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The *CJHP* is an academic journal that focuses on how pharmacists in hospitals and other collaborative health care settings optimize safe and effective drug use for patients in Canada and throughout the world.

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Medication Safety—A Global Health Priority

Rebekah Moles

As pharmacists, we know that medications constitute the most common intervention in health care. Because of this widespread use, however, drug-related problems (DRPs) are common. Although DRPs have been researched and categorized for the past few decades, no true consensus on a classification system or definition exists.[1] In 1999, the working conference of the Pharmaceutical Care Network Europe (PCNE) developed a classification scheme for DRPs. Version 7, released in 2016, incorporated a drastic change, whereby the "Problems" section of the tool was reduced to just 3 domains: (1) treatment effectiveness—"There is a (potential) problem with the (lack of) effect of the pharmacotherapy"; (2) treatment safety—"Patient suffers, or could suffer, from an adverse drug event"; and (3) other. These domains remain in today's version of the tool (version 9, released in 2019).[2]

After reading much of the medication safety literature, I have concluded that there are really only 2 DRPs: "It doesn't work" and "It hurts". This summary is very much in line with the PCNE definitions quoted above.[2] Often, the thing we consider to be the problem is actually the *antecedent* to the negative outcome. For example, instances of "dose too high" and "price too high" are causes, or potential causes, of DRPs.[1]

These concepts are important because they are at the heart of medication safety. The actual DRPs or negative outcomes of "It doesn't work" or "It hurts" often result from both individual and system failures. Understanding why these DRPs do or may occur is important for preventing medication safety issues in the future. As health care professionals and researchers, we need to continually strive to uncover the causes underlying DRPs and to monitor changes when implementing interventions. However, despite our best efforts in producing standards, evidence-based guidelines, and practice tools, we are still a long way from having systems that will prevent DRPs on a global or even local level.

The statistics about medication-related harm are alarming. The World Health Organization (WHO) notes that unsafe medication practices and medication errors are the leading cause of avoidable harm around the world, with the costs of medication errors reaching US$42 billion annually.[3] In response to these numbers, the WHO announced its third global patient safety challenge in 2017, known as "Medication without Harm".[3] This and previous WHO patient safety challenges aim for improvement and risk reduction and "blend evidence-based interventions with multi-modal implementation strategies. They [also] seek to achieve widespread engagement and commitment."[3]

Individual countries are helping to improve the safe use of medicines. Canada's medication safety initiatives are undertaken by organizations such as the Canadian Patient Safety Institute (CPSI) and the Institute for Safe Medication Practices Canada. In 2018, the CPSI reported that it would lead the Canadian arm of the WHO's "Medication without Harm" campaign. Strategies include medication review, the "5 Questions to Ask About Your Medications" program, and opioid stewardship initiatives to improve opioid safety and appropriate treatment of pain.[4]

In my own country, the Pharmaceutical Society of Australia (PSA) and the Society of Hospital Pharmacists of Australia have been lobbying the government to take note of medication-related issues. An estimated AU$1.4 billion (about Can$1.25 billion) is spent annually on medication-related problems.[5] Furthermore, medication problems result in an estimated 250 000 hospital admissions annually and an additional 400 000 presentations to the emergency department.[5] The most worrisome estimate is that 50% of these costs and associated harms are preventable.[5]

In response, the Australian government recently announced that it would make medication safety a national health priority.[6] In a statement released in late 2019, the PSA president stated that "Pharmacists are medicines experts. They must be supported to spend more time … reviewing patients' medications, providing advice to members of the health care team, and educating consumers about medicine safety."[6] It is apparent that to improve medication safety all over the world, pharmacists need to go anywhere that medications are used, rather than being limited to traditional roles in the community and in hospitals. In addition, we must have a workforce sufficient to provide appropriate services to all. We must also seek to understand the causes of DRPs through research and audit, and we must be open to uncovering system-based issues so that improvements can be trialled.

The broad topic of medication safety is interwoven throughout the *Canadian Journal of Hospital Pharmacy* (*CJHP*), with the current issue featuring particularly strong themes related to pain management and pediatrics, two areas where medication safety issues are often reported. Pain is complex and difficult to treat, and many analgesic agents have narrow therapeutic margins. In addition, pain can be difficult to measure. The pharmacist's role in pain management is expanding, as evidenced by the study on opioid controls reported by Videau and others,[7] the comparison of topical amitriptyline formulas to improve clinical efficacy in neuropathic pain reported by Shakshuki and others,[8], and the investigation of methadone stability by Friciu and others.[9] These papers all provide evidence on how to improve the safety and efficacy of pain medicines, and they all reflect work to ensure that medicines do their work without hurting the patient.

