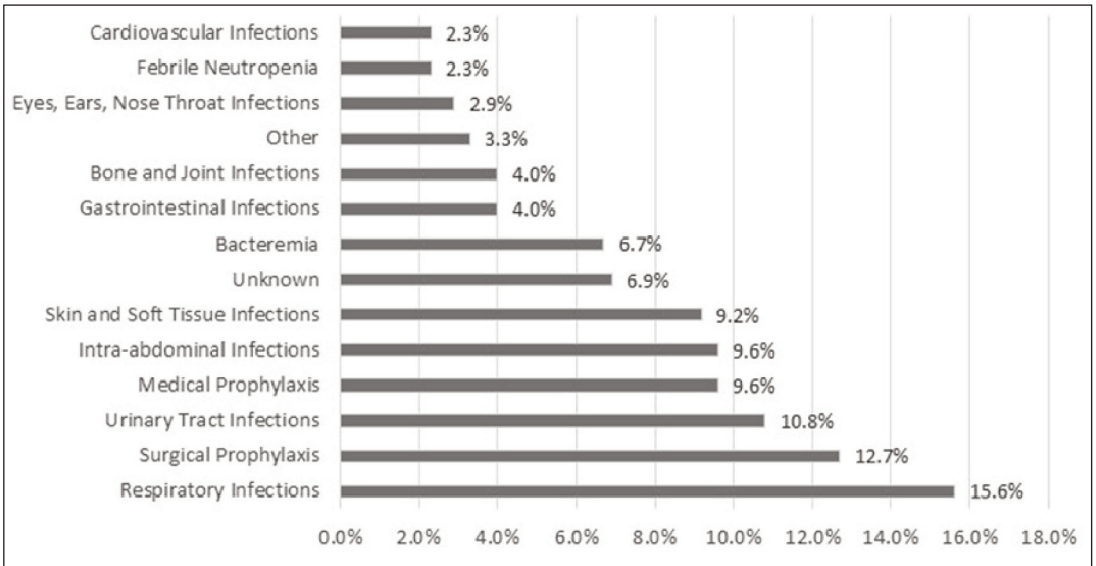

Figure 1. Indications for antimicrobial use at acute care hospitals in Nova Scotia (*n* = 520).

(27.9%, 192/687) and "other" specialty wards (11.1%, 32/289) ($p < 0.001$). The other specialty wards were obstetrics/gynecology, pediatrics, family/newborn, palliative care, geriatrics, and mental health; area of specialty was unknown for 5 patients. Prevalence throughout the province, by hospital, ranged from 22.6% (53/234) to 43.5% (30/69). Prevalence of antimicrobial use at the community hospitals in small to medium population centres was significantly lower than at the teaching hospitals in large population centres (27.6% [233/845] versus 34.4% [225/654]; $p = 0.005$).

Overall, 62.0% (409/660) of the prescriptions were for parenteral antimicrobial agents. There was a statistically significant trend for younger patients to receive parenteral antimicrobials more often than older patients ($p < 0.001$). Parenteral administration was highest in the pediatric population up to 16 years of age (82.8%, or 48 of the 58 prescriptions for patients in this age group) and was lower in adults aged 17–65 years (65.7%, 197/300) and those > 65 years of age (54.3%, 163/300); data on route of administration by age were missing for 2 antimicrobial orders. There was no statistically significant difference in rate of parenteral administration between large and small population centres (62.9%, 217/345, versus 60.95%, 192/315; $p = 0.08$).

Antimicrobial use by drug class, based on the third level (pharmacologic subgroup) of the WHO ATC classification system, 2015 edition,[27] is summarized in Figure 2. The most common class of antimicrobial agents prescribed was "other beta-lactam antibacterials" (31.2%, 206/660), with cephalosporins representing the majority of antimicrobial agents (27.6%, 182/660) prescribed in this category. The most frequently prescribed antimicrobial agents at acute care hospitals in Nova Scotia were metronidazole (11.1%, 73/660), cefazolin (10.9%, 72/660), and ceftriaxone (8.9%, 59/660). Antimicrobial use was similar by population size, with the exception of ciprofloxacin, which was prescribed more often in small to medium population centres than in large population centres (11.1% [35/315] versus 4.1% [14/345]; $p < 0.001$), and cefazolin, which was prescribed more often in large population centres than in small to medium population centres (13.3% [46/345] versus 8.3% [26/315]; $p = 0.045$). The drugs prescribed most commonly, overall and by population size, are shown in Figure 3.

Antimicrobial use by age for adult patients at acute care hospitals in Nova Scotia was also summarized, with similar utilization rates in patients aged 17 to 65 years and those older than 65 years, with the exception of ciprofloxacin, which was prescribed more often for those older than 65 years (4.7% [14/300] versus 11.3% [34/300]) and piperacillin-tazobactam which was prescribed more often for those 17–65 years of age (10.7% [32/300] versus 6.0% [18/300]) (Figure 4). A greater proportion of patients admitted for surgery than for medical reasons had a prescription for cefazolin. Otherwise, the most commonly prescribed antimicrobial agents were comparable between specialties (Figure 5).

Adherence to Regional and Local Guidelines

Adherence to regional guidelines was assessed in relation to indication for 87 cases (involving community-acquired pneumonia, acute exacerbation of COPD, UTIs, or nonpurulent cellulitis). Adherence was unclear in 9 cases, which were sent for further independent review by 2 members of the research team. One case

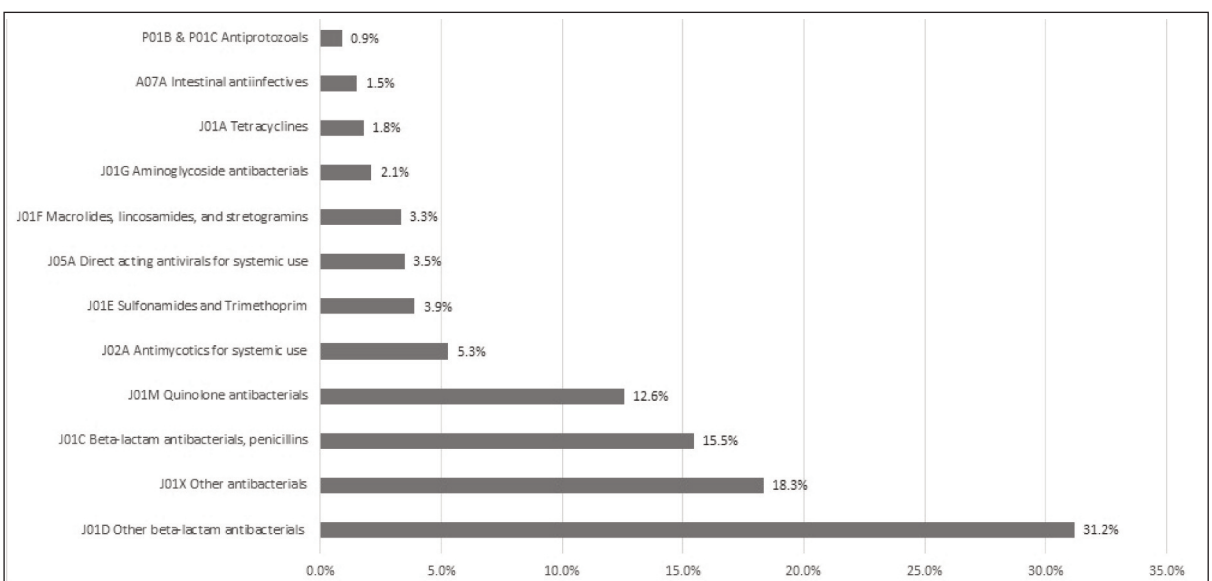

Figure 2. Antimicrobial use by drug class at acute care hospitals in Nova Scotia ($n = 660$). Class J01X includes oral and parenteral metronidazole, parenteral vancomycin, oral nitrofurantoin, and parenteral colistin. Drug class designations from the World Health Organization's classification index for the Anatomical Therapeutic Chemical system, 2015 edition.[27]

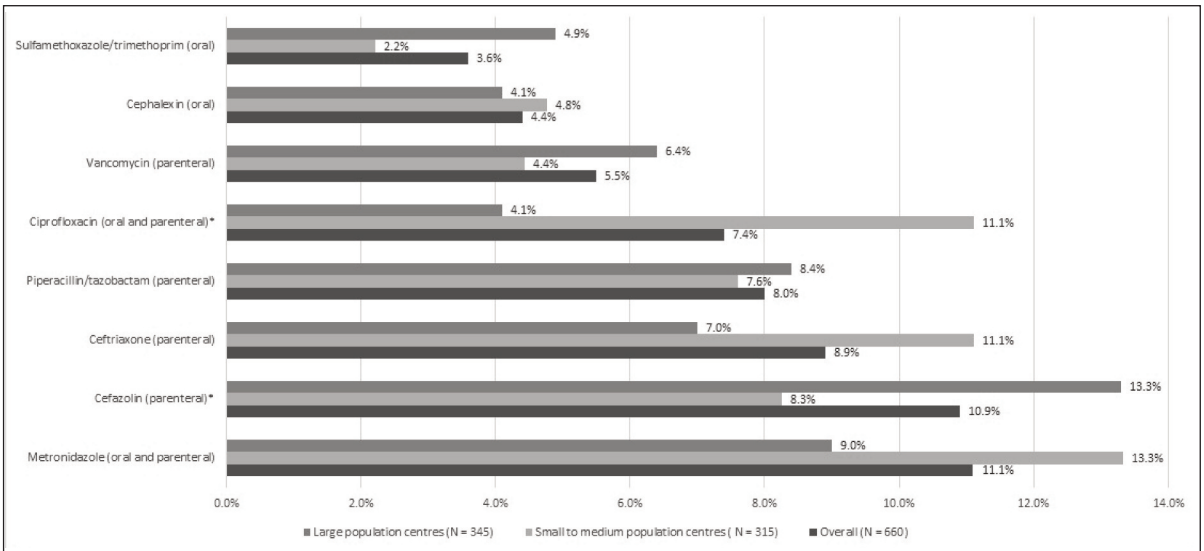

Figure 3. Antimicrobial agents prescribed most frequently at acute care hospitals in Nova Scotia. *$p < 0.05$.

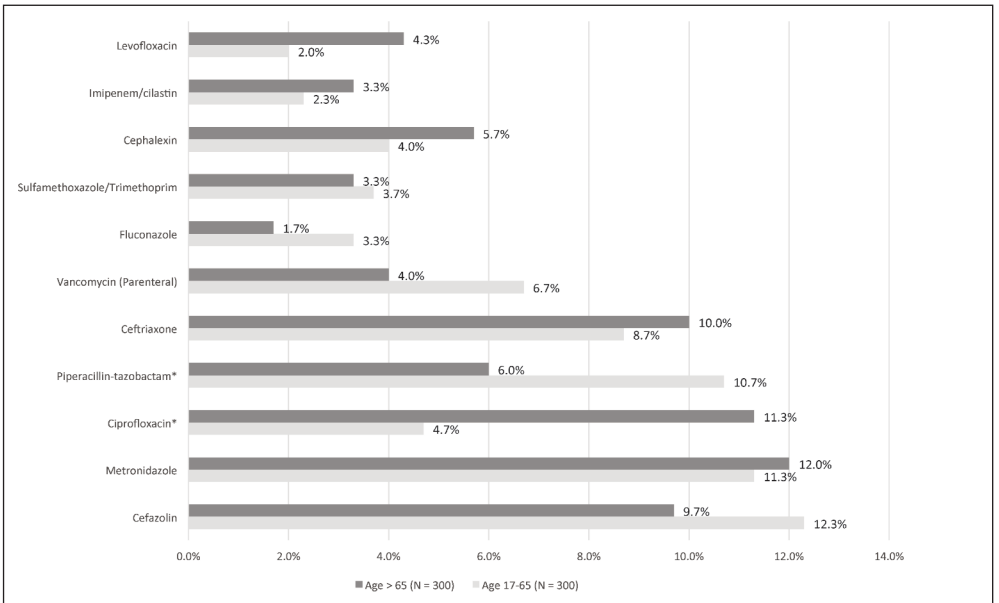

Figure 4. Antimicrobial agents prescribed most frequently for adult patients at acute care hospitals in Nova Scotia, categorized by patient age. *$p < 0.05$.

resulted in disagreement that required consideration by a third reviewer. Prescribers were adherent to regionally developed guidelines in 30% (26/87) of the cases assessed. The most common reason for nonadherence to regional guidelines was use of a second-line agent without a compelling reason to avoid the first-line antimicrobial (51% [31 of 61 cases with nonadherence]). Regional UTI guidelines were most commonly evaluated, with prescribers adhering to guidelines in 31% (16/51) of cases. Adherence to regional guidelines was 29% (5/17) for community-acquired pneumonia and 45% (5/11) for nonpurulent cellulitis. Adherence to guidelines for acute exacerbation of COPD cannot be reported here because of small cell size (as per ethics requirements). Adherence to locally developed guidelines at community hospitals was 77% (17/22) and at the IWK Health Centre was 71% (5/7).

Documentation

Documentation of the indication for antimicrobial prescribing occurred for 80.0% (416/520) of indications. Intended

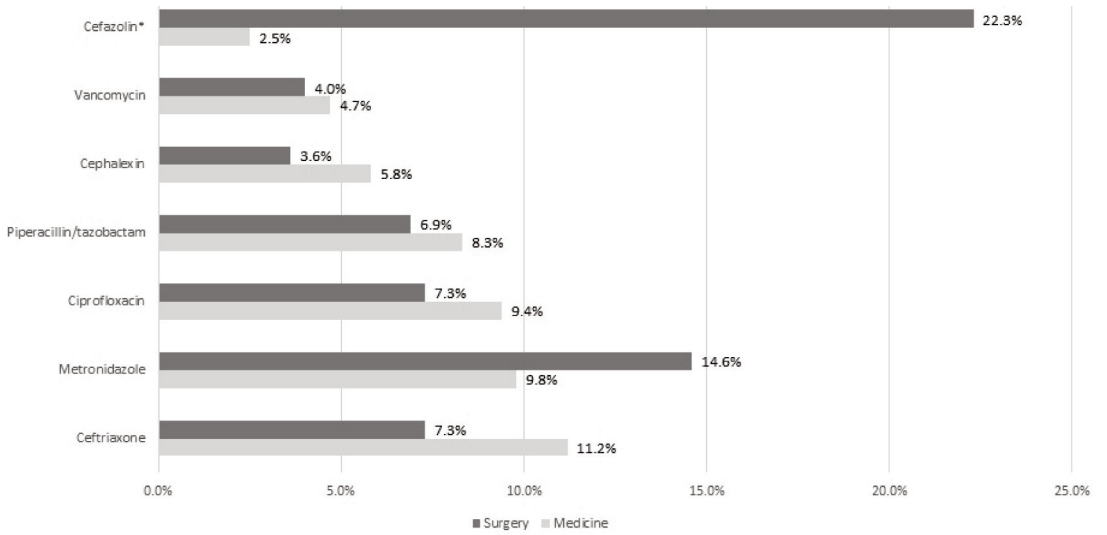

Figure 5. Antimicrobial agents prescribed most frequently for medical patients (n = 276 antimicrobial agents) and surgical patients (n = 247 antimicrobial agents) at acute care hospitals in Nova Scotia. *$p < 0.05$.

duration of antimicrobial therapy was documented for 37.3% (194/520) of indications.

DISCUSSION

In this 2015 study, about one-third (30.6%) of the acute care inpatient population in Nova Scotia received an antimicrobial agent during the study period. These findings are consistent with international and Canadian prevalence data. The most recent transnational point prevalence surveys of antimicrobial use by acute care inpatients in Europe, conducted in 2009 and 2011, reported prevalences of 29.0% and 34.6%, respectively.[9,15] A point prevalence survey of antimicrobial use in Ontario found that 30.8% of acute care inpatients were receiving an antimicrobial agent.[16] Similarly, a point prevalence survey of health care–associated infections at Canadian adult acute care hospitals reported that 36.0% of patients surveyed were receiving systemic antimicrobial agents.[30]

This study highlights a particularly high prevalence of parenteral antimicrobial use, and conversion from IV to oral therapy was therefore identified as a potential target for quality improvement. Consistent with our findings, frequent and potentially inappropriate use of parenteral antimicrobial agents has been reported elsewhere.[9] On the basis of findings from the current point prevalence survey and the published literature, the provincial antimicrobial stewardship team in Nova Scotia has developed and is implementing an IV-to-oral conversion protocol to reduce the use of parenteral antimicrobial agents.

Use of broad-spectrum antimicrobial agents should also be considered as a potential area for improvement in antimicrobial utilization, given the level of prescribing of such agents reported here. Particularly concerning was the frequent use of ciprofloxacin for the patients in this study. Consistent with these findings, increasing use of fluoroquinolones, including ciprofloxacin, was previously identified in Nova Scotia.[19] In addition, use of fluoroquinolones was highlighted as a concern in a point prevalence survey completed at a tertiary care hospital in Ontario.[16] Ciprofloxacin use represents an important target in small and rural population centres, where limited resources may require prioritization in implementing antimicrobial stewardship programs. Clinicians may benefit from increasing awareness of the risks associated with ciprofloxacin use. In addition, stewardship teams should pay particular attention to ciprofloxacin use in older patients, who are at greater risk from adverse events.[31]

Limited uptake of regional guidelines was also identified as an indicator requiring further attention. Although regional guidelines are disseminated throughout the province, only a third of antimicrobial orders were adherent to these guidelines. Rates of adherence to regional clinical practice guidelines in this study were lower than those described by others.[9] However, uptake of local guidelines (where available) was more consistent with international findings.[9] Interpretation of adherence to local guidelines was limited by the small sample size. Further exploration of reasons why prescribers are nonadherent to regional guidelines should be considered by the provincial antimicrobial stewardship team, given that for many conditions, few sites have their own local guidelines. Possible reasons why prescribers do not follow guidelines have been proposed in the literature, including lack of awareness or familiarity, lack of agreement, lack of self-efficacy, lack of outcome expectancy, inertia of previous practice, and external barriers.[32]

A need for improvement in documentation was noted at acute care hospitals in Nova Scotia. For the purposes of this study, full medical charts were reviewed, and approximately 1 in 5 had no documentation of indication, and only a third had documentation of the intended duration of therapy. Consistent with results

from this study, a large point prevalence survey completed in 25 European countries reported that the indication for antimicrobial prescribing was documented in only 75.7% of patients' medical charts.[9] The authors identified documentation (i.e., a statement of the indication in the chart notes) as 1 of the key performance indicators that should be monitored to assess change in targeted areas of practice.[9] Similarly, a point prevalence survey conducted in Belgium reported that indication for antimicrobial use was documented in only 83.4% of cases, and the intended duration or date of review was documented in medical records for only 31.9% of indications.[33] Documentation improved significantly after an intervention that included education and implementation of a policy requiring prescribers to document indication, name of antibiotic prescribed, and duration or review date in the computerized medical records. After this intervention, the indication was documented in 90.3% of records and intended duration was listed in 67.7% of medical records.[33] To our knowledge, ours is the first Canadian point prevalence survey to formally evaluate documentation.

This study had a number of strengths. To the authors' knowledge, it is the first Canadian point prevalence survey to report use of ESAC-Net methods. Use of these standardized methods allows for international comparison of the findings reported here with the findings of similar surveys completed through ESAC-Net and the ECDC. In addition, this is the first published provincial point prevalence survey in Canada to specifically highlight antimicrobial utilization in small and rural population centres. Researchers considering point prevalence surveys in other parts of Canada will be able to replicate our study using the standardized method that we have reported, which is based on the ESAC-Net protocol for completing point prevalence surveys in large and small population centres.

Although the results of this study provide valuable insight into antimicrobial use by acute care hospitals in Nova Scotia, a number of limitations should be considered. This study was completed as a 1-day survey of antimicrobial use on each participating ward; however, data were not collected on the same day at all participating sites. As a result, seasonal variation may have affected the results. Generalizability to other regions in Canada may also be limited, given that the survey was completed in a single province. Furthermore, pharmacy students and technicians collected some of the data on antimicrobial use, and pharmacy students assessed guideline adherence; all such activities were under the supervision of a pharmacist. To ensure accurate data collection by trainees and the technician, a second member of the research team reviewed data collection for a minimum of 10% of patient charts and also reviewed all data entry. Assessment of adherence was reviewed by the study investigators (E.B., H.N., K.A., K.S., L.J.). In addition, students participated in educational discussions with the investigators on infectious disease topics, to supplement their course work in the undergraduate pharmacy curriculum. Disagreements in data collection were not documented; however, data collectors subjectively reported few discrepancies. Guideline adherence was assessed for only a subset of the patient population (those with community-acquired pneumonia, acute exacerbation of COPD, UTI, or nonpurulent cellulitis). As a result, the sample size for assessing guideline adherence was limited. Finally, regional guidelines were developed by the tertiary care hospital in Nova Scotia (Queen Elizabeth II Health Sciences Centre) for management of infectious diseases in adults, and these guidelines were made available electronically to all health care providers in the province. However, some prescribers may not have been aware of the availability of guidelines from the tertiary care hospital. Although there are limitations to regional application of guidelines, we felt this was an important question to explore, given the intention of the antimicrobial stewardship team to have a provincial approach.

CONCLUSION

This study contributes to knowledge about the prevalence of antimicrobial utilization, guideline adherence, and documentation in Canada and can be used locally for benchmarking against internationally published point prevalence data and to identify priorities for antimicrobial stewardship interventions. Key targets for quality improvement that should be prioritized by antimicrobial stewardship teams include conversion from IV to oral route of administration, reduction in the use of broad-spectrum antimicrobials, adherence to guidelines (with particular attention to potentially inappropriate prescribing of ciprofloxacin for UTIs), and improvement in documentation of indication and intended duration of antimicrobial use.

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Development of Pictograms to Enhance Medication Safety Practices of Health Care Workers and International Preferences

Régis Vaillancourt, Mike P Zender, Laurie Coulon, and Annie Pouliot

ABSTRACT

Background: A panel of medication management experts previously identified 9 key medication safety issues and high-alert drug classes as representing the most pressing medication-handling issues in health care.

Objective: To develop medication safety pictograms depicting medication safety issues and high-alert drug classes that represent medication-handling risks for health care personnel.

Methods: An iterative design process, including activities such as semiotic analysis, design/redesign, and evaluation, was used to develop medication safety pictograms. Nurses, physicians, pharmacists, and students listed and drew graphic elements to depict each of the 9 key medication safety issues. Graduate students in graphic design developed the preliminary pictograms for the study. A Delphi survey was then conducted with experts recruited from the International Pharmaceutical Federation to reach consensus on the pictograms and provide feedback to the graphic designers. Health care providers from around the world were invited to participate in a survey to determine a preferred pictogram for each safety warning.

Results: For each medication safety issue, 3 to 5 pictograms were developed on the basis of graphic elements suggested by 52 health care providers. These pictograms were then presented to 58 experts in 2 rounds of a Delphi process. For each medication safety issue, consensus on the 2 best pictograms was reached and feedback provided. A total of 799 participants from 61 countries responded to the international preference survey. Most of the participants (n = 536, 67.1%) were Canadian, and of those, 385 (71.8%) were pharmacists. In 8 categories, consensus on the preferred pictogram was reached across the health care professions; however, a difference in preference was apparent for the pictogram representing "neuromuscular blocking agent", with nurses' preferred pictogram differing from the preference of other participants.

Conclusion: This project produced pictograms to illustrate 9 important medication safety issues, which can now be validated through comprehension and recall assessments. Further study can also determine their potential to reduce medication administration errors.

Keywords: pictograms, medication safety

RÉSUMÉ

Contexte : Un groupe d'experts en gestion des médicaments avait auparavant établi neuf principales questions de sécurité des médicaments ou classes de médicaments de niveau d'alerte élevé qui méritaient l'attention la plus urgente en santé du point de vue de la manipulation des médicaments.

Objectif : Concevoir des pictogrammes de sécurité des médicaments qui illustrent adéquatement les questions de sécurité des médicaments et les classes de médicaments de niveau d'alerte élevé représentant des risques pour le personnel en santé lors de la manipulation des médicaments.

Méthodes : Un processus de conception itératif (comprenant des activités comme l'analyse sémiotique, la conception et la rectification, et l'évaluation) a été employé pour créer des pictogrammes de sécurité des médicaments. Du personnel infirmier, des médecins, des pharmaciens et des étudiants ont dressé une liste d'éléments graphiques qu'ils ont dessinés afin d'illustrer chacune des neuf principales questions de sécurité des médicaments. Des étudiants diplômés en graphisme ont conçu les ébauches de pictogrammes destinées à l'étude. Un sondage Delphi a ensuite été mené auprès d'experts recrutés au sein de la Fédération internationale pharmaceutique afin de dégager un consensus quant aux pictogrammes et de fournir des commentaires constructifs aux graphistes. Des fournisseurs de soins de santé de partout dans le monde ont été invités à répondre à un sondage pour déterminer quel pictogramme privilégier pour chacune des mises en garde.

Résultats : Pour chaque question de sécurité des médicaments, entre trois et cinq pictogrammes ont été conçus à partir d'éléments graphiques proposés par 52 fournisseurs de soins de santé. Ces pictogrammes ont ensuite été présentés à 58 experts au cours d'un processus Delphi à deux phases. Pour chacune des questions de sécurité des médicaments, un consensus sur les deux meilleurs pictogrammes a été atteint et des commentaires constructifs ont été émis. Au total, 799 participants de 61 pays ont répondu au sondage international sur leurs préférences. La majorité des participants (n = 536, 67,1 %) étaient Canadiens et parmi eux, 385 (71,8 %) étaient pharmaciens. Dans huit catégories, l'ensemble des professions ont atteint un consensus quant au pictogramme à privilégier. Cela n'a pas été le cas pour le pictogramme représentant les « bloqueurs neuromusculaires », car le personnel infirmier a privilégié un pictogramme différent de celui préféré par les autres professions participantes.

Conclusions : Ce projet a produit des pictogrammes pour illustrer neuf importantes questions de sécurité des médicaments. Ces pictogrammes peuvent maintenant être validés à l'aide de tests de compréhension et de mémoire. De plus amples études pourront aussi déterminer dans quelle mesure ces pictogrammes aident à réduire les erreurs d'administration de médicaments.

Mots clés : pictogrammes, sécurité des médicaments

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INTRODUCTION

Medication errors and adverse drug events occur frequently, producing substantial costs for treatment and further increasing already-burdened health care systems.[1,2] Medication errors may occur at any point in the medication process—prescribing, transcribing, dispensing, or administration[2,3]—but studies have shown that the 2 leading sources of medication errors are prescribing and administration, with administration errors representing more than half of all errors.[2,4-6] An analysis of the literature on medication errors and/or adverse drug events in hospital inpatients published between 1990 and 2005 showed that, on average, medication errors occurred in 5.7% of all episodes of drug administration.[2] The reported number of medication errors is variable, because it depends greatly on the detection method used and the route of administration studied.[2] For instance, IV administration of drugs is associated with the highest frequency of errors.[2]

Medication administration errors in hospitals have been analyzed to determine causation. Multiple factors contribute to medication administration errors, ranging from inadequate written communication to staff working conditions.[7] Medication errors are strong risk factors for preventable adverse events or reactions and remain unacceptably high; therefore, strategies to reduce medication errors could potentially decrease serious adverse events.[2,3,6,8] Various interventions, such as computerized prescriber order entry (CPOE), have been developed to reduce medication administration errors.[9] However, despite technological advancements, a review of the literature estimated that the rate of dispensing errors was between 0.04% and 24% in community pharmacies and between 0.008% and 18% in hospital pharmacies.[10] Given the complex processes involved in administration of medicines, reducing medication administration errors requires a multifaceted approach involving both education and risk management strategies.[11]

Pictograms, when combined with training, can be used as tools for improving medication management by health care providers.[3,12] Pictograms are graphic representations of concepts or ideas that can be used to communicate messages to a wide audience. They are considered advantageous in communicating messages because they can represent information regardless of language or literacy skills and can do so in a compact manner.[12,13] In the development of pictograms, researchers should connect to the existing knowledge of the users, gain the attention and hold the interest of the learner, and present the information in a way that helps the learner to remember.[14] There are 2 elements to every pictogram: a symbol (the graphic representation) and a referent (the intended meaning).[12,13,15] The referent can be context dependent and culture mediated; therefore, context and culture must be reflected in the design and implementation of a pictogram.[16] As an example, one of the most striking social innovations in recent years—the emoji—was originally introduced by Japanese telecom carriers in 1999.[17] Emojis have been adopted into online conversations and have become a universal language used across the world through multiple platforms and applications.[17,18]

Nonverbal symbols such as pictograms are increasingly being recommended to convey warnings and safety information. It is common to find warning signs and labels on consumer products.[12,14,19] In health care, pictograms have been shown to improve comprehension, recall, and adherence among patients for whom medications have been prescribed.[3,20] Cautionary pictograms from the Globally Harmonized System of Classification and Labelling of Chemicals are being used by the Workplace Hazardous Materials Information System to increase workplace safety during the handling of chemicals.[21] A similar tool for medication handling by health care providers could have great benefit for medication safety, especially during medication administration.

The development and testing of pharmaceutical pictograms involves a stepwise approach that must follow standardized processes.[12,22] Pictogram development begins with the identification of the explicit information needs or behaviour changes necessary within a target audience.[12] Once the messages to be depicted have been identified, a pool of pictograms is generated and then tested to determine whether the proposed pictograms convey the intended message.[12] Validation of the pictograms within the target audience is then performed, with redesign as indicated.[12]

In a previous study,[3] a panel of medication management experts identified 9 key medication safety issues and high-alert drug classes that represent the current most pressing medication-handling issues in health care (Table 1). Building on that study,[3] the objective of the current project was to use feedback from health care providers in developing pictograms to depict these 9 complex medication safety issues and then to survey preferences for the draft pictograms in an international sample of health care providers.

Table 1. Top 9 Medication Safety Issues Previously Identified Through a Delphi Process[3]

1	Drug that requires airway management before administration
2	Medication with a significant risk of harm if administered improperly
3	Neuromuscular blocking agent
4	Concentrated electrolyte formulation
5	Medication that can be given only via central line
6	Drug that must always be diluted before administration
7	Medication that has a minuscule volume dose
8	Medication that has a high incidence of calculation/dosage errors
9	Drug names that look alike and sound alike

METHODS

Phase 1: Semiotic Analysis and Preliminary Designs

A semiotic analysis using "List It" and "Draw It" methods was conducted to determine the key graphic elements for each of the safety messages to be conveyed. Semiotic analysis is the study, through breakdown and analysis, of the key components making up an image and how the population perceives them.[23] A questionnaire was distributed to nurses, physicians, pharmacists, and health care students from the Children's Hospital of Eastern Ontario (CHEO) in Ottawa, Ontario. Participants were asked to list and draw graphic elements that could help to depict each of the 9 medication safety issues in response to the following 2 questions: "Which graphic elements should be included in the pictograms?" and "How would you draw this issue/message?"

Phase 2: Pictogram Design and Optimization

Through an iterative process and in collaboration with a group of pharmacists and experts in health communication at CHEO, graduate students from the School of Design, University of Cincinnati, in Cincinnati, Ohio, designed between 3 and 5 pictograms for each of the 9 medication safety issues using the graphic elements and the feedback received from the "List It" and "Draw It" surveys in Phase 1.

Phase 3: Delphi Process to Identify 2 Preferred Medication Safety Pictograms

The Delphi method is a technique used to reach a reliable consensus in a group of experts.[24] The Delphi method involves a series of 2 or more surveys, called "rounds", in which a panel of experts provides their opinions on a question. After each round, the panelists receive aggregated information on the responses of the full panel, and are then asked follow-up questions in the next round. The process continues until consensus is reached.[24]

An invitation to participate in selecting medication pictograms was sent through the Hospital Pharmacy Section of the International Pharmaceutical Federation (FIP). Interested participants, who self-identified as being experts in medication management, were invited to complete a modified Delphi survey to reach consensus on their preferred pictograms and to provide feedback for the graphic designers to improve the pictograms.

Participants were presented with the pictograms developed in Phase 2 and were asked to rank the pictograms from their most preferred (first choice) to least preferred (fifth choice) pictograms and to provide comments on how to improve them. After refinement by the designers, a new set of pictograms depicting the medication safety issues was presented to the group of experts for another round. The experts were asked to select 2 preferred pictograms for each medication safety issue and to again provide feedback on the proposed pictograms.

Phase 4: International Preference Survey

An international preference survey was conducted to determine which of the 2 top pictograms identified during the Delphi survey best depicted each of the 9 medication safety issues. Health care professionals involved in medication management were targeted for this survey. The online survey invitation was sent electronically to participants through mass distribution using a snowball sampling strategy. An invitation was sent to the FIP, which forwarded the invitation to its membership and also to the World Health Professions Alliance for forwarding, in turn, to its membership. Among the member organizations of the World Health Professions Alliance are the International Council of Nurses and the World Medical Association. In Canada, the Medbuy hospital pharmacy directors group, the Institute for Safe Medication Practices Canada, and the Medication Safety Pharmacy Specialty Network of the Canadian Society of Hospital Pharmacists received an e-mail invitation to participate in the study and were asked to distribute the invitation within their respective networks. We expected to reach about 5000 health care workers. Pharmacy technicians, pharmacists, nurses, and physicians were the principal groups of potential participants.

Respondents who agreed to participate in the international preference survey were asked to select the pictogram that best represented each medication safety issue and to provide comments on how to improve the pictograms.

Data Collection and Analysis

Ethics approval for the project was obtained from the CHEO Research Ethics Board before project initiation. Participants did not receive any incentive to participate. Development of the pictograms and data collection took place in Ottawa, Ontario, over a 6-month period (February 2016 to July 2016). REDCap (Research Electronic Data Capture), a secure web-based application designed to build and manage surveys and databases,[25] was used to administer the surveys. The Statistical Package for the Social Sciences (SPSS version 23.0, IBM, Armonk, New York) was used to analyze the demographic and descriptive data. Categorical variables were summarized using frequencies and percentages.

RESULTS

Phase 1: Semiotic Analysis and Preliminary Designs

Fifty-two health care professionals from CHEO provided feedback for any of the 9 medication safety issues for which they had ideas. They suggested elements to include in pictograms (Table 2) and suggested how to draw the pictograms (providing their own drawings) (Figure 1). Participants in this phase were nurses, physicians, pharmacists, pharmacy technicians, dieticians, development service workers, and medicine, pharmacy, and nursing students.

Table 2 (part 1 of 2). Key Graphic Elements Identified for Inclusion in Pictograms*

Issue or High-Alert Drug Class	Participant's Profession	Elements to Include in Pictograms†
Drug that requires airway management before administration	Total *n* = 14 Nurse (*n* = 5) Nursing student (*n* = 2) Physician (*n* = 2) Medical student (*n* = 2) Specialist technologist (*n* = 1) Dietician (*n* = 1) Respiratory therapist (*n* = 1)	• Profile image of mouth/throat/nose: 4 • Lungs and "monitor airway": 4 • Red warning colour/"!": 3 • Airway equipment (bag/mask/valve): 3 • Endotracheal tube/ laryngoscope: 1
Medication with a significant risk of harm if administered improperly	Total *n* = 20 Pharmacy student (*n* = 2) Nurse (*n* = 4) Nursing student (*n* = 3) Physician (*n* = 2) Medical student (*n* = 3) Specialty technologist (*n* = 1) Medical radiation technologist (*n* = 1) Development service worker (*n* = 1) Laboratory technologist (*n* = 1) Health professional (*n* = 1) Student (*n* = 1)	• Caution sign: 2 • Warning: 6 • Red colour: 3 • "Morphine": 2
Neuromuscular blocking agent	Total *n* = 17 Clinical pharmacist (*n* = 1) Nurse (*n* = 5) Nursing student (*n* = 4) Physician (*n* = 2) Resident physician (*n* = 1) Medical student (*n* = 2) Specialist technologist (*n* = 1) Occupational therapist (*n* = 1)	• Muscle or nerve with "X" on it: 5 • Limb/bicep muscle: 2 • Warning symbol/red colour: 4 • Brain/neuron: 4
Concentrated electrolyte formulation	Total *n* = 14 Nurse (*n* = 5) Nursing student (*n* = 2) Physician (*n* = 2) Medical student (*n* = 2) Specialist technologist (*n* = 1) Dietician (*n* = 1) Respiratory therapist (*n* = 1)	• Up arrow "Na"/"K"/"Cl": 3 • Symbol (+) (–): 3 • Red sticker/Caution sign: 3 • Concentration in formulation: 1
Medication that can be given only via central line	Total *n* = 14 Nurse (*n* = 5) Nursing student (*n* = 2) Physician (*n* = 2) Medical student (*n* = 2) Specialist technologist (*n* = 1) Dietician (*n* = 1) Respiratory therapist (*n* = 1)	• Needle in tubing: 1 • Central line: 4 • Heart line: 2 • "ONLY": 3 • Catheter: 1 • Chest: 1
Drug that must always be diluted before administration	Total *n* = 20 Pharmacy student (*n* = 2) Nurse (*n* = 4) Nursing student (*n* = 3) Physician (*n* = 2) Medical student (*n* = 3) Specialty technologist (*n* = 1) Medical radiation technologist (*n* = 1) Development service worker (*n* = 1) Laboratory technologist (*n* = 1) Health professional (*n* = 1) Student (*n* = 1)	• Beaker with syringe/vial/ampoule: 7 • Word "Dilute": 2 • Volume of diluent: 2 • "Add water": 4 • Image of steps of dilution: 2 • Different colours: 2

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Table 2 (part 2 of 2). Key Graphic Elements Identified for Inclusion in Pictograms*

Issue or High-Alert Drug Class	Participant's Profession	Elements to Include in Pictograms†
Medication that has a minuscule volume dose	Total *n* = 17 Clinical pharmacist (*n* = 1) Nurse (*n* = 5) Nursing student (*n* = 4) Physician (*n* = 2) Resident physician (*n* = 1) Medical student (*n* = 2) Specialist technologist (*n* = 1) Occupational therapist (*n* = 1)	• Magnifying glass: 2 • Syringe: 6 • Small volume/number: 6 • Warning symbol: 2 • "< 1 mL": 2 • Dropper/micropipette/ measuring spoon: 3
Medication that has a high incidence of calculation/dosage errors	Total *n* = 17 Clinical pharmacist (*n* = 1) Nurse (*n* = 5) Nursing student (*n* = 4) Physician (*n* = 2) Resident physician (*n* = 1) Medical student (*n* = 2) Specialist technologist (*n* = 1) Occupational therapist (*n* = 1)	• Caution sign: 3 • Calculator: 7 • Numbers: 2 • Warning symbol/red colour/high alert: 7
Drug names that look alike and sound alike	Total *n* = 20 Pharmacy student (*n* = 2) Nurse (*n* = 4) Nursing student (*n* = 3) Physician (*n* = 2) Medical student (*n* = 3) Specialty technologist (*n* = 1) Medical radiation technologist (*n* = 1) Development service worker (*n* = 1) Laboratory technologist (*n* = 1) Health professional (*n* = 1) Student (*n* = 1)	• Eye and ear symbols: 5 • Capital letter: 3 • Warning symbols: 6 • Two drug names look similar (e.g., clobazam and clonazepam): 5

*A total of 52 individuals participated in this phase of the study.
†For each element, the number indicates the number of participants who included that specific element in their description or drawing.