Children are perhaps even more vulnerable to medication safety issues, because of complexities such as a lack of clinical trials and safety data leading to off-label and unlicensed use[10] and the need to manipulate doses before administration.[11] This issue also includes research into medication use in the pediatric setting. Caldwell and others[12] report their observational study describing the use of sedative medication in critically ill children. Vaillancourt and others[13] describe their audit of cannabis use in a pediatric hospital. The previously mentioned study by Friciu and others[9] is also of relevance to pediatric medication safety, as this formulation of methadone is used for acute and cancer pain in children. Audits are important for seeing patterns of medication use and informing future research and interventions, and the investigation of issues such as medication stability is also vital to ensure patient safety.

These articles highlight the role that all pharmacists can play in improving medication safety, given that medication safety is our core business. We should encourage one another to start locally, and we should share our work globally. Disseminating our efforts through various media is important, and shows that we are contributing to this safety challenge. The *CJHP* will continue to report the medication safety research of our authors. I encourage each of you to reflect on your own role as a pharmacist, your importance in making medication safety a global health priority, and your ability to ensure that unnecessary harm is diminished. Let's work together to reduce or even eliminate patients' experience of medication that "hurts" or "doesn't work".

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La sécurité des médicaments – Une priorité sanitaire mondiale

par Rebekah Moles

En tant que pharmaciens, nous savons que les médicaments constituent l'intervention la plus répandue en matière de soins de santé. Cependant, à cause de cette utilisation généralisée, les problèmes liés aux médicaments (PLM) sont monnaie courante. Bien que les PLM aient fait l'objet de recherches et aient été catégorisés au cours de ces dernières décennies, aucun véritable consensus portant sur un système de classification n'existe actuellement[1]. En 1999, la conférence de travail du Pharmaceutical Care Network Europe (PCNE) a élaboré un système de classification des PLM. La septième version, publiée en 2016, intégrait un changement majeur, de telle sorte que la section « Problèmes » de l'outil a été réduite à trois domaines : (1) l'efficacité des traitements — « Il y a un problème (potentiel) lié à l'effet (ou à l'inefficacité) de la pharmacothérapie »; (2) la sécurité des traitements — « Le patient souffre, ou pourrait souffrir, d'un effet iatrogène médicamenteux »; et (3) autre. Ces domaines demeurent dans la présente version de l'outil (version 9, publiée en 2019) (*trad. libre*)[2].

Après la lecture de larges extraits de la littérature consacrée à la sécurité des médicaments, j'en ai conclu qu'il n'existait que deux PLM : « Ça ne fonctionne pas » et « Ça fait mal. » Ce résumé correspond plutôt bien aux définitions du PCNE indiquées ci-dessus[2]. Souvent, ce que nous estimons être le problème est en fait l'*antécédent* de l'effet négatif. Par exemple, une « dose trop élevée » et un « prix trop élevé » sont des causes réelles ou potentielles des PLM[1].

Ces concepts sont importants, car ils sont au cœur de la sécurité des médicaments. Les véritables PLM ou les effets négatifs de « Ça ne fonctionne pas » ou de « Ça fait mal » découlent souvent de défaillances des personnes et des systèmes. Comprendre pourquoi ces PLM surviennent ou pourraient survenir est important pour prévenir de futurs problèmes liés à la sécurité des médicaments. En tant que professionnels de la santé et chercheurs, nous devons continuellement faire notre possible pour découvrir les causes sous-jacentes des PLM et pour faire le suivi des changements lors de la mise en œuvre des interventions. Cependant, en dépit de tous nos efforts pour définir des normes, des lignes directrices fondées sur des données probantes et des outils de pratique, nous sommes encore très loin d'avoir des systèmes qui préviendront les PLM à une échelle mondiale, voire même locale.