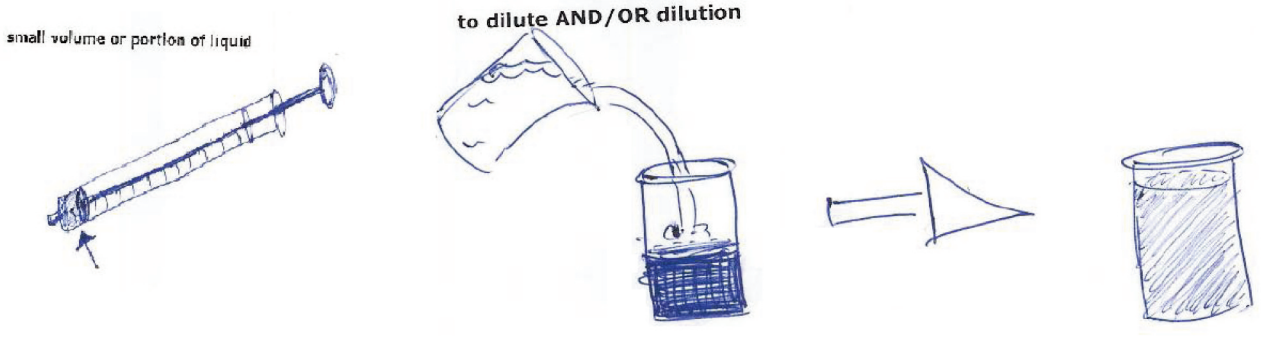
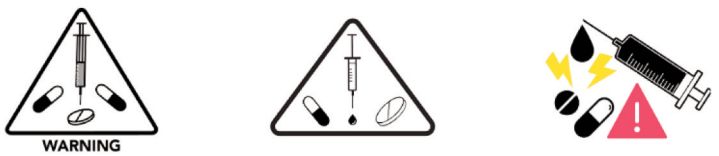


Figure 1. Examples of hand drawings from "Draw It" survey.

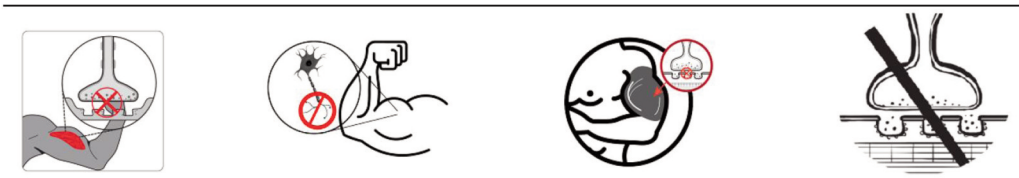
Table 3 (part 1 of 2). Medication Safety Pictograms Developed for Consideration in the International Consultation Survey (Phase 2)

1. Drug that requires airway management before administration: 5 pictograms

2. Medication with a significant risk of harm if administered improperly: 3 pictograms



3. Neuromuscular blocking agent: 4 pictograms



4. Concentrated electrolyte formulation: 5 pictograms

5. Medication that can be given only via central line: 4 pictograms

6. Drug that must always be diluted before administration: 5 pictograms

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Table 3 (part 2 of 2). Medication Safety Pictograms Developed for Consideration in the International Consultation Survey (Phase 2)

7. Medication that has a minuscule volume dose: 5 pictograms

8. Medication that has a high incidence of calculation/dosage errors: 3 pictograms

9. Drug names that look alike and sound alike: 3 pictograms

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Phase 2: Pictogram Design and Optimization

Based on the suggestions of these 52 health care workers from CHEO, in collaboration with the School of Design, University of Cincinnati, 3 to 5 pictograms for each medication safety issue were developed (Table 3).

Phase 3: Delphi Process to Identify 2 Preferred Medication Safety Pictograms

The international Delphi process began with 58 participants and involved 2 rounds (Table 4). The distribution of health care providers was 32 clinical pharmacists (55%), 20 pharmacy managers (34%), and 6 other health care professions (10%). Although 58 participants participated in the Delphi survey, they were not obliged to provide input on all 9 medication safety pictograms.

For the first round, pictograms were ranked according to preference, where 1 represented the most preferred pictogram. The 2 pictograms that most often received a first-choice ranking were selected for inclusion in the second round of the Delphi process. In addition, the pictograms were improved between rounds to reflect the comments from round 1. Of the initial group of 58 experts, 32 (55%) participated in the second Delphi round (Table 5).

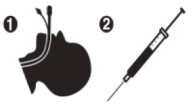
Phase 4: International Preference Survey

Finally, the preferred pictogram for each of the 9 medication safety issues was identified through the international preference survey (Table 6). A total of 799 health care providers from 61 countries participated in this final phase of pictogram selection. The following countries were represented: Canada (n = 536, 67.1%), Republic of Ireland (n = 41, 5.1%), Nigeria (n = 36, 4.5%), United States (n = 19, 2.4%), Australia (n = 17, 2.1%), Malta (n = 17, 2.1%), Denmark (n = 10, 1.3%), Germany (n = 7, 0.9%), Ghana (n = 6, 0.8%), the Netherlands (n = 6, 0.8%), and the Philippines (n = 6, 0.8%). The remaining 98 participants (12.3%) were from 50 other countries, with 1 to 5 participants per country. These countries were Albania, Argentina, Austria, Brazil, Chile, China, Costa Rica, Croatia, Czech Republic, Ecuador, Finland, France, Gabon, Greece, Haiti, Hungary, India, Indonesia, Iraq, Japan, Jordan, Latvia,

Table 4 (part 1 of 3). Delphi Round 1 Pictograms, Ranked First and Second, with Participant Comments*†

1. Drug that requires airway management before administration

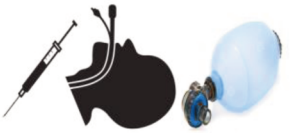
First rank: 17/54 (31%)



Second rank: 17/56 (30%)

Comments:

- Keep the first choice and a self-inflating bag
- Elements to improve pictograms :



2. Medication with a significant risk of harm if administered improperly

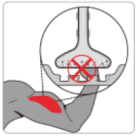
First rank: 34/54 (63%)

Second rank: 18/57 (32%)

Improved pictograms

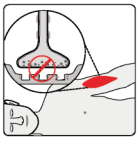
3. Neuromuscular blocking agent

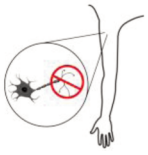
First rank: 17/52 (33%)



Second rank: 16/54 (30%)

Improved pictograms:

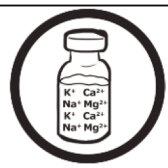
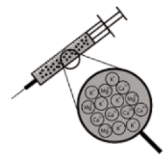




continued on page 251

Table 4 (part 2 of 3). Delphi Round 1 Pictograms, Ranked First and Second, with Participant Comments*†

4. Concentrated electrolyte formulation

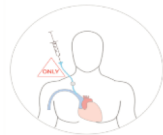
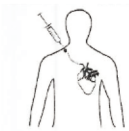
	
First rank: 29/55 (53%)	Second rank: 18/56 (32%)

Comments:

- We will also keep the first choice pictogram above, but could you also put "+" signs instead of putting the "Ca2+, Mg2+, K+, and Na+".

Improved pictograms:

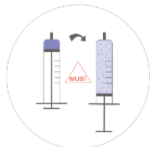
5. Medication that can be given only via central line

	
First rank: 41/55 (75%)	Second rank: 5/52 (10%)

Comments:

- Word "Only" is necessary.
- The catheter actually goes through the arm and joins the veins under the clavicle.
- Make sure to use all of the space the circle offers (over the head).
- Make a pictogram without the rest of the vein. As shown below.

6. Drug that must always be diluted before administration

	
First rank: 26/57 (46%)	Second rank: 18/56 (32%)

Improved pictograms:

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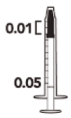
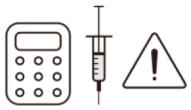
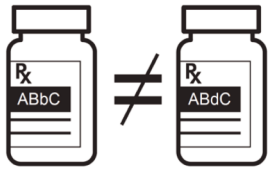
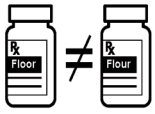
Table 4 (part 3 of 3). Delphi Round 1 Pictograms, Ranked First and Second, with Participant Comments*†

7. Medication that has a minuscule volume dose	
 First rank: 23/54 (43%)	 Second rank: 11/57 (19%)
Improved pictogram: 	
8. Medication that has a high incidence of calculation/dosage errors	
 First rank: 36/56 (64%)	 Second rank: 11/57 (19%)
9. Drug names that look alike and sound alike	
 First rank: 24/57 (42%)	 Second rank: 22/55 (40%)
Improved pictogram: 	

*Pictograms © 2016 by Régis Vaillancourt, The CHEO Research Institute, and Mike P Zender; reproduced with permission.
†A total of 58 individuals participated in this phase of the study.

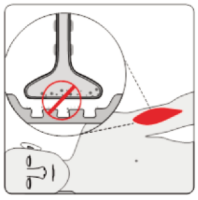
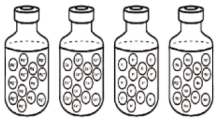
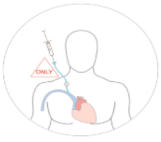
Macedonia, Malaysia, Montenegro, New Zealand, Norway, Oman, Pakistan, Qatar, Romania, Russia, Saudi Arabia, Serbia, Singapore, South Africa, South Korea, Spain, Sri Lanka, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, United Arab Emirates, United Kingdom, Uruguay, Yemen, and Zimbabwe. Among the health care providers who participated were 572 pharmacists (71.6%), 101 nurses (12.6%), 62 pharmacy technicians (7.8%), and 43 physicians (5.4%). Among the 536 Canadian participants, 385 (71.8%) were pharmacists.

For 8 of the 9 medication safety issues, members of each profession preferred the same pictogram; however, a clear consensus was not reached on the preferred pictogram for neuromuscular blocking agents. More specifically, nurses preferred a different pictogram from that preferred by all other participants.

DISCUSSION

Pictograms have been used for many years as a way to illustrate safety-related messages on consumer products such as

Table 5 (part 1 of 2). Preferred Pictograms as Determined in Delphi Round 2*†

1. Drug that requires airway management before administration (*n* = 32)	
 *n* = 22 (69%)	 *n* = 10 (31%)
2. Medication with a significant risk of harm if administered improperly (*n* = 32)	
 *n* = 5 (16%)	 *n* = 27 (84%)
3. Neuromuscular blocking agent (*n* = 32)	
 *n* = 24 (75%)	 *n* = 8 (25%)
4. Concentrated electrolyte formulation (*n* = 32)	
 *n* = 14 (44%)	 *n* = 18 (56%)
5. Medication that can be given only via central line (*n* = 32)	
 *n* = 5 (16%)	 *n* = 27 (84%)

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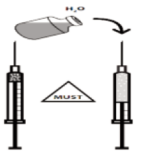
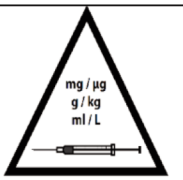
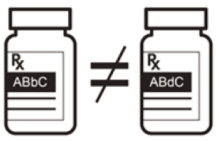
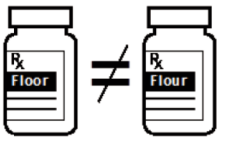
toys, clothes, and food. Warning signs could also be used to help mitigate risk related to the administration of medications. To the authors' knowledge, this is the first study to specifically design pictograms for health care professionals warning of important medication administration errors and to test preferences for these pictograms internationally. Following best practice recommendations, we developed a comprehensive and iterative design process for the pictograms, because studies have shown that poorly designed pictograms may be poorly understood.[26] In particular, we followed the steps proposed by Montagne and identified key issues and elements in medication safety to be targeted for pictogram design.[3,12]

Table 5 (part 2 of 2). Preferred Pictograms as Determined in Delphi Round 2*†

6. Drug that must always be diluted before administration (*n* = 31)	
 *n* = 16 (52%)	 *n* = 15 (48%)
7. Medication that has a minuscule volume dose (*n* = 32)	
 *n* = 17 (53%)	 *n* = 15 (47%)
8. Medication that has a high incidence of calculation/dosage errors (*n* = 31)	
 *n* = 18 (58%)	 *n* = 13 (42%)
9. Drug names that look alike and sound alike (*n* = 31)	
 *n* = 17 (55%)	 *n* = 14 (45%)

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†A total of 32 individuals participated in this phase of the study.

For 9 medication safety issues and high-alert drug classes established by consensus, in an earlier study, as being most important for medication safety, we designed between 3 and 5 pictograms using the "Draw it" and "List it" methodology and redesign by graphic designers. For each issue of concern, we selected the 2 pictograms that garnered the most "first choice" votes from a panel of experts. This method did not consider the accumulation of all ranks, a method that could produce different results.

The "List It" and "Draw It" methodology allowed the graphic designer to include important elements that might not have been independently identified by the group of experts or the graphic designer. It provided a wider range of suggestions and accelerated the process of obtaining the final pictogram. However, some of the medication safety issues were very challenging to represent visually (e.g., "medication that requires airway management before administration" and "medication with a significant risk of harm"). These pictograms were designed in a more abstract way, and users will likely require education in order to understand them. The literature suggests a strong correlation between the complexity of a message and the level of comprehension,[27] which means that for complex messages, a lower level of comprehension

Table 6 (part 1 of 2). International Preferences for Medication Safety Pictograms*†

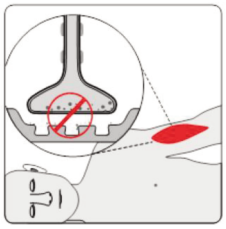
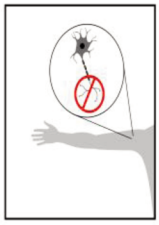
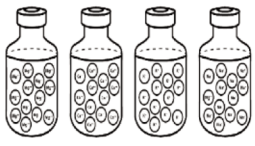
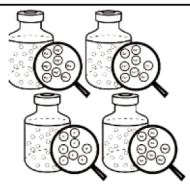
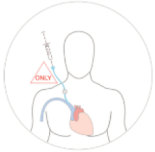
1. Drug that requires airway management before administration (*n* = 792)	
	
n = 562 (71.0%)	*n* = 230 (29.0%)
2. Medication with a significant risk of harm if administered improperly (*n* = 782)	
	
n = 56 (7.2%)	*n* = 726 (92.8%)
3. Neuromuscular blocking agent (*n* = 783)	
	
n = 476 (60.8%)	*n* = 307 (39.2%)
4. Concentrated electrolyte formulation (*n* = 782)	
	
n = 177 (22.6%)	*n* = 605 (77.4%)
5. Medication that can be given only via central line (*n* = 797)	
	
n = 136 (17.1%)	*n* = 661 (82.9%)

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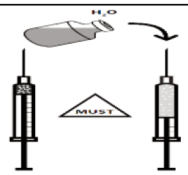
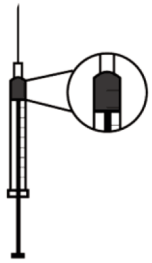
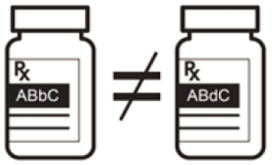
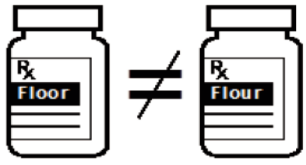
Table 6 (part 2 of 2). International Preferences for Medication Safety Pictograms*†

6. Drug that must always be diluted before administration (*n* = 788)	
	
n = 285 (36.2%)	*n* = 503 (63.8%)
7. Medication that has a minuscule volume dose (*n* = 789)	
	
n = 301 (38.1%)	*n* = 488 (61.9%)
8. Medication that has a high incidence of calculation/dosage errors (*n* = 776)	
	
n = 504 (64.9%)	*n* = 272 (35.1%)
9. Drug names that look alike and sound alike (*n* = 787)	
	
n = 339 (43.1%)	*n* = 448 (56.9%)

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†A total of 799 individuals participated in this phase of the study.

is typically observed. In the case of pictograms for the 2 issues that were particularly challenging to represent, we anticipate lower comprehension in the validation phase, because of the complexity of the messages we are trying to convey. Nonetheless, the aim of these pictograms is to warn health care professionals of possible danger, and it might be possible to test for the perception of danger, along with comprehension of the specific pictograms.

This study had a number of limitations. First, the international Delphi consultation included only pharmacists but might have benefited from inclusion of practitioners in other health care professions involved in the administration of medications. The international survey also lacked substantial numbers of participants from developing countries, with most participants coming from Canada. This is a limitation in the sense that the

pictograms are primarily based on materials and procedures from Canada and the United States.

Finally, this study did not look at comprehension of the pictograms that were developed. This step is crucial in the identification of pictograms that can be used in practice.[12] Instead, this project started with multiple designs for each safety issue, so as to present multiple choices to health care providers. We also thought that selecting the preferred pictogram using an international sample of health care providers would help in designing more internationally recognized and accepted pictograms. The next step will be to test these pictograms for comprehension using standards of the International Organization for Standardization (ISO) to validate these pharmaceutical safety pictograms for use around the world.[22] The ISO standards require that at least 66% of participants be able to comprehend a pictogram without explanation.

CONCLUSION

This study has presented international preferences for pictograms developed for 9 issues identified by Canadian experts as safety risks in the management and administration of medications. Testing of these pictograms for comprehension is the next step before their implementation in practice.[12,28] Future studies will look at rates of comprehension for these pictograms and rates of recall after participants are trained on their meaning.

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ORIGINAL RESEARCH

Validation of Pictograms for Safer Handling of Medications: Comprehension and Recall among Pharmacy Students

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ABSTRACT

Background: Medication preparation and administration are higher-risk steps in the medication management process. Therefore, medication management strategies, such as warnings and education about medication safety, are essential in preventing errors and improving the safe handling of medications by health care workers.

Objectives: To validate comprehension of 9 pictograms designed to improve medication safety, and to assess long-term recall of these pictograms in a sample of pharmacy students.

Methods: First- and second-year pharmacy students were recruited as participants. The study was divided into 2 phases: comprehension (Phase 1) and long-term recall (Phase 2). In Phase 1, a slideshow of the 9 pictograms was presented to participants, who were asked to write the meaning of and required action for each pictogram. The intended meaning of each pictogram was then presented to the participants. Four weeks later, long-term recall was assessed in Phase 2 of the study using the same method. The meaning and required action that participants provided for each pictogram were reviewed by 3 independent raters. A pictogram was considered to be validated in the pharmacy student population if at least 67% of participants identified the correct meaning or required action during the recall phase.

Results: A total of 101 pharmacy students participated in Phase 1 and 67 in Phase 2. In Phase 1, 4 pictograms met the 67% threshold for comprehension. In Phase 2, after training, 7 of the 9 pictograms were validated.

Conclusions: Given the results obtained with pharmacy students, redesign may be necessary for 2 of the pictograms. The use of validated medication safety pictograms on medication labels and other identifiers may prevent errors during medication handling and administration; this is an important avenue of investigation for future studies.

Keywords: pictograms, medication safety, safe medication handling

RÉSUMÉ

Contexte : La préparation et l'administration des médicaments sont des étapes à risque plus élevé dans le processus de gestion des médicaments. Or, les stratégies de gestion des médicaments, dont les mises en garde et les informations sur la sécurité des médicaments, sont essentielles à la prévention des erreurs et à une manipulation plus sécuritaire des médicaments par les travailleurs de la santé.

Objectifs : Valider la compréhension de neuf pictogrammes conçus pour accroître la sécurité des médicaments et vérifier si ces pictogrammes s'inscrivent dans la mémoire à long terme des étudiants en pharmacie.

Méthodes : On a recruté des participants auprès des étudiants de première et de deuxième année en pharmacie. L'étude était composée de deux phases : compréhension (phase 1) et mémoire à long terme (phase 2). Dans la phase 1, un diaporama de neuf pictogrammes a été présenté aux participants à qui l'on a demandé d'interpréter chaque pictogramme et la mesure qu'il impose. On a ensuite présenté aux participants la signification qu'on voulait donner à chaque pictogramme. Quatre semaines plus tard durant la phase 2, un test de mémoire à long terme employant la méthode de la phase 1 a été effectué. Les réponses des participants quant à la signification et à la mesure à prendre pour chaque pictogramme ont été analysées par trois évaluateurs indépendants. Un pictogramme était considéré comme validé dans la population des étudiants en pharmacie si un minimum de 67 % des participants se souvenait de la signification adéquate et de la mesure à prendre recherchée pendant la phase de test de mémoire à long terme.

Résultats : Au total, 101 étudiants en pharmacie ont participé à la phase 1 et 67 à la phase 2. Dans la phase 1, quatre pictogrammes ont atteint le seuil de 67 % pour la compréhension. Dans la phase 2, après une formation, 7 pictogrammes sur 9 ont été validés.

Conclusions : Compte tenu des résultats obtenus auprès des étudiants en pharmacie, deux des pictogrammes pourraient être appelés à retourner à la planche à dessin. L'ajout de pictogrammes validés de sécurité des médicaments sur les étiquettes et autres marques d'identification de médicaments pourrait éviter des erreurs pendant la manipulation et l'administration de médicaments. Il s'agit là d'une piste de recherche importante pour de futures études.

Mots clés : pictogrammes, sécurité des médicaments, manipulation sécuritaire des médicaments

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INTRODUCTION

The medication management process includes prescribing, transcribing, dispensing, and administering medication. When there is a breakdown or oversight during any of these steps, a medication error may occur, exposing the patient to harm.[1,2] Evidence shows that the leading sources of medication errors are the prescribing and administration steps, with administration representing more than half of all errors.[1,3-5] Medication administration is a complex process that encompasses counting, calculating, mixing, measuring, and ensuring that the right patient receives the right medication, in the right dose, by the right route, for the right reason, at the right time.[1,6] Medication routes such as IV administration are associated with the highest frequencies of errors, with some studies reporting error rates as high as 50%.[1,7]At particular risk of medication errors is the pediatric population. Medication error rates up to 20% have been reported for the pediatric population, or 3 times higher than in the adult population.[4,8]

Visual aids can help draw attention to a document and improve the comprehension of information.[9] Pictograms are visual aids that represent concepts through visual synthesis to communicate messages and information.[10] They are intended to provide information in an effective manner without the use of words and therefore can prove advantageous in settings with language or literacy challenges.[10,11] The Dual Coding Theory was proposed in 1971 by Canadian psychology professor Allan Paivio. The Dual Coding Theory posits that verbal and nonverbal information are stored in long-term memory as 2 distinct systems, whereby activation of one of the systems can trigger activation of the other.[12] It has also been suggested that there is improved recall of information when pictures are presented instead of words, through activation of both coding systems.[13] Improved recall of information from pictures, as opposed to words alone, is known as the "pictorial superiority effect".[12] The Dual Coding Theory proposes that pictograms, with associated text, could provide optimal processing and improve recall of medication information. A few studies have shown the superiority of pictograms used in conjunction with verbal communication,[14-19] whereas other studies have failed to demonstrate that pictograms improve long-term recall of instructions.[17,20] However, in recent years, health care systems have recognized the value of pictograms, and studies are showing improved comprehension, recall, and adherence with use of pictograms among patients receiving prescribed medications.[2,21]

The use of pictograms is increasingly being recommended to convey warnings and safety information; indeed it is common to find warning signs and labels on consumer products.[11,22,23] The Workplace Hazardous Materials Information System has implemented cautionary pictograms from the Globally Harmonized System of Classification and Labelling of Chemicals to increase workplace safety in the handling of chemicals.[24] Similar strategies for medication handling could improve medication safety, particularly the medication administration process. Furthermore, these pictograms would align with the Basel Statements put forward by the International Pharmaceutical Federation (FIP), including the statement that "Hospital pharmacists should ensure that medicines are packaged and labeled to ensure identification and to maintain integrity until immediately prior to administration to the individual patient".[25] The FIP also recommends that hospitals develop and implement policies and practices to prevent errors associated with the route of administration.[25]

In an initial, recently conducted study, our team identified 9 key medication safety issues that could benefit from the implementation of safety pictograms for health care providers.[2] Pictograms were then developed to represent each of these safety issues and underwent an iterative design process. A Delphi survey with self-declared experts from the FIP was conducted to identify international preferences for the pictograms to represent these 9 key medication safety issues (published elsewhere in this issue).[26] For these pictograms to be implemented in practice, not only must they be designed with input from members of the target population, but they must also undergo validation by members of the target population. In this case, the target population consists of health care professionals, such as pharmacy technicians, pharmacists, nurses, and physicians. As a first step in this validation process, a sample of pharmacy students was recruited for the current pilot study, for initial validation of comprehension and recall of the 9 pictograms designed to improve medication safety.

METHODS

Participants

Students from the School of Pharmacy of the University of Waterloo, Waterloo, Ontario, were invited to participate in the study. Students were recruited between May and July 2017 from 2 classes of first- and second-year students in the pharmacy program. The demographic data collected from participants were age, year of study, and whether they had previous experience in the hospital setting. There were no benefits or risks associated with participating in the study, and written consent was obtained from each participant. This study was approved by the Children's Hospital of Eastern Ontario Research Ethics Board and the Research Ethics Board at the University of Waterloo.

Pictogram Validation

Phase 1: Comprehension Assessment

Comprehension was assessed during regularly scheduled classes at the School of Pharmacy. A slide show was presented to participants, with the 9 pictograms presented sequentially. After each pictogram was presented, participants were asked to record their responses to the following 3 questions on a paper questionnaire: What do you think this symbol means? In the context of

health care professionals prescribing, preparing, dispensing, or administering a medication with this symbol on it, what action should you take in response to this symbol? How could this pictogram be improved? The same 3 questions were asked for each of the 9 pictograms presented. Once the comprehension test was completed, the pictograms were displayed again and the intended meaning was explained to participants.

To avoid research team bias, 3 independent raters evaluated participants' responses. Answers were scored as "correct", "incorrect", or "no response is given". A response was rated as correct if a correct answer was provided for either the first question or the second question, which were considered together as prompts to elicit the meaning of the pictogram. The percentage of participants who understood the pictograms was calculated using only the "correct" and "incorrect" responses for each pictogram. In accordance with ISO standard 9186 from the International Organization for Standardization (ISO), a comprehension rate of at least 67% was needed for a pictogram to be considered validated.[27] The ISO standards were chosen because they are international and directly applicable to the design of pharmaceutical pictograms.[11] Participants' comments on pictogram improvement were considered only for those pictograms that did not meet this validation standard.

Phase 2: Recall Assessment

Long-term recall of pictogram meaning was assessed after 4 weeks. The same slide-show method was used, and the same questions were asked as in Phase 1.

Data Analysis

Differences in comprehension rates for between-subject comparisons (e.g., first-year students compared with second-year students) were assessed using the Fisher exact test with α set at 0.05. Differences in comprehension rates for within-subject comparisons (i.e., comprehension compared with recall) were assessed using the McNemar test for paired dichotomous data.

RESULTS

Study Participants

In Phase 1 of the study, 101 students participated. In Phase 2 of the study, 67 students completed the recall assessment. Demographic information for these participants is presented in Table 1.

Pictogram Validation

Phase 1: Comprehension Assessment

Four of the pictograms were understood by more than 67% of participants. These pictograms represented "Drug that requires airway management before administration", "Drug that must always be diluted before administration", "Medication that has a high incidence of calculation/dosage errors", and "Drug names that look alike and sound alike". The remaining 5 pictograms were each understood by less than 67% of participants (Table 2).

A subgroup analysis was performed according to participants' year of study (see Appendix 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/177/showToc). Comprehension rates were compared between the 33 first-year students and the 68 second-year pharmacy students. Despite having more education in the field of pharmacy, second-year students were no more likely to understand the pictograms, with one exception: second-year students were more likely to understand the pictogram for "Drug that must always be diluted before admin-

Table 1. Demographic Characteristics of Study Participants

Characteristic	Phase of Study; No. (%) of Participants			
	Phase 1: Comprehension (*n* = 101)		Phase 2: Long-Term Recall (*n* = 67)	
Age*				
≥ 20 and < 25 years	75	(82)	49	(83)
≥ 25 and < 30 years	15	(16)	9	(15)
≥ 30 years	1	(1)	1	(2)
Level of education				
First-year pharmacy school	33	(33)	29	(43)
Second-year pharmacy school	68	(67)	38	(57)
Participant has some hospital experience†				
Total	35	(35)	20	(31)
First-year pharmacy school‡	2	(6)	2	(10)
Second-year pharmacy school‡	33	(94)	18	(90)

*Ten participants in Phase 1 and 8 participants in Phase 2 did not provide their age.
†Based on yes/no response. Three participants in Phase 2 did not respond.
‡Percentages in this row are based on the total number with hospital experience (i.e., 35 in Phase 1 and 20 in Phase 2).

Table 2 (part 1 of 2). Pictogram Comprehension (Phase 1)

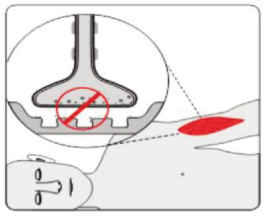
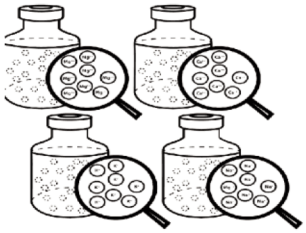
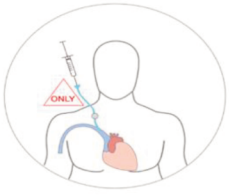
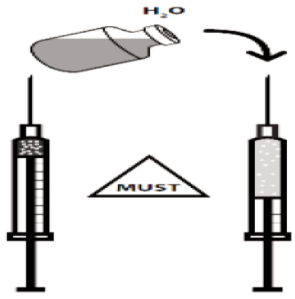
Safety Message	Pictogram*	No. (%) of Participants Who Correctly Guessed Meaning (*n* = 101)
Drug that requires airway management before administration		70 (69)
Medication with a significant risk of harm if administered improperly		32 (32)
Neuromuscular blocking agent		53 (52)
Concentrated electrolyte formulations		11 (11)
Medication that can be given only via central line		48 (48)
Drug that must always be diluted before administration		85 (84)

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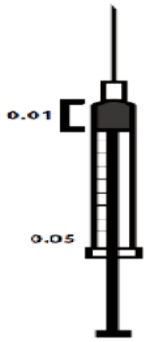
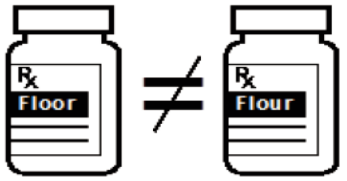
Table 2 (part 2 of 2). Pictogram Comprehension (Phase 1)

Safety Message	Pictogram*	No. (%) of Participants Who Correctly Guessed Meaning (*n* = 101)
Medication that has a minuscule volume dose		21 (21)
Medication that has a high incidence of calculation/dosage errors		94 (93)
Drug names that look alike and sound alike		91 (90)

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istration" (22/33 [67%] for first-year students versus 63/68 [93%] for second-year students, $p = 0.002$ by Fisher exact test).

Another subgroup analysis was performed to examine whether pharmacy students with hospital experience were more likely than those without such experience to understand the pictograms (see Appendix 2, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/177/showToc). Among the participants who completed the demographic questions, 35 had prior hospital experience and 62 did not. Participants with hospital experience were no more likely to understand the pictograms, with one exception. The participants with hospital experience were more likely than those without to understand the pictogram for "Drug that requires airway management before administration" (29/35 [83%] for those with experience versus 37/62 [60%] for those without experience, $p = 0.024$ by Fisher exact test).

Phase 2: Recall Assessment

A total of 67 participants from the first phase of the study completed the second phase. For each pictogram, comprehension and recall rates for participants who completed both Phases 1 and 2 are presented in Table 3. At recall, 7 of the 9 pictograms reached the ISO standard of at least 67% comprehension, with only "Concentrated electrolyte formulations" (37/67 [55%]) and "Medication with a significant risk of harm if administered improperly" (41/67 [61%]) not reaching the minimum threshold for comprehension. All but 2 of the pictograms were understood by more participants during Phase 2 than Phase 1. The 2

Table 3 (part 1 of 2). Comprehension (Phase 1) and Recall (Phase 2) for Subset of Participants Who Completed Both Phases of Study

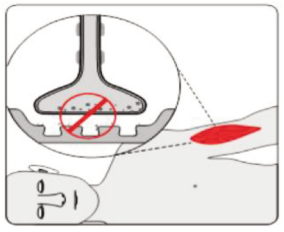
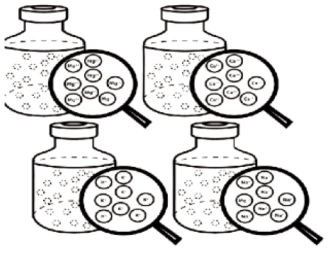
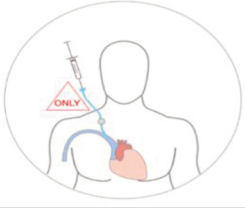
Safety Message	Pictogram*	Study Phase; No. (%) of Participants (*n* = 67)		*p* Value†
		Correct Guess in Phase 1	Correct Recall in Phase 2	
Drug that requires airway management before administration		47 (70)	53 (79)	0.31
Medication with a significant risk of harm if administered improperly		19 (28)	41 (61)	< 0.001
Neuromuscular blocking agent		37 (55)	57 (85)	< 0.001
Concentrated electrolyte formulations		5 (7.5)	37 (55)	< 0.001
Medication that can be given only via central line		28 (42)	48 (72)	0.001

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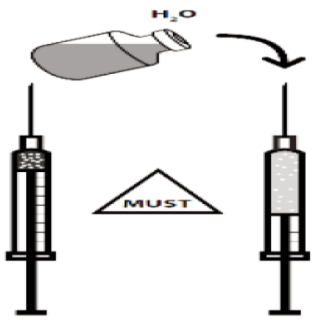
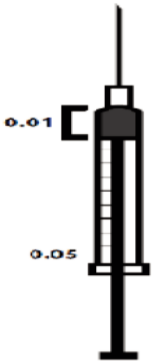
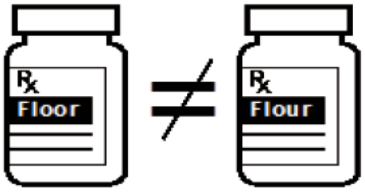
Table 3 (part 2 of 2). Comprehension (Phase 1) and Recall (Phase 2) for Subset of Participants Who Completed Both Phases of Study

Safety Message	Pictogram*	Study Phase; No. (%) of Participants (*n* = 67)		*p* Value†
		Correct Guess in Phase 1	Correct Recall in Phase 2	
Drug that must always be diluted before administration		54 (81)	66 (98)	0.002
Medication that has a minuscule volume dose		17 (25)	46 (69)	< 0.001
Medication that has a high incidence of calculation/dosage errors		61 (91)	66 (99)	0.06
Drug names that look alike and sound alike		59 (88)	66 (99)	0.016

*Pictograms © 2016 by Régis Vaillancourt, The CHEO Research Institute, and Mike P Zender; reproduced with permission.
†By McNemar exact test. The number of discordant pairs was less than 10 for each analysis; therefore, a binomial distribution was used.

pictograms without a statistically significant increase in understanding were "Drug that requires airway management before administration" (47/67 [70%] in Phase 1 versus 53/67 [79%] in Phase 2; $p = 0.31$) and "Medication that has a high incidence of calculation/dosage errors" (61/67 [91%] in Phase 1 versus 66/67 [99%] in Phase 2; $p = 0.06$ by Fisher exact test). In both cases, the pictograms were relatively well understood in Phase 1, leaving less room for improvement in comprehension after training.

Subgroup analyses were performed to examine the influence of year of study and prior hospital experience on the comprehension of the pictograms at recall. Overall, 29 first-year students and 38 second-year students participated in the long-term recall comprehension test. No statistically significant differences were found in rates of comprehension between first- and second-year students. Students without prior hospital experience were less likely to recall the pictogram for "Medication that can only be given via central line" than were students who did have prior hospital experience (28/44 [64%] among those without prior experience versus 18/20 [90%] among those with prior experience; $p = 0.026$ by Fisher exact test). No other statistically significant differences were found.