Les statistiques relatives aux préjudices liés aux médicaments sont alarmantes. L'Organisation mondiale de la Santé (OMS) note que les pratiques dangereuses en matière de médicaments et les erreurs médicamenteuses sont les causes principales des préjudices évitables dans le monde. Ces erreurs médicamenteuses engendrent des coûts annuels de 42 milliards de dollars américains[3]. En réponse à ces chiffres, l'OMS a annoncé en 2017 son troisième défi mondial en faveur de la sécurité des patients, aussi connu sous le nom de « Une médication sans erreurs »[3]. Ce défi ainsi que les précédents que doit relever l'OMS visent à améliorer la sécurité des patients, à réduire les risques et à « associer les interventions basées sur des données probantes aux stratégies de mise en œuvre multimodales. Ils cherche [aussi] à obtenir une mobilisation et un engagement généralisés » (*trad. libre*)[3].

Chaque pays contribue à améliorer l'utilisation sécuritaire des médicaments. Au Canada, les initiatives en la matière proviennent d'organisations, comme l'Institut canadien pour la sécurité des patients (ICSP) et l'Institut pour la sécurité des médicaments aux patients (ISMP). En 2018, l'ICSP a indiqué qu'il serait le fer de lance pour le Canada de la campagne « Une médication sans erreurs » de l'OMS. Les stratégies comprennent l'examen des médicaments, le programme « Cinq questions à poser à propos de vos médicaments » ainsi que des initiatives en matière de gestion des opioïdes pour améliorer la sécurité de leur administration et le traitement approprié de la douleur[4].

Dans mon propre pays, la Pharmaceutical Society of Australia (PSA) et la Society of Hospital Pharmacists of Australia ont fait pression sur le gouvernement pour qu'il prenne en considération les problèmes liés aux médicaments. On estime que ceux-ci coûtent chaque année 1,4 milliard de dollars australiens (environ 1,25 milliard de dollars canadiens)[5]. De plus, les complications dues aux médicaments sont responsables d'environ 25 000 admissions à l'hôpital chaque année et 400 000 visites supplémentaires aux urgences[5]. Les estimations le plus pessimistes indiquent que 50 % des coûts et des préjudices associés à ces complications sont évitables[5].

Le gouvernement australien a récemment répondu qu'il élèverait la sécurité des médicaments au rang de priorité sanitaire nationale[6]. Dans une déclaration publiée à la fin de 2019, le président du PSA a indiqué que les « pharmaciens sont des

experts en matière de médicaments. Il convient de les aider à passer plus de temps […] à la révision des médicaments des patients, à conseiller les membres de l'équipe de soins et à sensibiliser les consommateurs à la sécurité des médicaments. »[6] Il semble que, pour améliorer la sécurité des médicaments partout dans le monde, les pharmaciens doivent aller dans tous les endroits où où ils sont utilisés, plutôt que de se limiter aux rôles traditionnels dans la communauté et dans les hôpitaux. De plus, nous devons avoir suffisamment de main d'œuvre pour fournir à chacun les services appropriés. Il nous faut également chercher à comprendre les causes des PLM au moyen d'études et d'audits, mais aussi rester ouverts pour découvrir les problèmes inhérents au système, afin de tenter des améliorations.

Le vaste sujet de la sécurité des médicaments est intimement lié au *Journal canadien de la pharmacie hospitalière* (JCPH). Le présent numéro met en lumière des thèmes particulièrement importants liés à la gestion de la douleur et à la pédiatrie, deux domaines dans lesquels on rapporte souvent des problèmes en matière de sécurité des médicaments. La douleur est complexe et difficile à traiter, et de nombreux agents analgésiques ont des marges thérapeutiques très étroites. Le rôle du pharmacien dans la gestion de la douleur s'élargit, comme en témoignent l'étude sur le contrôle des opiacées de Videau et collab.[7], celle sur la comparaison des formules topiques d'amitriptyline visant à améliorer l'efficacité clinique en cas de douleur neuropathique signée Shakshuki et collab.[8] ainsi que l'enquête portant sur la stabilité de la méthadone de Friciu et collab.[9] Ces articles fournissent des données probantes sur la manière d'améliorer la sécurité et l'efficacité des analgésiques, et tous reflètent le travail visant à faire en sorte que les médicaments agissent conformément aux attentes tout en ne nuisant pas aux patients.