DISCUSSION

Pharmaceutical pictogram development involves a step-wise approach that must follow standardized processes.[11,27] Development begins with identifying and understanding a specific population's needs.[11,28] This step was accomplished in a prior study by identifying the 9 key medication safety issues that could benefit from implementation of safety pictograms.[2] In the current study, we started the validation process by piloting the pictograms with a sample of pharmacy students. As health care workers in training, these students lack the experience of professionals, but given their education so far, they can represent a starting point for validation. The first phase of the study showed that participants could correctly guess the meaning of only 4 of the 9 pictograms designed to improve medication safety. At recall, 4 weeks later, at least 67% of participants were able to correctly recall the meaning of 7 of the 9 pictograms, thus reaching the standard set by the ISO.[27] Hence, this study supports the idea that training on the meaning of pictograms can increase comprehension of more complex messages. Long-term recall was intentionally chosen as the primary outcome because of the complexity of the safety messages depicted in the 9 pictograms. Recall is the process of retrieving individual words or picture elements from memory and is closely related to comprehension, the process of interpreting the meaning of words or pictures to understand their collective meaning.[9]

The pictograms depicting "Concentrated electrolyte formulations" and "Medication with a significant risk of harm if administered improperly" did not reach the ISO threshold for validation in this study, even though there was a statistically significant increase in the rate of comprehension at recall. In relation to the first of these pictograms, it is possible that the students, who were in their first or second year of study, had not yet received instruction on many topics related to the use and significance of electrolyte solutions. Even though the meaning of the pictogram was explained, supporting information about the harms associated with concentrated electrolyte solutions and the effect on patient outcomes was not provided. Health care workers or more senior pharmacy students may be more likely to understand this pictogram. Participant feedback was collected during the study for those pictograms that were not validated. Participants suggested changing and redesigning the pictogram for "Medication with a significant risk of harm if administered improperly" because they found that the thunderbolts confused the message. Participants also suggested that including words within the pictogram would help to elucidate its meaning. Future studies should target practising health care workers for validation of these pictograms. We will continue to consult health care workers to gather additional comments on how these pictograms can be improved.

Limitations

Although the study sample approximates, in some ways, the target population, it is difficult to draw firm conclusions concerning the low rates of comprehension for 5 of the 9 pictograms in Phase 1. It is impossible to know, without further validation in a sample of health care workers, whether the problem lies with the pictograms themselves, or whether the pharmacy students participating in the study simply were not yet knowledgeable enough concerning all aspects of medication safety to identify the pictograms' meaning. The fact that study participants were more likely to understand the pictograms after training suggests that health care workers likely would be able to identify the meaning of the pictograms, because they would already be well educated about all aspects of medication safety and would have encountered these medication safety issues in practice. Validation of these pictograms in health care professionals must be the next step.

CONCLUSION

Implementation of medication safety programs has the potential to save health care systems substantial costs and to prevent serious patient injury, thereby leading to better patient outcomes.[29] In this study, we assessed the comprehensibility of 9 pictograms developed to increase medication safety through interception and prevention of medication administration errors. Further studies will be needed to validate the pictograms in a sample of health care professionals and possibly to redesign and validate the pictograms depicting "Concentrated electrolyte formulations" and "Medication with a significant risk of harm if administered improperly". It will be important to determine how these pictograms can be simplified or how the messages themselves could be clarified to represent the same ideas. Future studies will

focus on the impact of the 9 pictograms in preventing medication administration errors in a health care setting and in improving clinical outcomes.

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Inappropriate Prescription of Proton Pump Inhibitors in a Community Setting

Patrick Viet-Quoc Nguyen and Raja Tamaz

ABSTRACT

Background: Proton pump inhibitors (PPIs) are widely prescribed for gastrointestinal conditions, such as gastroesophageal reflux disease and dyspepsia, and for prevention of gastric ulcer. Although previous reports have described inappropriate prescription of PPIs in the hospital setting, data from the community are lacking.

Objective: To assess PPI prescriptions in the ambulatory setting.

Methods: Patients presenting to the emergency department of a teaching hospital between June 2016 and March 2017 were prospectively assessed for use of a PPI at home. The appropriateness of PPI prescription was evaluated on the basis of an interview with the patient and review of the medical record. The indication for PPI therapy was verified against current guidelines for the province of Quebec.

Results: Over the 9-month study period, 2417 patients were screened, of whom 871 were included in the study. In relation to the Quebec guidelines, PPI prescription was inappropriate for 267 (30.7%) of the patients. When prescription of PPI for ulcer prevention in certain groups of patients (age ≥ 65 years and using acetylsalicylic acid or platelet aggregation inhibitors; age ≥ 75 years and using celecoxib) was re-classified as appropriate, the proportion of inappropriate PPI prescriptions declined to 20.3% (177/871).

Conclusions: These findings suggest that inappropriate prescribing of PPIs remains problematic in the community setting in the province of Quebec.

Keywords: proton pump inhibitors, drug prescriptions, prescription drug misuse

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RÉSUMÉ

Contexte : Les inhibiteurs de la pompe à protons (IPP) sont largement prescrits pour traiter les troubles gastro-intestinaux, comme le reflux gastro-œsophagien et la dyspepsie, et pour prévenir l'ulcère gastrique. Bien que des rapports antérieurs aient parlé de la prescription inadéquate des IPP dans les établissements de santé, il n'y a pas de données provenant de la communauté.

Objectif : Évaluer la pertinence des prescriptions d'IPP dans un milieu ambulatoire.

Méthodes : Les patients se présentant au service des urgences d'un hôpital universitaire entre juin 2016 et mars 2017 ont été évalués de façon prospective relativement à l'utilisation d'un IPP à la maison. La pertinence de la prescription d'un IPP a été jugée d'après une entrevue avec le patient et l'analyse du dossier médical. On a vérifié si l'indication pour un traitement par IPP respectait les lignes directrices actuelles du Québec.

Résultats : Sur une période de neuf mois, 2 417 patients ont été évalués et 871 d'entre eux ont été admis à l'étude. Par rapport aux lignes directrices du Québec, la prescription d'IPP était inadéquate pour 267 (30,7 %) des patients. Or, si la prescription d'IPP pour prévenir l' ulcère gastrique chez certains groupes de patients (âgés de 65 ans ou plus et prenant de l'acide acétylsalicylique ou un antiagrégant plaquettaire; âgés de 75 ans ou plus et prenant du célécoxib) était reclassée comme adéquate, la proportion de prescriptions d'IPP inadéquates reculait à 20,3 % (177/871).

Conclusions : Ces résultats laissent croire que les prescriptions inadéquates d'IPP demeurent un problème dans le contexte communautaire au Québec.

Mots clés : inhibiteurs de la pompe à protons, prescriptions de médicaments, mauvais emploi d'un médicament d'ordonnance

INTRODUCTION

Proton pump inhibitors (PPIs) are widely prescribed acid suppressant drugs. In 2015, PPI prescriptions accounted for $253.3 million in public drug program spending in Canada.[1] These drugs tend to be used for long periods for the treatment of chronic conditions such as gastroesophageal reflux disease (GERD) and dyspepsia, or for the prevention of gastric ulcers in people who are taking nonsteroidal anti-inflammatory drugs (NSAIDs).[2] However, the safety of long-term PPI use remains controversial. PPIs have been associated with increased risk of various adverse effects such as kidney disease, pneumonia, *Clostridium difficile* infection, fracture, and hypomagnesemia.[3] Recently, an increased risk of death was reported for PPI use relative to no PPIs, with a hazard ratio of 1.15 (95% confidence interval [CI] 1.14–1.15).[4]

Previous publications have described inappropriate prescription of PPIs. The recent literature (2012–2015) reported rates of inappropriate prescribing that ranged from 19% to 86%.[5-13] However, all but 2 of these reports involved retrospective chart-based studies. Since the indication for PPI use may not be rigorously documented in patient charts, use of this type of study design may have led to overestimation of inappropriate prescribing. Differences in usage criteria, practice guidelines, study populations, and local medical practices may also explain the wide range in reported prevalence of inappropriate PPI prescriptions. Moreover, all of these studies were carried out in a hospital setting, such that they mainly described PPI prescription patterns by hospital physicians for inpatients. Appropriateness of PPI prescribing in the community setting has been addressed by only a few investigators.[14,15] Recent data for this setting, especially in the Canadian population, are still lacking.

The objective of this study was to document the prevalence of inappropriate PPI prescriptions in an ambulatory population.

METHODS

This prospective cross-sectional study was performed in the emergency department of the Centre hospitalier de l'Université de Montréal (CHUM) in Montréal, Quebec. This institution is a multispecialty tertiary care teaching hospital spread over 3 physical locations, each with its own emergency department. Eligible patients were adults presenting to any of the 3 emergency departments and taking a PPI at home at the time of admission. Using the list of patients registered in the emergency department computer system, research assistants identified all potential PPI users from information recorded in the Quebec Health Record or available from the institution's outpatient pharmacy or from long-term care home medication lists. The Quebec Health Record is a computerized medical record for all patients in the province of Quebec, which documents clinical information and prescription drugs.

Screening was done on weekdays, during regular working hours, from June 20, 2016, to March 29, 2017. To further ascertain outpatient use of PPIs, patients were interviewed during their stay in the emergency department. Patients who initiated a PPI during their visit to the emergency department and those who were readmitted over the study period were excluded. The data were collected using medical and nursing observation sheets in patient charts and the patient interview. Demographic data were age, sex, and reason for the consultation. PPI data recorded were the indication for PPI treatment or prophylaxis, the type of PPI, and the dose and dosage regimen. The duration of PPI therapy was assessed for all PPI indications. The indication for PPI prescription was identified through patient inquiry, review of clinical notes, and previous hospital medical records. Medical data included the gastrointestinal medical history, as well as medical history related to neurologic, psychiatric, cardiovascular, pulmonary, nephrologic, endocrinologic, and rheumatologic conditions, and to chronic kidney failure and cancer. Concomitant use of NSAIDs, oral and parenteral anticoagulants, steroids, platelet aggregation inhibitors, and selective serotonin reuptake inhibitors (SSRI) was also determined.

PPI prescriptions were compared with the guideline published by the Conseil des médicaments (now incorporated within the Institut national d'excellence en santé et en services sociaux [INESSS]), published in 2010.[2] The mission of the INESSS is to promote clinical excellence and the efficient use of health resources. PPI prescriptions were considered appropriate if dyspepsia, GERD, Zollinger–Ellison syndrome, or esophagitis secondary to GERD was present. The use of a PPI was considered appropriate if the duration of therapy was 8 weeks following diagnosis of ulcer or 4 months for *Helicobacter pylori* infection. PPI for ulcer prophylaxis in patients using NSAIDs was considered appropriate under the following conditions:

- presence of one or more of the following risk factors: age 75 years or older; history of peptic ulcer; use of warfarin, heparin (unfractionated and low molecular weight), or direct oral anticoagulants
- presence of 2 or more of the following risk factors: age 65–74 years; comorbid diseases (arthritis, diabetes mellitus, or cardiovascular disease); use of steroids, acetylsalicylic acid (ASA), platelet aggregation inhibitors, or SSRI.

Patients using low-dose ASA were not considered to be NSAID users. The use of PPI for ulcer prophylaxis in patients 65 years or older who are taking ASA or platelet aggregation inhibitors and in patients 75 years or older who are taking celecoxib without other risk factors remains controversial. Use of PPI in these patients was not considered "appropriate" for purposes of the main analysis, because these indications are not mentioned in the INESSS guidelines; however, they were analyzed separately.

Continuous and categorical variables were described using means and proportions, respectively. Analyses were performed

using SPSS 24 (IBM, Armonk, New York). The study protocol was approved by the CHUM research ethics board. Verbal consent was required and obtained before each patient interview.

RESULTS

During the 9-month study period, 2417 patients were screened, of whom 1458 were not taking a PPI at home before their visit to the emergency department and 24 were unable to answer the survey. Of the remaining 935 patients who met the inclusion criteria, 64 refused to participate; therefore, 871 patients were included in the study. The mean age ± standard deviation was 68 ± 15 years, and 476 (54.6%) of the patients were women. Comorbid conditions identified in the study population are listed in Table 1. The most common reasons for medical consultation in the emergency department were shortness of breath (105, 12.1%), gastrointestinal pain (78, 9.0%), general deterioration (69, 7.9%), pain other than gastrointestinal (97, 11.1%), and infection (44, 5.1%).

Characteristics of PPI use in the study population are reported in Table 2. A total of 769 patients (88.3%) took their PPI once daily, 101 patients (11.6%) took their PPI twice daily, and 1 patient took the PPI three times daily. The most common indication for a PPI prescription reported during the patient interview was "heartburn" (*n* = 247 patients), followed by ulcer prophylaxis (*n* = 220), GERD (*n* = 170), dyspepsia (*n* = 51), and gastric ulcer therapy (*n* = 38); 123 patients did not know the indication for their PPI prescription, and 22 had other indications. In addition to the PPI therapy, an SSRI was prescribed for 113 patients (13.0%), steroids for 154 patients (17.7%), NSAIDs for 63 patients (7.2%), and platelet aggregation inhibitors for 67 patients (7.7%). Direct oral anticoagulants, warfarin, and parenteral anticoagulants were prescribed for 101 (11.6%), 66 (7.6%), and 28 (3.2%) patients, respectively.

Overall, for 604 patients (69.3%), the PPI was prescribed for an appropriate indication. Some patients had more than 1 appropriate indication for the PPI prescription (Table 3). No patient was taking a PPI for Zollinger–Ellison syndrome. When the controversial indications for PPI prescriptions were counted as appropriate, the incidence of appropriate prescription was 694 patients (79.7%). Some patients had more than 1 controversial indication for the PPI prescription. No patient aged 65 to 74 years had a prescription for NSAID therapy without any other risk factor.

The mean age of patients with inappropriate PPI prescription was significantly higher than the age of patients with appropriate

Table 1. Medical Characteristics of the Study Population

Medical History*	No. (%) of Patients (*n* = 871)
Gastrointestinal condition	656 (75.3)
Gastroesophageal reflux	470 (54.0)
Dyspepsia	282 (32.4)
Gastric ulcer	125 (14.4)
Duodenal ulcer	10 (1.1)
Esophagitis	105 (12.1)
Laryngitis	62 (7.1)
Gastric acid hypersecretion	27 (3.1)
Helicobacter pylori history	23 (2.6)
Irritable bowel syndrome	74 (8.5)
Crohn disease	23 (2.6)
Hiatal hernia	9 (1.0)
Neurologic condition	98 (11.3)
Psychiatric condition	180 (20.7)
Cardiovascular condition	645 (74.1)
Pulmonary condition	267 (30.7)
Endocrinologic condition	368 (42.3)
Rheumatologic condition	162 (18.6)
Chronic kidney failure	67 (7.7)
Cancer	213 (24.5)

*Some patients had more than one medical condition (as reported during an interview and/or documented in the medical chart).

Table 2. Characteristics of Prescriptions for Proton Pump Inhibitor (PPI)

PPI	No. (%) of Patients	Median Total Daily Dose (mg)
Pantoprazole	626 (71.9)	40
Deslansoprazole	139 (16.0)	60
Esomeprazole	50 (5.7)	40
Lansoprazole	30 (3.4)	30
Omeprazole	21 (2.4)	20
Rabeprazole	5 (0.6)	20

Table 3. Appropriate Prescription of Proton Pump Inhibitors

Indication	No. (%) of Patients
Appropriate indications*	
Gastroesophageal reflux	470 (54.0)
Dyspepsia	282 (32.4)
Esophagitis	105 (12.1)
Ulcer	15 (1.7)
Positive for *Helicobacter pylori*	5 (0.6)
Ulcer prophylaxis	20 (2.3)
Controversial indications†	
Ulcer prophylaxis in patient ≥ 65 years who is taking ASA	82 (9.4)
Ulcer prophylaxis in patient ≥ 75 years who is taking celecoxib	5 (0.6)
Ulcer prophylaxis in patient ≥ 65 years who is taking platelet aggregation inhibitor	18 (2.1)

ASA = acetylsalicylic acid.
*Some patients had more than 1 appropriate indication for a proton pump inhibitor.
†Some patients had more than 1 controversial indication.

PPI therapy, with a difference of 3.8 years (95% CI 1.6–6.0 years). A higher proportion of patients with a history of psychiatric disease had an appropriate PPI prescription regimen. Neurologic, cardiovascular, and pulmonary comorbid diseases and patients' sex were not associated with inappropriate PPI prescribing.

DISCUSSION

The appropriate use of PPIs has been studied in the hospital setting in various studies, but only a few authors have addressed the prescribing of PPIs in the community setting. In 2007, Batuwitage and others[14] published their prospective assessment of PPI indications in 66 patients, reporting that PPI therapy was appropriate for 30 patients (46%), according to guidelines of the UK National Institute for Health and Care Excellence (NICE). In a retrospective study, Heidelbaugh and others[15] evaluated 946 patients with a PPI prescription, of whom 341 (36.1%) did not have an appropriate indication.

Overall, this study found a 30.7% incidence of inappropriate PPI prescriptions in the community setting, according to the INESSS practice guidelines; the incidence was 20.3% if controversial indications were considered appropriate. These findings suggest that inappropriate prescribing of PPIs remains problematic in the community setting in the province of Quebec, despite the publication, in 2010, of guidelines concerning the use of PPIs from the INESSS (formerly the Conseil des médicaments), an agency of the Quebec health ministry.[2]

The difference between the current results and those of Batuwitage and others[14] can be explained by our consideration of PPI prescriptions for all patients with dyspepsia as appropriate, whereas the NICE guideline accepted PPI therapy for this condition only if the duration was 1 month and the dyspepsia had not been investigated. The lower rate of inappropriate PPI prescribing in the current study relative to that of Heidelbaugh and others[15] may be attributed to our prospective study design, which allowed more accurate detection of gastrointestinal diseases through patient interviews.

For one of our analyses, we defined PPI therapy for controversial indications as appropriate. Despite the absence of clear guidelines on PPI use for these controversial indications, recent evidence has shown the efficacy of PPIs in the prevention of gastrointestinal events, especially for the elderly population. In a study published in 2013, Hedberg and others[16] compared the risk of gastrointestinal ulcers and bleeding in patients using low-dose ASA with and without PPI. The hazard ratio was 1.14 (95% CI 1.05–1.23) for the group not taking PPI relative to the continuous PPI users, who had high adherence. Rahme and others[17] studied the risk of hospital admission for a gastrointestinal problem among patients taking celecoxib with and without a PPI. Overall, there was no significant difference between the 2 groups. However, in a subgroup analysis, the authors detected a reduction of events in elderly patients (75 years and older) using celecoxib and a PPI; the hazard ratio was 0.56 (95% CI 0.38–0.81) relative to those not taking a PPI. Hsu and others[18] studied the incidence of recurrent peptic ulcer in patients using clopidogrel with and without esomeprazole and found a statistically significant difference favouring the combination therapy.

One strength of the current study was that patients were recruited prospectively, which allowed us to collect more accurate data on patients' medical history and indication for PPI therapy. Inclusion of patients who were not actually taking PPIs was avoided by directly questioning potential participants about their PPI use. In contrast, a retrospective study might have included patients who had a PPI prescription but were not actually taking the drug.

This study also had limitations. The study design did not permit systematic recruitment of patients arriving in the emergency department. Patients who arrived for consultation during the evening, at nighttime, and on weekends may have left without being screened for this study, which increased selection bias. However, this bias was reduced by collecting the data over a 9-month period and performing the analyses on a large sample. Young patients may visit the emergency department outside of regular working hours, which might explain the high mean age of study participants. A prescription for PPI may not necessarily reflect prescribing practices of the hospital's medical staff, since the PPI prescriptions for many of the included patients were dispensed in the ambulatory setting. The results related to PPI prescribing patterns may reflect the larger Montréal region, rather than the vicinity of the hospital centre. Because the study took place in a single health centre, the results may not be generalizable to the province or the country. Similarly, because the study included only patients visiting the emergency department, the results may not be generalizable to the entire ambulatory population. Nonetheless, PPI prescribing guidelines are the same across the province, and these provincial guidelines are very similar to national and international guidelines, so it may be reasonable to extrapolate the results to a larger population.

Despite the use of patient interviews and a medical chart review, it is possible that some medical data were missing because of memory bias or data missing from the charts. The indication for PPI use was determined in part from the patient interview, but patients may report gastric disease not based on a medical diagnosis, which may also lead to overestimation of appropriate PPI prescriptions. The cross-sectional design impeded accurate estimation of PPI use over time, and data on drug use was not available from the insurer database. Hence, the time since diagnosis of gastric ulcer and the duration of PPI use were estimated by the patient, which could lead to misclassification of appropriateness. The provincial guideline suggests initial PPI therapy for 4 weeks for uninvestigated dyspepsia with or without GERD for symptoms that are present at least 3 days/week. Long-term PPI therapy must be re-evaluated and continued only

if the dyspepsia symptoms persist. Adherence with this recommendation could not be assessed in this study. The lack of evaluation of PPI use over time, and the lack of data on medical follow-up may have led to overestimation of appropriate PPI prescriptions. Patients' compliance with prescribed therapy was not evaluated in the current study but could be an interesting topic for further investigations.

In addition to safety concerns related to inappropriate prescribing of PPIs, the economic burden to the health care system is substantial. According to the INESSS, the monthly cost of PPI prescriptions in March 2014 was $8.9 million,[19] or an estimated annual cost of about $106.8 million. Using the rates determined in the current study, $21.7 million to $32.8 million of this total may relate to inappropriate PPI prescribing. Furthermore, this amount does not take into account patients with private insurance coverage, so the true cost may be greater.

CONCLUSION

Inappropriate prescription of PPIs remains high, despite the existence of guidelines and even when controversial indication criteria were counted as appropriate. Inappropriate prescribing of PPIs may expose patients to adverse reactions such as hypomagnesemia, pneumonia, and fractures. Inappropriate prescribing also carries substantial financial costs.

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CASE REPORT

Successful Treatment of Stevens–Johnson Syndrome with Cyclosporine and Corticosteroid

Jessica Auyeung and Monica Lee

INTRODUCTION

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, severe idiosyncratic reactions characterized by extensive necrosis and detachment of the epidermis, commonly triggered by medications. The annual incidence is 1 or 2 cases per million.[1] There is usually a prodrome of malaise and fever, followed by rapid onset of erythematous or purpuric macules and plaques that progress to epidermal necrosis and sloughing. SJS and TEN are considered to lie along the same spectrum of disease, differing only in terms of how much of the skin surface is affected. If less than 10% of the body surface is affected, the diagnosis is SJS, and if more than 30% is affected, the diagnosis is TEN; if between 10% and 30% is affected, the diagnosis is SJS–TEN overlap. Although medications such as allopurinol, antibiotics, and antiepileptics are the leading causes in most cases, infections, vaccines, and food have been implicated.[1,2] Although fluoroquinolone-associated SJS/TEN has been reported in the literature, the number of cases due to this group of drugs has been relatively small compared with cases due to other drugs. Systemic corticosteroids and immunosuppressive therapies have been used in the management of SJS/TEN, but high-quality evidence supporting their use is lacking.

We describe a probable case of ciprofloxacin-induced SJS treated with methylprednisolone, prednisone, and cyclosporine.

CASE REPORT

A 66-year-old woman presented to the emergency department of a tertiary care hospital with a 2-day history of rash that had developed on her trunk and spread to her neck, arms, and legs.* Her other symptoms were fever, progressive dysphagia, odynophagia, dysuria, and painful ulcerations to her oral and genital mucosa. The Nikolsky sign was positive (i.e., application of mechanical pressure to the skin resulted in epidermal detachment), which indicated necrolysis.[1] The patient was febrile, with a temperature of 38.2°C. Her blood pressure was 116/66 mm Hg, heart rate 93 beats/min, respiratory rate 20 breaths/min, and oxygen saturation 100% on 2 L/min via nasal prongs. Her past medical history included chronic obstructive pulmonary disease, osteoporosis, osteoarthritis with left total hip replacement, stress urinary incontinence, and migraines. She had allergies to sulfonamides and azithromycin, with a reported reaction of rash to both agents. She also reported abdominal pain associated with acetaminophen compound with codeine. Eight days before the admission, she had undergone a urethral sling procedure, and was started on ciprofloxacin 500 mg orally twice daily for 10 days as prophylaxis for urinary tract infection. Her other long-term home medications were fluticasone–salmeterol, salbutamol, tiotropium, ipratropium, quetiapine, and risedronate.

The results of laboratory investigations on admission were unremarkable. The leukocyte count was 9.6×10^9/L, and eosinophils were not detected. C-reactive protein and erythrocyte sedimentation rate were not checked at the time of admission, but 2 days after admission, C-reactive protein was 110.1 mg/L and erythrocyte sedimentation rate was 85 mm/h. The patient was admitted with a working diagnosis of SJS. Skin biopsy showed transepidermal necrosis with perivascular chronic inflammation, and the morphologic findings were consistent with SJS/TEN.

Methylprednisolone 50 mg IV every 12 h was initiated. Supportive therapy included morphine, lubricating eye drops, and mucositis mouthwash (consisting of nystatin and lidocaine). Her preadmission medications were continued, with the exception of ciprofloxacin. On day 3 of the admission, a dermatologist initiated cyclosporine 3 mg/kg IV daily as adjunctive treatment. The patient weighed 66 kg and therefore received cyclosporine

*The patient provided verbal consent for publication of this case report.

195 mg daily. At 3.5 weeks, the cyclosporine therapy was converted to oral administration, and at 1 month, it was tapered to 2 mg/kg for 4 days, then 1 mg/kg for 7 days. Cyclosporine was discontinued on day 44 of the hospital stay. After 12 days of IV methylprednisolone, the corticosteroid therapy was stepped down to oral prednisone 50 mg daily. After 1 week, the prednisone was tapered to 40 mg for 1 day and then 20 mg the following day; the dose was then reduced by 5 mg every 5 days. At the time of discharge (2 months after admission), 5 days of prednisone therapy remained to be completed.

Improvement to her skin rash became apparent 1 week after initiation of cyclosporine. Skin sloughing and formation of bullae halted after 1 month of therapy. However, other complications prolonged the patient's hospital stay. The most significant complication was continued dysphagia and odynophagia because of severe esophagitis and ulceration, as seen on endoscopy. These problems were thought to be related to the SJS. The patient was unable to tolerate oral intake and required total parenteral nutrition for 40 days. Other complications included significant pain, a urinary tract infection, and thrombosis related to the central catheter.

With respect to therapeutic drug monitoring, serum cyclosporine trough concentrations were monitored periodically during the course of IV therapy to ensure the drug did not reach toxic levels. The trough concentration never exceeded 286 µg/L.

The patient was discharged home after a 2-month hospital stay, with full recovery of her skin and some residual dysphagia.

DISCUSSION

In this patient, it was presumed that ciprofloxacin, administered prophylactically following the urethral sling procedure, had caused the SJS. The Naranjo probability scale[3] was used to assess the likelihood of the adverse reaction being due to this drug. The Naranjo score was 6/13, indicating a probable adverse drug reaction associated with ciprofloxacin. Points were assigned for previous conclusive reports of this adverse reaction (+1), appearance of the adverse event after administration of the medication (+2), no alternative cause that on its own could have caused the reaction (+2), and confirmation by objective evidence (+1). Rechallenge with ciprofloxacin, administration of a placebo, and measurement of serum ciprofloxacin concentrations were not performed. It was also unknown whether the patient had ever received ciprofloxacin previous to this encounter, or whether the severity of her adverse reaction would have changed with adjustment of the ciprofloxacin dose. Also, the SJS did not improve when the drug was discontinued (although it improved subsequently, after initiation of treatment). Eleven other cases involving ciprofloxacin-induced SJS or TEN were identified in the literature.[4-13] Most of the cases were treated with supportive care only, with systemic corticosteroids being used in 5 cases.[4,6,9,10,12] In one case, the patient was treated with systemic corticosteroids and tacrolimus.[12]

Although the use of systemic corticosteroids in SJS or TEN is common in clinical practice, there is a lack of strong evidence for their use.[1] The rationale for using immunosuppressive agents is that they may suppress the cytotoxic reaction that results in keratinocyte apoptosis, the theorized pathophysiologic process of SJS/TEN. Given the lack of evidence for benefit of corticosteroids, consideration of alternative therapies, such as cyclosporine, is warranted. The studies evaluating cyclosporine for the management of SJS/TEN are summarized in Table 1.[14-18]

It is difficult to draw conclusions from these studies, which were a case series,[18] a chart review,[17] and open-label, uncontrolled studies using a variety of cyclosporine regimens and treatment durations.[14-16] In most of these studies, individuals treated with cyclosporine monotherapy were compared with historical controls treated with other therapies. No randomized controlled trials were identified in the literature, and given the rarity of TEN/SJS, recruiting a sufficient number of participants for such a trial would be challenging.

Three studies[15-17] compared the observed mortality rate with the predicted mortality rate, as determined by the severity-of-illness score for toxic epidermal necrolysis (SCORTEN), a validated TEN-specific prognostic score,[19] in the intervention and comparator groups. An observed mortality rate that is lower than the predicted rate implies treatment benefits. In all 3 studies, the observed death rate was lower than the predicted death rate in the cyclosporine group, but higher than predicted in the comparator group. These results suggest a survival benefit associated with cyclosporine treatment, which needs to be further explored with controlled clinical trials. Statistical analysis between the intervention and comparator groups was performed only by Arévalo and others[14] and Singh and others.[15] Both of these studies found significant differences in favour of cyclosporine in terms of survival, time to arrest of disease progression, and timing of re-epithelization of skin. Singh and others[15] also found that the duration of hospitalization was significantly lower in the cyclosporine group relative to those who received corticosteroids, but Arévalo and others[14] found no significant difference in length of stay between the 2 treatment groups.

With respect to safety, Singh and others[15] described development of corneal ulceration in one patient in the cyclosporine group; no adverse effects were reported in the group that received systemic steroids. The authors attributed the observed adverse effect to inadvertent continued use of the offending drug in eye drop form. Arévalo and others[14] compared cyclosporine with cyclophosphamide and corticosteroids, and found no significant difference in terms of sepsis (8/11 versus 5/6, $p = 0.99$) and overall organ failure (mean number of organs affected 1.1 versus 2.3, $p = 0.11$). However, the cyclophosphamide group had significantly more cases of organ failure in 4 or more organs (2/11 versus 3/6, $p = 0.029$) and significantly more cases of leukopenia (0/11 versus 4/6, $p = 0.006$). Valeyrie-

Table 1. Summary of Evidence for Using Cyclosporine to Treat Stevens–Johnson Syndrome (SJS) and/or Toxic Epidermal Necrolysis (TEN)

Study	Population	Intervention	Comparator	Outcomes
Arévalo et al.[14]	Patients with TEN admitted to an intensive care burn unit	Cyclosporine 3 mg/kg daily via nasogastric tube in 2 divided doses for 2 weeks, then tapered by 10 mg every 48 h (*n* = 11)	Cyclophosphamide 150 mg IV every 12 h and corticosteroids (*n* = 6)	Survival: 11/11 versus 3/6 (p = 0.029) Time to arrest of disease progression (mean ± SD): 1.4 ± 0.3 days versus 3.6 ± 1.5 days (*p* = 0.0002) Time to complete re-epithelialization (mean ± SD): 12.0 ± 3.6 days versus 17.6 ± 3.1 days (*p* = 0.0058) Length of stay (mean ± SD): 27 ± 25 days versus 15 ± 8 days (*p* = 0.31)
Singh et al.[15]	Patients with SJS or TEN admitted to a tertiary care hospital	Cyclosporine 1 mg/kg daily orally in 3 divided doses for 7 days, then 2 mg/kg daily in 2 divided doses for 7 days (*n* = 11)	Dexamethasone IV followed by prednisolone orally at dosage ≥ 1 mg/kg daily (*n* = 6)	Predicted death (SCORTEN): 1.11/11 (10.1%) versus 0.51/6 (8.5%) Observed death: 0/11 (0%) versus 2/6 (33.3%) (*p* = 0.04321) Time to arrest of disease progression (mean ± SD): 3.18 ± 1.32 days versus 4.75 ± 2.98 days (*p* = 0.04282) Time to complete re-epithelialization (mean ± SD): 14.54 ± 4.08 days versus 23 ± 6.68 days (*p* = 0.009956) Length of stay (mean ± SD): 18.09 ± 5.02 days versus 26 ± 6.48 days (*p* = 0.02597)
Valeyrie-Allanore et al.[16]	Patients with SJS or TEN admitted to a dermatological intensive care unit	Cyclosporine 3 mg/kg daily via nasogastric tube in 2 divided doses for 10 days, then 2 mg/kg daily via nasogastric tube in 2 divided doses for 10 days, then 1 mg/kg daily via nasogastric tube in 2 divided doses for 10 days (*n* = 29)	IVIG, dose not specified (*n* = 34)	Predicted death (SCORTEN): 2.75/29 (9.5%) versus 8/34 (23.5%) Observed death: 0/29 (0%) versus 11/34 (32.4%) Stabilization of body surface area involvement between day 0 and day 3: 18/29 (62.1%) versus 12/34 (35.3%) Progression of skin detachment between day 0 and day 3: 11/29 (37.9%) versus 22/34 (64.7%)
Kirchhof et al.[17]	Patients with SJS or TEN admitted to a tertiary care hospital	Cyclosporine 3–5 mg/kg daily orally or intravenously for an average of 7 days (*n* = 17)	IVIG average dose 1 g/kg daily for 3 days (*n* = 37)	Predicted death (SCORTEN): 2.4/17 (14.1%) versus 7.7/37 (20.8%) Observed death: 1/17 (5.9%) versus 11/37 (29.7%) Standardized mortality ratio for intervention group: 0.42 (95% CI 0.11–2.32) Standardized mortality ratio for comparator group: 1.43 (95% CI 0.71–2.56)
Reese et al.[18]	Patients with SJS or TEN treated in a burn unit	Cyclosporine 5 mg/kg daily in 2 divided doses for 5 days to 1 month (*n* = 4)	None	Predicted death (SCORTEN): 0.217/4 (5.4%) Observed death: 0/4 (0%)

CI = confidence interval, IVIG = intravenous immunoglobulin, SCORTEN = Severity-of-Illness Score for Toxic Epidermal Necrolysis, SD = standard deviation.

Allanore and others[16] did not discuss the occurrence of adverse effects in their comparison group, but among the 29 patients receiving cyclosporine, 3 had to stop therapy because of acute hallucinations that were suspected to be related to reversible posterior leukoencephalopathy, transitory neutropenia, and severe infection, respectively. Among the 26 individuals who completed treatment, adverse effects were increased blood pressure (*n* = 3), renal impairment (*n* = 2), and sensitive neuropathy (*n* = 1).

Very little information is available about therapeutic drug monitoring of cyclosporine in this setting, and there are no target concentrations for cyclosporine for this indication. Valeyrie-Allanore and others[16] reported the performance of therapeutic drug monitoring to avoid toxicity.[16] In the case reported here, trough cyclosporine concentration never exceeded the upper limit of the target concentration range as defined for solid organ transplant, which is 100–400 µg/L.[20] Future studies should explore the optimal dose and duration of cyclosporine, and the utility of therapeutic drug monitoring.

CONCLUSION

This case illustrates further experience with the combination of cyclosporine and corticosteroids in the treatment of SJS. This combination could be considered for patients with SJS that is unresponsive to corticosteroids alone.

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CASE REPORT

Identifying Drug Interactions between Enzalutamide and Complementary Alternative Medications in a Patient with Metastatic Prostate Cancer: A Case Report

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INTRODUCTION

Prostate cancer cells are dependent on intratumoral androgens for survival, growth, and proliferation.[1] For this reason, treatments that reduce the effects of androgens on the prostate, such as enzalutamide and leuprolide, are commonly used to treat prostate cancer and slow disease progression.[1] Serum free testosterone and prostate-specific antigen (PSA) are often monitored to determine the effectiveness of such treatment.[1,2]

Enzalutamide is a pure androgen receptor signalling inhibitor that is effective for the treatment of metastatic castration-resistant prostate cancer (MCRPC).[3,4] Enzalutamide is a major substrate of hepatic cytochrome P450 2C8 and 3A4 isozymes (CYP2C8 and CYP3A4), and is commonly subject to pharmacokinetic interactions, which could reduce its effectiveness by changing levels of the drug or active metabolites.[5-7] Loss of enzalutamide effectiveness could be indicated by a resultant increase in PSA. Because one goal of treating MCRPC is to reduce serum free testosterone to castrate levels, it is also not in the patient's best interest to use products that increase testosterone levels.

To the authors' knowledge, there have been no case reports documenting interactions among enzalutamide, leuprolide, and complementary and alternative medications (CAMs). CAMs are commonly used by patients with cancer and are often perceived to be free from adverse reactions or interactions, a perception that contributes to lack of disclosure of CAM use to health care professionals.[6,8,9] The lack of disclosure can minimize investigation of adverse effects or interactions associated with CAM use, ultimately endangering patient health. This case report documents outcomes of concurrent use of CAMs, enzalutamide, and leuprolide in a patient with MCRPC.

CASE REPORT

At the end of May 2017, a middle-aged man (in his late 50s) presented with a 3-year history of metastatic adenocarcinoma of the prostate with left sacral and acetabular involvement.* His disease was stable, and he was otherwise healthy. Since the cancer diagnosis, he had experienced intermittent back pain, abdominal pain secondary to shingles (early May 2017; resolved before current presentation), intermittent hematuria, and nocturia. No other significant symptoms were documented beyond May 2017.

At the time of presentation, the patient's treatment regimen consisted of the following medications: leuprolide 22.5 mg IM every 3 months (since August 11, 2016), denosumab 120 mg SC every 4 weeks (since January 8, 2016), and enzalutamide 160 mg PO daily (since January 18, 2016) to which he appeared to be adherent. Previously, he had also received degarelix 80 mg SC every 4 weeks (December 28, 2015, to July 13, 2016) and palliative radiotherapy to the left hip and sacroiliac joint.