Les enfants sont peut-être encore plus vulnérables aux problèmes de sécurité des médicaments à cause de complexités telles que le manque d'essais cliniques et de données portant sur la sécurité, ce qui mène à une utilisation des médicaments non conforme et non approuvée[10], ainsi que la nécessité de manipuler les doses avant leur administration[11]. Ce numéro comporte également des études sur l'utilisation des médicaments en milieu pédiatrique. Caldwell et collab.[12] ont réalisé une étude observationnelle décrivant l'utilisation de médicaments sédatifs pour les enfants gravement malades. Vaillancourt et collab.[13] décrivent leur audit portant sur l'utilisation du cannabis dans un hôpital pédiatrique. L'étude précédemment citée de Friciu et collab.[9] est également pertinente en matière de sécurité médicamenteuse en pédiatrie, car cette formulation de la méthadone est utilisée pour les douleurs aigües et celles dues au cancer chez les enfants. Les audits sont importants, puisqu'ils révèlent les tendances en matière d'utilisation des médicaments et renseignent sur les recherches et les interventions futures, car l'investigation des problèmes, comme la stabilité des médicaments, est également cruciale pour assurer la sécurité des patients.

Ces articles soulignent le rôle que peuvent jouer les pharmaciens pour améliorer la sécurité des médicaments, puisque celle-ci est au cœur de notre profession. Nous devrions nous entraider à commencer à agir localement et à diffuser notre travail à l'échelle mondiale. Nous devons faire notre possible pour diffuser nos travaux au moyen des divers médias et démontrer l'importante contribution que nous apportons à relever ce défi en matière de sécurité. Le JCPH continuera de communiquer les études de nos auteurs relatives à la sécurité des médicaments J'invite chacun de vous à réfléchir à votre rôle de pharmacien, à l'importance de votre contribution pour faire que la sécurité des médicaments soit une priorité sanitaire mondiale ainsi qu'à votre capacité à diminuer les douleurs inutiles. Travaillons ensemble à réduire, voire à éliminer, l'expérience médicamenteuse « néfaste » ou « inopérante» pour les patients.

[Traduction par l'éditeur]

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Cannabis Use for Therapeutic Purposes by Children and Youth at a Tertiary Teaching Hospital in Canada: A Retrospective Chart Review

Régis Vaillancourt, Maria Moreno, Annie Pouliot, and Erick Sell

ABSTRACT

Background: The study of the use of cannabis for therapeutic purposes in the pediatric population is increasing, yet data on efficacy and safety are limited. Characterization of pediatric cannabis use for therapeutic purposes will improve understanding of the circumstances under which it occurs and the associated outcomes.

Objective: To describe the use of cannabis for therapeutic purposes, regardless of authorization, in a pediatric tertiary teaching hospital.

Methods: A retrospective chart review was completed for patients 18 years of age or younger who used cannabis for therapeutic purposes, regardless of authorization, between May 1, 2014, and May 1, 2017. Patients whose cannabis use was documented as recreational were excluded.

Results: In total, 300 patients were identified, of whom 37 met the inclusion criteria. Of these, 30 patients had documentation of medically supervised cannabis use. Most were using cannabis for seizures (n = 28), and many of these (n = 23) were patients with seizures described as intractable or refractory. Of the 27 patients who were experiencing seizures at initiation of medical cannabis, 21 had documentation of a decrease in seizure frequency. This decrease was transient for 16 patients, with a mean duration of 130.4 days (standard deviation 99.1 days). Seven patients self-medicated with cannabis. They obtained cannabis without authorization and used it for chronic pain (n = 5) and/or anxiety (n = 5).

Conclusions: Medically supervised cannabis use occurred most often in patients with intractable or refractory seizures. According to these data, seizure response is variable, and initial decreases may be transient for pediatric patients using cannabis. To ensure greater consistency and rigour in the conduct of prospective research and thus to generate better-quality research on the therapeutic effects of medical cannabis, development of a standardized care record is needed.

Keywords: cannabis, pediatrics, tertiary care, seizures, therapeutic

RÉSUMÉ

Contexte : Les études portant sur l'utilisation du cannabis à des fins thérapeutiques par les enfants augmentent, mais les données concernant l'efficacité et la sécurité de cette drogue sont limitées. La caractérisation de l'usage du cannabis à des fins thérapeutiques permettra de mieux comprendre les circonstances de l'utilisation de cette drogue ainsi que les effets qui lui sont associés.

Objectif : Décrire l'utilisation du cannabis à des fins thérapeutiques, qu'elle soit autorisée ou non, dans un hôpital d'enseignement de soins pédiatriques tertiaires.

Méthodes : Un examen rétrospectif des dossiers a été mené auprès de patients d'âge égal ou inférieur à 18 ans, qui ont fait un usage autorisé ou non de cannabis à des fins thérapeutiques entre le 1er mai 2014 et le 1er mai 2017. Les patients qui utilisaient du cannabis à des fins récréatives ont été exclus de l'étude.

Résultats : Au total 300 patients ont été identifiés et 37 d'entre eux répondaient au critère d'inclusion. La prise de cannabis sous supervision médicale de 30 d'entre eux était documentée. La plupart utilisaient le cannabis en cas de crise (n = 28) et bon nombre d'entre eux (n = 23) étaient des patients dont les crises étaient décrites comme insolubles ou réfractaires. Des 27 patients qui avaient des crises au début de la prise de cannabis médical, 21 ont enregistré une diminution de la fréquence des crises. Seize patients ont obtenu une diminution éphémère, qui a duré en moyenne 130,4 jours (écart type : 99,1 jours). Sept patients se soignaient eux-mêmes à l'aide de cannabis. Ils obtenaient du cannabis sans autorisation et l'utilisaient pour soulager des douleurs chroniques (n = 5) ou leur anxiété (n = 5).

Conclusions : Les patients qui subissaient des crises incurables ou réfractaires utilisaient le plus souvent du cannabis sous supervision médicale. Selon ces données, la réponse aux crises est variable et les baisses initiales du nombre de crises pourraient être éphémères chez les enfants utilisant du cannabis. Il convient de préparer un dossier de soins normalisé pour mener des recherches prospectives plus cohérentes et rigoureuses et donc générer des recherches de meilleure qualité sur les effets thérapeutiques du cannabis médical.

Mots-clés : cannabis, pédiatrie, soins tertiaires, crises, thérapeutique

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INTRODUCTION

In children, cannabis and pharmaceutical cannabinoids have been studied for multiple conditions, including refractory epileptic seizures,[1-10] such as those associated with Dravet syndrome, Doose syndrome, Lennox-Gastaut syndrome, hypoxic damage, and idiopathic epilepsy; tics secondary to Tourette syndrome[11]; neuropathic pain[12] and chronic pain from headaches[13] and abdominal and musculoskeletal sources[13]; chemotherapy-induced nausea and vomiting[14-18]; spasticity[19]; and post-traumatic stress disorder.[20] In practice, cannabis has been used as a last-line therapy in pediatric cases where satisfactory improvement was not observed and conventional therapies were ineffective.[6,10] Much of this evidence for the use of cannabis for therapeutic purposes in children comes from case reports and retrospective chart reviews,[20] and stronger evidence is often lacking.[20,21] Nonetheless, there is some good quality evidence, in the form of double-blind, crossover, randomized controlled trials, that pharmaceutical cannabinoids are effective in treating chemotherapy-induced nausea and vomiting in children.[20] In addition, there have been several randomized, controlled, open-label trials of a 99% pure oral cannabidiol (CBD) extract that has been approved by the US Food and Drug Administration.[22] A recent review of these trials indicated significant improvement in seizure frequency and severity in patients with medically refractory epilepsy.[22]

The outcomes used to evaluate the efficacy of cannabis therapy in children vary by indication, with the typical aim being a reduction in frequency or severity of symptoms (e.g., vomiting, seizure frequency, pain, or spasticity).[20] In addition, some side effects of cannabis may be considered beneficial, such as improvement in sleep quality, increase in alertness, and improvement in mood, language, and motor skills.[8] The most commonly reported side effects of tetrahydrocannabinol (THC) are drowsiness and dizziness,[20] whereas the most common side effects of CBD are somnolence, diarrhea, and decreased appetite.[20] Other side effects include anxiety/agitation,[23] fatigue,[8,10,13] decrease in reflex responses,[13] amotivation,[13] hallucinations,[23,24] emesis,[23] increased appetite,[6] tachycardia,[6] and hypertension or hypotension (especially postural hypotension).[24,25] As well, some patients using cannabis for seizure control experience a worsening of seizures.[6,8] Some rare but serious adverse events may be linked to cannabis use and abuse, including atrial fibrillation,[25,26] stroke,[24,27] and status epilepticus in seizure-prone patients.[8] Many adverse effects of long-term use of cannabis have been described, such as bronchitis, asthma, oropharyngitis,[28] and impairment of school performance[21] and social function.[13] This group of side effects, however, is often related to intake of cannabis by smoking, which is not an accepted route of administration when cannabis is used for therapeutic purposes.[21]