The patient was seen in late May 2017 in follow-up for rising serum free testosterone and PSA, despite continued androgen deprivation therapy with enzalutamide and leuprolide. From October 20, 2016, to January 13, 2017, serum free testosterone had remained near castrate levels, whereas PSA had risen steadily from 6.67 µg/L to 8.70 µg/L (normal range

*Details not pertinent to the diagnosis or treatment in this case have been omitted to protect patient confidentiality.

0–4.0 µg/L). By March 14, 2017, serum free testosterone and PSA had risen to 0.97 nmol/L and 12.16 µg/L, respectively (Table 1).

During the appointment in May 2017, it was discovered that the patient was using multiple CAMs. At that time, his oncologist instructed him not to take any testosterone-containing products. At the oncologist's request, pharmacy staff met with the patient to discuss the CAMs and agreed to conduct research on each product being used and to offer a recommendation to be discussed in a follow-up interview. During the course of this research, the patient discontinued all CAMs and continued androgen deprivation therapy as prescribed by his oncologist.

Most of the CAMs being used by the patient were oral products containing numerous herbal ingredients (listed without quantities) that were extemporaneously compounded and dispensed by an alternative medicine practitioner. Seven products were also described by the patient as homeopathic. After analyzing each container, it was determined that the patient was taking 119 CAMs in total (Table 2).

Enzalutamide and leuprolide were initially considered as potential sources of interactions with the CAMs. However, leuprolide is not metabolized by cytochrome P450 enzymes and has low protein binding, so interactions with this drug are not expected and were not investigated further. A literature search of Ovid MEDLINE, Embase, PubMed, and Google Scholar from inception to August 2017 using the search terms "enzalutamide" and "herb" revealed no case reports or pharmacokinetic studies of concurrent use of the CAMs identified in this case and enzalutamide. However, multiple studies were found confirming changes in enzalutamide concentration when used concurrently with known CYP2C8 and CYP3A4 inducers and inhibitors, which alludes to the potential of CAMs with similar metabolism to cause clinically significant drug interactions.[7,10,11] A review of various drug interaction resources, including the *Natural Medicines* database, the Lexicomp *Interactions* database, and S*tockley's Drug Interactions*, revealed possible interactions between 17 of the CAMs and enzalutamide, with differing levels of evidence. The interactants identified were activated charcoal, *Aloe*, black walnut, garlic, goldenseal, licorice, *Echinacea*, cat's claw, *Boswellia*, *Gingko biloba*, *Rhodiola*, *Berberis vulgaris*, milk thistle, guggul, sage, Turkish rhubarb, and *Panax ginseng*.[12-14] These interactions are mediated primarily by the CYP3A4 isozyme; however, there are some exceptions, such as activated charcoal, which may reduce or prevent drug absorption (Table 3).[12] Agents that may negatively affect disease control by increasing testosterone were also identified, including ginger, chondroitin, licorice, *Tribulus terrestris*, clove, and *Panax ginseng*.[12] Furthermore, both arsenic trioxide and leuprolide carry a risk of causing QTc prolongation (highest risk and moderate risk categories, respectively), and together they have an additive risk of QTc prolongation.[13]

Table 1. Patient's Disease Markers, Adapted from Bloodwork Flow Sheet in Electronic Chart

Date	Free Testosterone (nmol/L)	Prostate-Specific Antigen (µg/L)
October 20, 2016	< 0.42	6.67
November 21, 2016	< 0.42	6.70
December 20, 2016	< 0.42	9.59
January 13, 2017	< 0.42	8.70
February 11, 2017	0.52	10.23
March 14, 2017	0.97	12.16
April 22, 2017	0.94	14.20
May 23, 2017	0.46	15.01
June 20, 2017	0.67	17.51
June 26, 2017	0.59	17.75
July 10, 2017	0.58	18.62
August 8, 2017	< 0.42	22.64
August 21, 2017*	1.14	29.09
October 13, 2017†	< 0.42	35.1

*The patient discontinued enzalutamide about 7 days before bloodwork performed on August 21, 2017. The patient was asymptomatic.
†On October 13, 2017, the patient declined further computed tomography. The patient was asymptomatic.

On the basis of these findings, it was recommended that the patient discontinue all products that might negatively affect disease control by potentially interacting with enzalutamide or increasing serum testosterone. Several products with no evidence of a drug interaction or testosterone-augmenting effect were also discontinued, because they were formulated in combination with the agents listed in Table 3. This left only a short list of products to be continued (Box 1). The rationale for continuing these products included indications for bone health, lack of drug interactions or testosterone-augmenting effect, and patient preference.

Bloodwork on August 8, 2017, following discontinuation of CAMs for at least 28 days, revealed serum free testosterone returning to near-castrate levels, whereas PSA had risen to 22.64 µg/L. On the same date, his creatinine clearance was 108 mL/min (Cockcroft–Gault equation), and the results of liver function tests were normal. At this time, the patient reported musculoskeletal pain, which resolved on its own. On both August 21 and October 13, the patient claimed to be asymptomatic, although the trend of rising PSA continued, reaching a peak of 35.1 µg/L; testosterone remained near castrate levels. No computed tomography (CT) was performed between CAM discontinuation in May 2017 and the time of writing (late 2017). On October 13, the patient declined further CT and communicated his decision to discontinue all therapies. The patient discontinued enzalutamide about 1 week before his appointment on August 21, 2017.

Table 2. List of Ingredients in Patient's Herbal/Alternative Medications*

Activated charcoal
Adscendes [sic] root
Aele [sic] *marmelos*
Ajwon [sic]
Allium sativum
Aloe vera
Amaltas powder
Angelica sinses [sic]
Annona muricata
Anti-oxidants essential oil
Apple cider vinegar
Arjuna Terminalia [sic]
Arkarkara root powder
Arsenic trioxide
Arsenicum album
Ashwaganda [sic]
Asparagus
Astralagus [sic] root
Basil extract
Berberis vulgaris
Black musli root powder
Black walnut hull
Boswellia
Burdock
Calcium
Calendula
Caraway
Carcinosium [sic]
Cardamom
Catnip
Cat's claw
Cayenne pepper
Chaste tree berries
Chicory
Chinese skullcap
Chondroitin
Cinnamomum zeylanicum
Cinnamon extract
Clove extract
Coccap [sic]
Coral mineral
Cypress
Dandelion
Dong Qui [sic]
Echinacea
Ferrous bisglycinate
Frankincense extract
Garcinia cambogia
Garlic
Ginger root
Gingko biloba extract
Ginseng
Glucosamine
Goksura powder
Golden seal
Grape seed extract
Green tea
Guar gum
Guggul
Gymneme [sic] *sylvestre* leaves powder
Hadjora
Hawthorn
Hekla lava
Honey goat weed powder
Ipecha [sic]
Juniper berries
Kachnara bark
Kalmeg
Kutki
Lavendulla [sic] extract
Lemongrass extract
Licorice root
Long pepper
Lycopene
Ma Huang
Magnesium
Magnesium glycinate
Majuphal
Manjistha
Mezereum
Milk thistle
Multivitamin
Neem leaves powder
Nutmeg extract
Omega-3 EPA + DHA
Pau d'Arco
Pearl powder
Pearls
Peom [sic] root
Peony root
Piper longum
Poria cocos
Probiotic
Psyllium
Punctured vine extract
Rhodiola
Sage
Sanicle tincture
Sarphankha
Sarsaparilla
Saw palmetto
Seabuk thorne [sic] extract
Shilajit powder
Sida cordifolia
Tracanthus [sic] gum
Tribulus terrestris
Triphala
Tulsi
Turkish rhubarb
Turmeric
Utangan powder
Vital [sic]
Vitamin C
Vitamin D
White willow bark
Wild yam root
Withinia semniflora [sic]
Worm wood
Yohimbine bark powder

DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid.
*Ingredient names, listed alphabetically, are reported here as they appeared on product labels provided by the patient. It was not possible to verify all of the ingredients directly, so the notation "sic" indicates names that are (or may be) spelled incorrectly. Some product labels listed scientific names (e.g., genus names of plants), whereas others used common names; if the scientific and common names for the same plant appeared on different labels, both are presented.

DISCUSSION

CAMs are widely used by patients with cancer, and their popularity is increasing worldwide.[6,9,15,16] The public generally considers these agents to be safe and nontoxic, which means that potentially modifying effects on chemotherapy or other cancer treatment are often overlooked.[6,16] Herbal supplements may compromise the therapeutic efficacy or safety profile of chemotherapy by interacting with the pharmacokinetics of anticancer drugs.[6,16] Additionally, CAMs often lack premarket demonstration of safety and efficacy, quality control in manufacturing and labelling, and disclosure of usage to health care professionals, all of which contribute to the unpredictability of interactions between CAMs and cancer therapies.[7,9,16]

In the case reported here, elevation of serum free testosterone and PSA after initiation of several CAMs was observed in a patient who had been previously stable on androgen deprivation therapy. The probability of a drug interaction was assessed using the Drug Interaction Probability Scale (DIPS), a tool for evaluating the potential of a drug interaction in

Table 3. Summary of Drug Interactions with Enzalutamide and/or Leuprolide*

Drug	Interaction Rating†	Severity‡ and Likelihood	Level of Evidence	Details
Activated charcoal	Moderate	Moderate, probable	D (theoretical)	May reduce or prevent absorption of enzalutamide
Black walnut	Moderate	Moderate, possible	D (theoretical)	Concomitant oral administration may cause precipitation of some drugs
Garlic	Moderate	Moderate, possible	B (PK study)	Inducer of CYP3A4, which could reduce levels of enzalutamide
Goldenseal	Moderate	Moderate, possible	B (PK study)	Inhibitor of CYP3A4, which could increase levels of enzalutamide
Licorice	Moderate	Moderate, possible	B (PK study; CYP3A4) D (in vitro evidence; CYP2C8)	Inducer of CYP3A4, which could reduce levels of enzalutamide Inhibitor of CYP2C8, which could increase levels of enzalutamide
Echinacea	Moderate	Moderate, possible	B (PK study)	Inducer of CYP3A4, which could reduce levels of enzalutamide
Cat's claw	Moderate	Moderate, possible	D (in vitro evidence)	Inhibitor of CYP3A4, which could increase levels of enzalutamide
Boswellia	Moderate	Moderate, possible	D (in vitro evidence)	Inhibitor of CYP3A4, which could increase levels of enzalutamide
Gingko biloba	Moderate	Moderate, possible	B (nonrandomized clinical trial)	Conflicting evidence as to whether *Gingko biloba* induces or inhibits CYP3A4
Rhodiola	Moderate	Moderate, possible	D (in vitro evidence)	Inhibitor of CYP3A4, which could increase levels of enzalutamide
Berberis vulgaris	Moderate	Moderate, possible	D (theoretical)	Inhibitor of CYP3A4, which could increase levels of enzalutamide
Milk thistle	Moderate	Moderate, possible	D (in vitro evidence)	Inhibitor of CYP3A4, which could increase levels of enzalutamide Inhibits mitogenic signalling pathways involved in proliferation of androgen-dependent cancer cells
Guggul	Moderate	Moderate, probable	D (in vitro evidence)	Inducer of CYP3A4, which could reduce levels of enzalutamide
Sage	Moderate	Moderate, possible	D (in vitro evidence)	Inhibitor of CYP3A4, which could increase levels of enzalutamide
Panax ginseng	Moderate	Moderate, probable	B (nonrandomized clinical trial)	Inhibitor of CYP3A4 which could increase levels of enzalutamide *Panax ginseng* may increase levels of testosterone in the blood
Turkish rhubarb	Moderate	Moderate, probable	D (theoretical)	Might reduce absorption of enzalutamide because of reduced GI transit time
Arsenic trioxide	Major	High, probable	B (epidemiologic study)	Known high-risk QT-prolonging agent; additive QT-prolonging effect with leuprolide
Aloe	Moderate	Moderate, possible	D (theoretical)	*Aloe* can reduce drug absorption of some drugs due to decreased GI transit time
Clove	Unknown	Unknown	D (animal studies)	Increased levels of testosterone
Ginger	Unknown	Unknown	D (animal studies)	Increased levels of serum testosterone
Chondroitin	Unknown	Unknown	B (nonrandomized clinical trial)	May be associated with spread or recurrence of prostate cancer
Tribulus terrestris	Unknown	Unknown	D (animal studies) B (nonrandomized clinical trial)	May increase levels of testosterone 10–20 mg/kg daily for 4 weeks did not increase serum testosterone in young, healthy men

CYP = cytochrome P450, GI = gastrointestinal, PK = pharmacokinetic.
*Only interactions rated moderate to severe were included in this analysis. Numerous other agents received minor interaction ratings.
†Interaction ratings: major = do not use in combination, contraindicated, strongly discourage patients from using this combination, a serious adverse outcome could occur; moderate = use cautiously or avoid combination, warn patients that a significant interaction or adverse outcome could occur; minor = be aware that there is a chance of an interaction, advise patients to watch for warning signs of a potential interaction.
‡Severity ratings: high = life-threatening or severe impairment possible; moderate = moderate impairment or significant discomfort possible; mild = mild impairment or mild discomfort possible; insignificant = drug levels may be affected, but a clinically significant interaction is not likely.

Box 1. Drugs with No Hormonal or CYP 3A4/2C8 Activity

Omega-3 fatty acids (EPA + DHA)
Multivitamin
Probiotic
Calcium
Vitamin D
Ferrous bisglycinate
Ipecha [sic]
Hekla lava
Carcinosium [sic]

CYP 3A4/2C8 = cytochrome P450 3A4 and 2C8 isozymes, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid.

patients.[17] The DIPS consists of 10 questions about potential drug interactions, with the results being used to estimate the probability of an interaction (Table 4). In this case, the calculated DIPS score was 5, which suggested a probable drug interaction between enzalutamide and the CAMs that the patient was using.[17] Notably, the DIPS tool was created to predict the probability of an interaction between 2 drugs, and as such there are limitations to its use in this case; however, no tool evaluating drug interactions among multiple agents (including CAMs) was found.

This case report has several limitations. First, the study was limited by its reliance on subjective information provided by the patient. Also, although serum free testosterone returned to near-castrate levels upon discontinuation of CAMs, the PSA continued to rise. PSA lacks specificity and may increase for reasons other than prostate cancer, such as infection, inflammation, and benign prostate hyperplasia,[18] which effectively does not rule out the possibility of CAM–drug interactions; however, to the authors' knowledge, the patient did not have any of these conditions. Finally, the large number of CAMs used, the lack of information about doses, the potential for multiple interactions, and the lack of good-quality evidence confirming interactions between CAMs and enzalutamide made it difficult to confirm whether the CAMs had caused clinically significant interactions. Many of the interactions identified were theoretical or based on in vitro evidence, which often does not translate to clinical significance.[6]

CONCLUSION

CAM usage among cancer patients is growing increasingly popular. CAMs are commonly perceived to be nontoxic, leading to a lack of disclosure. For health care professionals, it is important to identify CAM usage when obtaining patients' medication history and to educate patients about the risks of using CAMs concurrently with cancer therapies. Providing appropriate education can be difficult, as there is little clinical evidence outlining interactions between CAMs and cancer therapies. For this reason, when health care professionals are making recommendations, they commonly rely upon in vitro data and the theoretical risk based on mechanisms of action. Because many patients using CAMs strongly believe in the benefits of these agents, pharmacists recommending discontinuation of such products on the basis of weak evidence risk losing the patient's trust and must be careful to present objective, balanced information. Further study identifying and measuring the significance of interactions among CAMs, enzalutamide, and other cancer therapies is needed.

Table 4. Scoring Chart for Drug Interaction Probability Scale

Score	Interpretation
> 8	Drug interaction is highly probable
5–8	Drug interaction is probable
2–4	Drug interaction is possible
< 2	Drug interaction is doubtful

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ON THE FRONT COVER

Centennial Ridge Kananaskis, Alberta

This issue's cover photograph was taken in July 2014 on the Centennial Ridge Trail (with a Sony Cyber-Shot Digital Still Camera) by June Chen, who was then a student pharmacist. To June's disappointment, strong winds and pelting rain forced the unprepared hiker to turn back and forgo the summit of Mount Allan. During her descent, the storm passed, leaving a rainbow in its wake. Three years later, on Canada's 150th anniversary, June returned to complete the hike, but now as a clinical pharmacist working at the Mazankowski Alberta Heart Institute.

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.ca.

Should All Patients with Type 2 Diabetes Mellitus and Cardiovascular Disease Receive an SGLT2 Inhibitor?

THE "PRO" SIDE

Innovations—ordering groceries online, moving your files to cloud storage, using an app to have a stranger give you a ride— are often approached with uncertainty. Healthy skepticism is useful, particularly for new drugs. In type 2 diabetes mellitus, the story of the ill-fated drug rosiglitazone serves as a cautionary tale: new does not necessarily equal better. In response, the US Food and Drug Administration mandated that pharmaceutical manufacturers be required to conduct randomized controlled trials with the goal of establishing cardiovascular safety for all new antidiabetic drugs.[1] Two recent trials (EMPA-REG OUTCOME[2] and CANVAS[3]) have demonstrated that sodium glucose co-transporter 2 (SGLT2) inhibitors, a novel class of medications that promote glycosuria by inhibiting glucose reabsorption in the proximal convoluted tubule independent of insulin secretion, are not only safe from a cardiovascular perspective, but actually reduce the risk of meaningful cardiovascular outcomes. The "flozins", as they are known, have purported health benefits beyond glycemic control, including weight loss, reduction in blood pressure, and increase in high-density lipoprotein cholesterol.[4] SGLT2 inhibitors should be utilized with watchful optimism, as the observed cardiovascular benefit is nontrivial. However, enthusiasm for these agents is being tempered with appropriate trepidation—no one wants to get "rosiglitazoned" again.

The affirmative in this debate can be distilled into 2 key arguments: first, SGLT2 inhibitors have reduced clinically meaningful cardiovascular outcomes in multiple large randomized controlled trials, and second, this evidence stands alone, given that for most other antidiabetic drugs there is an appalling lack of cardiovascular benefit.

The EMPA-REG OUTCOME trial compared empagliflozin with placebo in 7020 patients with type 2 diabetes and established cardiovascular disease.[2] After 3.1 years, the primary composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower with empagliflozin, for a number needed to treat (NNT) of 63. As well, empagliflozin significantly reduced all-cause death (NNT 39), cardiovascular death (NNT 46), serious adverse events (NNT 53), hospital admissions for heart failure (NNT 72), and incident/worsening nephropathy (NNT 17).[2,5,6] The CANVAS trial compared canagliflozin with placebo in 10 142 patients with type 2 diabetes who had established, or were at high risk of, cardiovascular disease.[3] After 3.6 years, the primary composite outcome (which was the same as in the EMPA-REG OUTCOME study) was significantly lower with canagliflozin, for an NNT of 61. However, all-cause and cardiovascular death were not significantly reduced with treatment. Hospital admissions for heart failure (NNT 87), adverse renal outcomes (NNT 80), and serious adverse events (NNT 18) were significantly lower with canagliflozin. Adverse events associated with SGLT2 inhibitor therapy included genital infections (number needed to harm [NNH] 6–14 for women and 12–29 for men), as well as volume depletion (NNH 38), amputations (NNH 96), and fractures (NNH 286), the latter 3 of which were associated only with canagliflozin. Despite these adverse events, it is reasonable to conclude that the potential cardiovascular benefit far exceeds the potential harm. Although one cannot draw firm conclusions from indirectly comparing 2 different trials, it appears that empagliflozin has more favourable evidence than canagliflozin.