The Canadian Paediatric Society states that there are currently insufficient data to support the efficacy and safety of cannabis for any therapeutic indication in children.[21] Case reports discussing the successful use of cannabis to treat refractory epilepsy in children have spurred interest in using cannabis as pharmacotherapy for multiple indications.[10,29] Conversely, a growing body of evidence has begun to delineate potential harms associated with cannabis use by adolescents,[30] especially those with comorbid conditions, such as attention deficit hyperactivity disorder.[31] The Canadian Paediatric Society has therefore provided recommendations for the therapeutic use of cannabis in exceptional pediatric cases, emphasizing the need for ongoing research to characterize its efficacy and safety.[21]

The objective of the current study was to describe, through a retrospective chart review, inpatient and outpatient use of cannabis for therapeutic purposes, regardless of authorization, at the Children's Hospital of Eastern Ontario (CHEO) over a 3-year period, from 2014 to 2017. CHEO is a 167-bed pediatric tertiary teaching hospital in Ottawa, Ontario. CHEO has administered medical cannabis to patients in a number of exceptional circumstances, for multiple indications, with authorization from various health care practitioners. Given the lack of strong evidence for cannabis use for therapeutic purposes in children[21] and the wide variety of indications, efficacy and safety outcomes, doses, dosage forms, and patient characteristics, the findings of this chart review will be useful to improve understanding of the circumstances under which cannabis is used for therapeutic purposes among children and youth in Canada and the associated outcomes.

METHODS

Sample Selection

In Canada, for the entire period of this chart review (2014–2017), it was permissible to obtain medical cannabis from a licensed producer or to grow it oneself with authorization (Table 1).[32] The authorization for medical cannabis is obtained through a licensed health care professional, who provides suitable documentation to the patient; this documentation of authorization must then be presented to obtain medical cannabis from a licensed producer. Until 2016, medical cannabis was limited to dried marijuana[32]; however, changes to the regulations governing medical cannabis use in Canada that occurred partway through the study period (Table 1) included granting permission to those with authorization to buy cannabis oil and/or to make cannabis oil themselves.

For purposes of a study such as ours, confirmation of medical authorization for cannabis can be achieved either by verifying the source of cannabis to be a licensed producer or by verifying the medical authorization document. Given the retrospective nature of the study and the lack of standardization of documentation in patient charts, it was not possible to confirm medical authorization in each case. Therefore, we included all inpatients and outpatients 18 years of age or younger who were followed at CHEO between May 1, 2014, and May 1, 2017, and whose charts contained

Table 1. Evolution of Canadian Medical Cannabis Regulations*

Year	Regulation Name	Key Elements
2001	*Marihuana Medical Access Regulations*	• Allowed access to **dried marijuana** for medical purposes with authorization from a health care practitioner • Approved sources: ◦ Growing one's own plants ◦ Designating someone to grow plants ◦ Purchasing Health Canada supply
2013	*Marihuana for Medical Purposes Regulations*	• Expansion of approved sources of **dried marijuana** for medical purposes to include licensed producers • Created opportunity for development of a commercial industry
2016	*Access to Cannabis for Medical Purposes Regulations*	• Allowed individuals with authorization for medical cannabis to use and **make** cannabis products other than dried marijuana, such as **cannabis oil** • Allowed production and sale by licensed producers of **fresh** and dried marijuana, **cannabis oil**, and marijuana seeds and plants as starting materials • Approved sources: ◦ Growing one's own plants ◦ Designating someone to grow plants ◦ Purchasing Health Canada supply

*Source of information on cannabis regulations: *Understanding the New Access to Cannabis for Medical Purposes Regulations*. Health Canada; 2016.[32]

documentation of use of cannabis for therapeutic purposes, regardless of authorization.

Eligible patients were categorized as either using medical cannabis (i.e., using cannabis under medical supervision) or self-medicating with cannabis (see Box 1 for definitions of terms). Patients were considered to be using cannabis under medical supervision if any of the following criteria were met (as documented in the chart): a medical authorization document was verified; the source of the cannabis was verified as a licensed producer; or a physician was supervising the cannabis use, for example, by titrating the dose. Patients were considered to be self-medicating with cannabis if there was documentation that they were using cannabis for therapeutic purposes without medical supervision. Patients with documentation of self-medication with cannabis were included only if they also met all other inclusion criteria.