This evidence is exceptional when compared with the evidence for other antihyperglycemic agents. Sulfonylureas have been associated with increased cardiovascular events in observational trials, whereas a neutral effect has been observed in randomized controlled trials.[7] Regardless, there is no robust evidence suggesting even a glimpse of cardiovascular benefit. Among the thiazolidinediones, rosiglitazone was associated with an increased risk of myocardial infarction,[8] and in the PROactive trial, pioglitazone reduced a secondary composite cardiovascular end point, but also increased heart failure events and hospital admissions.[9] In the ORIGIN trial, insulin glargine failed to reduce cardiovascular outcomes relative to placebo.[10] More recently, dipeptidyl peptidase-4 (DPP-4) inhibitors have been shown to have a neutral cardiovascular effect (even when data were combined in a meta-analysis), except saxagliptin, which increased the risk of hospital admissions for heart failure.[11] Glucagon-like peptide-1 (GLP-1) agonists have shown promise with respect to cardiovascular benefit, although the data so far are heterogeneous, and a practical barrier to uptake is the need for injection. In the LEADER trial, liraglutide reduced a composite cardiovascular end point and all-cause mortality.[12] However, when data for multiple GLP-1 agonists were combined in a meta-analysis, there was a reduction in all-cause mortality, but not in cardiovascular death,

nonfatal myocardial infarction, or nonfatal stroke.[13] Finally, even metformin is fallible. In the UKPDS-34 trial, metformin reduced any diabetes-related end point and all-cause mortality when compared with dietary interventions in 753 overweight patients with type 2 diabetes.[14] However, I would challenge proponents of metformin to apply the same rigorous critical appraisal to UKPDS-34 that we do for contemporary trials—would metformin still be considered first-line therapy if that trial were to be published today? Just because something was promising 20 years ago does not mean it remains relevant now. If that were true, we would all still be using Windows 98.

A recently published Bayesian hierarchical network meta-analysis of 236 randomized controlled trials (including EMPA-REG OUTCOME and CANVAS) compared SGLT2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors.[15] Both the SGLT2 inhibitors and the GLP-1 agonists lowered all-cause and cardiovascular mortality relative to control (placebo or no treatment) and relative to DPP-4 inhibitors. Furthermore, the SGLT2 inhibitors were associated with lower rates of heart failure events and myocardial infarction relative to control.

Admittedly, more data are required to confirm (or potentially refute) the observed cardiovascular benefit of SGLT2 inhibitors. In this regard, at least 3 cardiovascular outcome trials are in progress: DECLARE-TIMI 58 with dapagliflozin,[16] VERTIS with ertugliflozin,[17] and SCORED with sotagliflozin.[18]

The SGLT2 inhibitors will continue to be aggressively marketed and prescribed, and thus it is imperative that clinicians understand the potential benefits and risks of therapy, so that they can help patients in making an informed decision. The observed benefit with SGLT2 inhibitors is encouraging, but has been limited to patients with, or at high risk of, cardiovascular disease. Additionally, long-term data are currently absent, and other practical barriers exist, such as cost. Pharmacovigilance is important, but I would caution readers not to dismiss the SGLT2 inhibitor data thus far, as they represent a potentially unparalleled advancement in the management of type 2 diabetes. Time will tell whether I am on the right side of history, but for now I would implore clinicians not to let apprehension bias your judgment. We should embrace SGLT2 inhibitors, albeit prudently, and avoid the temptation to pine for the "good old days" of treating type 2 diabetes with metformin and glyburide, just as we do not fondly reminisce about phenformin and chlorpropramide.

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THE "CON" SIDE

Emphasis has been placed on the cardiovascular safety of antihyperglycemic drugs for type 2 diabetes mellitus since the release of a meta-analysis[1] and randomized controlled trial[2] that signalled increased risk of myocardial infarction and heart failure with rosiglitazone. Given that the ultimate goal of treating diabetes is the prevention of macrovascular and microvascular events, the results of those studies highlighted a disconnect between lowering glycated hemoglobin (A1C) and reducing the long-term complications of diabetes. How the A1C is lowered appears more important than the A1C level itself. What has followed over the past decade is a disappointing series of trials evaluating the cardiovascular safety of a series of newer drugs for type 2 diabetes, most of which have found a "neutral" effect on major adverse cardiovascular events (MACE), despite these drugs having a positive effect on lowering A1C.[3-7] With the publication of 2 trials for sodium glucose co-transporter 2 (SGLT2) inhibitors[8,9] signalling a possible reduction in MACE, prescribers and guideline writers were quick to embrace adoption of the class as a preferred second-line drug (after metformin) in patients at high risk for cardiovascular events.[10] However, a closer analysis of the trials and safety profile of these drugs indicates that caution should be exercised when considering their use.

In EMPA-REG OUTCOME, an industry-sponsored trial in which 7 employees of Boehringer Ingelheim were study authors, 7020 participants with type 2 diabetes were randomly assigned to receive empagliflozin 10 mg or 25 mg or placebo, and were followed for a median 3.1 years.[8] At the end of the trial, the authors reported that there was a reduction in cardiovascular mortality (hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.49–0.77) and hospital admissions due to heart failure (HR 0.65, 95% CI 0.50–0.85). However, weaknesses in the trial methodology put these findings in serious doubt. The composite primary end point of MACE (HR 0.86, 95% CI 0.74–0.99) was driven almost exclusively by a statistically significant lower risk of cardiovascular deaths.[8,11] Deaths ruled as "non-assessable"—accounting for 40% of all cardiovascular deaths analyzed—were presumed to be cardiovascular deaths. In a sensitivity analysis performed by the US Food and Drug Administration (FDA) that removed these deaths from the cardiovascular death analysis, empagliflozin was no longer superior to placebo for MACE (HR 0.90, 95% CI 0.77–1.06).[11] In the original study, silent myocardial infarctions were not independently assessed, and were not included in the primary composite outcome. However, when the FDA included these events in the primary outcome as part of another sensitivity analysis, the primary outcome was no longer statistically significant. The study also found a statistically significant reduction in hospital admissions due to heart failure. However, this outcome was not controlled for type I error, and the trial was not designed to assess it. As a result, critical information needed to confirm heart failure status was not collected. In addition, several modifications to the definition of hospital admission due to heart failure were also made over the course of the trial, which introduced substantial bias in the collection and analysis of heart failure outcomes. As a result of these issues with the adjudication of outcomes and the statistical analysis, no confidence can be placed in any observed differences between empagliflozin and placebo for the main cardiovascular outcomes.

In CANVAS, an industry-sponsored trial program in which 4 employees of Janssen were study authors, data from 10 142 participants in 2 randomized controlled trials (CANVAS for cardiovascular outcomes and CANVAS-R for renal outcomes) were analyzed to assess the effect of canagliflozin 100 mg or 300 mg on cardiovascular outcomes relative to placebo.[9] According to the initial protocol for CANVAS, the study was to enroll 4330 participants in the first phase of the trial, and if the cardiovascular protection and safety end points were met, a further 14 000 participants were to be enrolled.[12] However, after the initial unblinding of results in 2012, a decision was made not to continue with enrolment, but to open a new trial (CANVAS-R) and combine its results with those of CANVAS. As a result, CANVAS was not a single trial with a homogenous population, but was instead 2 separate trials involving 2 different populations, with differences in several aspects of the study design, including inclusion and exclusion criteria, dosing of canagliflozin, and primary objectives. CANVAS-R had an apparently sicker population than CANVAS, with higher event rates and larger observed reductions in the HRs for many cardiovascular outcomes.[13] The fact that there were larger observed differences in some event rates in the second trial, after unblinding of data from the initial cohort, and subsequent modifications to trial design bring into question the amount of bias influencing the final outcome observed. In addition, the 2 cohorts had meaningful differences in follow-up: 295.9 weeks in CANVAS and 108.0 weeks in CANVAS-R.

The combined results from the 2 cohorts in CANVAS demonstrated a reduction of risk in a composite MACE end point (HR 0.86, 95% CI 0.75–0.97), with event rates of 26.9 versus 31.5 per 1000 patient-years.[9] This finding was counterbalanced by a statistically significant increase in amputations, fractures, infections of male genitalia, mycotic genital infections in women, volume depletion, and osmotic diuresis. For every 1000 patient-years, 4.6 cardiovascular events will be prevented, but at the expense of causing 2.9 amputations and 3.5 fractures. There is some speculation that these risks are exclusively linked to canagliflozin, as they were not observed in EMPA-REG OUTCOME; however, data for these outcomes were systematically collected in CANVAS but not in EMPA-REG OUTCOME. A statistically significant reduction in cardiovascular mortality was not seen with canagliflozin, as it was with empagliflozin, which could reflect differences in the patient populations of the 2 studies or could further bring into question the validity of the EMPA-REG OUTCOME result.

The cardiovascular safety trial for dapagliflozin is still in progress, with planned completion later in 2018.[14] Until then, we have to rely on surrogate A1C data for direction. Results from network meta-analyses suggest that the A1C-lowering effect of dapagliflozin is less than that observed with others in the same class, and it has a

reduced effect in patients with chronic kidney disease.[15-17] Given that up to 60% of patients with type 2 diabetes will have this comorbidity, this limitation substantially narrows the population eligible for treatment.[18]

In conclusion, the incremental reduction in MACE observed with canagliflozin in a pooled analysis[9] and the questionable result from a trial for empagliflozin that had low methodological quality[8] do not suggest that SGLT2 inhibitors are a panacea for patients living with type 2 diabetes. The small benefit, if it truly exists, must be balanced against a well-documented list of harms that elevate risks of already common conditions in type 2 diabetes, including a near-equivalent increase in the risk of amputation and fracture. FDA advisories about ketoacidosis, urinary tract infections, acute kidney injury, fractures, and amputations should also be weighed in the decision to prescribe these drugs.[19-22] Reduced efficacy or contraindication in later stages of chronic kidney disease substantially limits their use. We should also be concerned about the increase in infections in a population that is already prone to them. As we continue to learn more about this class of drugs, a healthy dose of skepticism should be prescribed when evaluating SGLT2 inhibitors for treating type 2 diabetes in patients with cardiovascular disease.

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Competing interests: Bradley Mitchelmore is a former employee of the Canadian Agency for Drugs and Technologies in Health (CADTH), which provides reimbursement recommendations to 18 public drug plans in Canada. This organization has previously reviewed empagliflozin, canagliflozin, and dapagliflozin for multiple indications in type 2 diabetes. The Canadian Drug Expert Committee, part of CADTH, has provided "reimburse with clinical criteria and/or conditions" recommendations for all 3 drugs for various indications, including a recommendation to "reimburse with clinical criteria and/or conditions" for empaglifozin to reduce the incidence of cardiovascular death. Of all indications reviewed for this class of drugs, CADTH recommended a "do not reimburse" recommendation only for dapagliflozin as triple therapy with metformin and a sulfonylurea.

Réalisez-vous le plein potentiel de la pratique de la pharmacie dans le système de santé?

par Lauza Saulnier

Dans le milieu contemporain de la santé complexe et trépidant, les leaders en pharmacie doivent assurer l'utilisation des ressources optimale à la prestation de services de première qualité, efficaces et sécuritaires. Les équipes de pharmacie hautement efficaces travaillent sans relâche à concevoir et mettre en œuvre des programmes et des services en vue d'améliorer les résultats cliniques et de faire évoluer les pratiques d'utilisation sécuritaire des médicaments.

Mais, notre profession a-t-elle maximisé son apport au système de santé? Quel progrès avons-nous réalisé pour élargir le champ de pratique? Quelles stratégies avons-nous déployées afin d'accorder la priorité aux activités de la pratique qui auraient le plus d'influence sur les soins aux patients?

Surveiller les indicateurs clés de rendement est une stratégie nécessaire pour évaluer la qualité de l'exercice de la pharmacie clinique et pour soutenir la transparence et la responsabilisation professionnelle. Malheureusement, une telle surveillance demeure mal intégrée dans bon nombre de programmes de pharmacie hospitalière partout au pays. Au cours des dernières années, plusieurs initiatives ont été mises en place afin de favoriser les pratiques de gestion des médicaments s'appuyant sur des données probantes et de faciliter l'évaluation du rendement.

Les indicateurs clés de rendement relatifs à la pharmacie clinique (ICRpc) au Canada ont été conçus grâce à un processus d'établissement de consensus dans le but de faire avancer la pratique de la pharmacie clinique pour ainsi améliorer la qualité des soins et les résultats thérapeutiques (consultez le https://cshp.ca/clinical-pharmacy-key-performance-indicators). L'ensemble fondamental des ICRpc fondés sur des données probantes permet aux pharmaciens qui travaillent dans les milieux hospitaliers de soins de courte durée de concentrer leurs efforts sur les principales interventions cliniques; il offre aussi une méthode structurée pour mesurer la qualité des soins directs aux patients et de la prestation des services.

Le document *Pratique de la pharmacie dans les hôpitaux et les autres milieux de soins collaboratifs : déclarations de principes* (disponible au https://cshp.ca/position-statements) présente la prise de position de la Société canadienne des pharmaciens d'hôpitaux (SCPH) et décrit le niveau de performance souhaité et réalisable qu'on peut attendre de la pratique de la pharmacie. Cet ensemble de déclarations de principes sert de fondement au programme Excellence en pharmacie hospitalière de la SCPH. Ce dernier est conçu pour aider les membres à s'appliquer à l'amélioration des résultats thérapeutiques grâce aux soins centrés sur le patient, aux meilleures pratiques, et à la communication et à la collaboration. Quinze indicateurs de rendement ont été choisis pour mesurer les progrès réalisés vers l'excellence dans la pratique de la pharmacie (https://www.cshp.ca/sites/default/files/Excellence/ExcellenceFlyer_Revised.pdf).

Depuis plus de 30 ans, le *Rapport sur les pharmacies hospitalières canadiennes* représente l'une des principales références et un outil d'étalonnage de premier choix pour les services de pharmacie hospitalière partout au Canada et dans le monde. En 2017, le conseil de la SCPH a accepté la demande du comité de rédaction du *Rapport sur les pharmacies hospitalières canadiennes* qui souhaitait devenir l'un des conseils affiliés de la Société. Le conseil de la SCPH chargé du sondage sur les pharmacies hospitalières canadiennes, comme il se nomme maintenant, a réalisé son sondage de 2016-2017 sous l'égide de la SCPH. Les résultats ont été publiés récemment au http://www.lillyhospitalsurvey.ca/hpc2/content/ReportsF3.asp .

Des mesures du rendement publiées dans le *Rapport sur les pharmacies hospitalières canadiennes* et celles comprises dans le programme Excellence en pharmacie hospitalière aident à suivre les progrès relatifs à l'atteinte des objectifs, à comparer le rendement à des étalons, à évaluer la valeur réelle des programmes et services, et à repérer les possibilités d'amélioration. Les mesures du rendement sont des éléments essentiels à l'incitation au changement dans une quête continuelle de l'excellence en pratique professionnelle.

La SCPH est depuis longtemps reconnue pour faire évoluer la pratique de la pharmacie dans les hôpitaux et les autres milieux de soins de santé misant sur la collaboration. Maintenant, défions-nous d'obtenir les meilleurs résultats thérapeutiques pour nos patients!

[Traduction par l'éditeur]

Lauza Saulnier, B. Sc. (Pharm.), A.C.P.R., est présidente sortante et agente de liaison pour la vision de la Société canadienne des pharmaciens d'hôpitaux.

Are You Realizing the Full Potential of Pharmacy Practice in the Healthcare System?

Lauza Saulnier

In today's complex and fast-paced healthcare environment, pharmacy leaders must ensure optimal utilization of resources for the delivery of efficient, safe, and high-quality services. High-performing pharmacy teams continuously strive to design and implement programs and services to improve patient health outcomes and to advance safe medication practices.

As a profession, though, have we maximized our contribution to the healthcare system? What progress have we made toward expanding the scope of practice? What strategies have we employed to prioritize practice activities that would have the greatest impact on patient care?

Monitoring of key performance indicators is one strategy that is required to assess the quality of clinical pharmacy practice and to support transparency and accountability. Unfortunately, such monitoring remains poorly integrated in many hospital pharmacy programs across the country. Several initiatives have been introduced in recent years to support evidence-informed medication management practices and to facilitate performance measurement.

The Canadian clinical pharmacy key performance indicators (cpKPIs) were developed, through a consensus process, to advance clinical pharmacy practice and thus to improve quality of care and patient outcomes (see https://cshp.ca/sites/default/files/files/CSPH-Can-Concensus-cpKPI-Knowledge-Mobilization-Guide.pdf). The core set of evidence-informed cpKPIs allows pharmacists working in acute care inpatient settings to concentrate their efforts on key clinical interventions; it also provides a structured approach to measuring the quality of direct patient care and delivery of services.

The *Pharmacy Practice in Hospitals and Other Collaborative Healthcare Settings: Position Statements* (available through https://cshp.ca/position-statements) express the stance of the Canadian Society of Hospital Pharmacists (CSHP) and describe a desired and achievable level of performance that is applicable to the practice of pharmacy. This set of position statements serves as one building block for the CSHP's Excellence in Hospital Pharmacy program. The Excellence program is designed to assist members in focusing their efforts on improving patient health outcomes through patient-centred care, best practice, and communication and collaboration. Fifteen performance indicators have been chosen to measure progress toward excellence in pharmacy practice (https://www.cshp.ca/sites/default/files/Excellence/ExcellenceFlyer_Revised.pdf)

For more than 30 years, the *Hospital Pharmacy in Canada Report* has been a leading reference and benchmarking tool for hospital pharmacy services across Canada and around the world. In 2017, the CSHP Board accepted a request from the Hospital Pharmacy in Canada Editorial Board to become one of the Society's affiliated boards. The CSHP Hospital Pharmacy in Canada Survey Board, as it is now known, conducted its 2016/17 survey under the auspices of CSHP. The results were recently published at http://hospitalpharmacysurvey.ca.

Performance measures published in the *Hospital Pharmacy in Canada Report* and those included in the Excellence in Hospital Pharmacy program help in monitoring progress toward objectives, comparing performance with benchmarks, assessing the real value of programs and services, and identifying improvement opportunities. Performance measures are crucial elements in driving change for the continuous pursuit of practice excellence.

CSHP has a long history of advancing pharmacy practice in hospitals and other collaborative healthcare settings. Let's challenge each other in achieving the best outcomes for our patients!

Lauza Saulnier, BSc(Pharm), ACPR, is Past President and Vision Liaison for the Canadian Society of Hospital Pharmacists.

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- favorisent la collaboration à des projets, à des recherches et à des programmes éducatifs pour répondre aux besoins des membres des RSP
- 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

La participation aux RSP est gratuite pour les membres de la SCPH.

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Canadian Society of Hospital Pharmacists

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