Patients were excluded if they were found, upon review of the medical record, to meet any of the following exclusion criteria: were using cannabis for therapeutic purposes, but with initiation outside the specified date range; were using cannabis for therapeutic purposes (e.g., anxiety, sleep), but with no further information documented; were using cannabis, but with documentation to indicate that use was recreational; were using a pharmaceutical cannabinoid only; or were not using cannabis.

Box 1. Definitions of Key Terms for This Study

Medically supervised use of cannabis: Cannabis was used under medical supervision, regardless of whether medical authorization was documented; does not include use of synthetic cannabinoids

Self-medication with cannabis: Cannabis was used for therapeutic purposes, but without medical supervision

Pharmaceutical cannabinoids: Manufactured drugs, such as delta-9-tetrahydrocannabinol-cannabidiol and nabilone, which have been approved for specific indications by Health Canada

Procedure

This retrospective chart review was approved by the Research Ethics Board of the Children's Hospital of Eastern Ontario Research Institute, which waived the requirement for informed consent.

The medical charts of inpatients and outpatients with documented use of cannabis for therapeutic purposes, regardless of authorization, were reviewed. Inpatients were identified by searching for cannabis in all medication orders logged in the hospital pharmacy's administrative software. Outpatients, for whom a different electronic health record was in use at the time, were identified in 2 ways. A search of medication orders and historical medications was performed for the medication numbers associated with the following 5 cannabis-related terms (or stems) in the outpatient electronic health record: cannabis, marijuana, cannabidiol/tetrahydrocann, cannabidiol-tetrahydrocannabin buccal, and cannabidiol-tetrahydrocannabinol 2.5–2.7 mg/actuation buccal spray. Patients taking only pharmaceutical cannabinoids (e.g., the last of the medications in the list above) were excluded, but their charts were reviewed to identify any use of plant-based cannabis. In addition, to ensure a thorough search, a text-based search of the "Progress Notes" and "Medication Orders" sections of patients' chart was conducted for the words "cannabis", "marijuana", and "marihuana" for patients seen in clinics where medical cannabis was most likely to be used (i.e., chronic pain, gastroenterology, neurology, neurosurgery, and oncology). Electronic charts (for outpatients) and physical charts (for inpatients) were then reviewed in detail for relevant information.

Data Collection

Data were extracted from the medical charts and entered into the Research Electronic Data Capture (REDCap) database (https://www.project-redcap.org/). Date of birth, sex, and allergies were collected. Information about the cannabis product, start date, dose, dosage changes, dosage form, route of administration, and end date (if applicable) was gathered, as well as information about use of tobacco and other substances. Any information about the indication, outcomes, side effects (adverse or beneficial), number of medications tried before cannabis, and nonpharmacological treatments used for the given indication were recorded. If cannabis had been discontinued, the reason was recorded. If cannabis had been used for a seizure disorder, the etiology of the disorder was recorded. For patients with documentation of a decrease in seizure frequency, the decrease was further classified as having been maintained or having been transient. To determine the duration of any observed decrease in seizure frequency, the number of days between initiation of cannabis and the first documented instance of increase in seizure frequency was calculated.

RESULTS

Sample Characteristics

Initial data capture identified a total of 300 unique patients whose medical charts were reviewed for eligibility. After review, 37 patients were included and 263 were excluded for the reasons specified in Figure 1. For most of those excluded (n = 128), review of the medical record showed that they were not using cannabis.

Patient characteristics for those included in the study are presented in Table 2, and the indications for use of cannabis in Table 3. Of the 37 patients included, 30 had documentation of medically supervised cannabis use (mean age at initiation 8.1 years, standard deviation [SD] 4.1 years), and 7 had documentation that they were self-medicating with cannabis (mean age at initiation 15.6 [SD 1.8] years). Of the 30 patients with medically supervised cannabis use, most were male (n = 23), the majority were being followed by the Neurology Clinic (n = 29), and most were using cannabis for seizures (n = 28). By contrast, among the 7 patients who were self-medicating with cannabis, most were female (n = 5), the majority were being followed by the Gastroenterology, Hepatology and Nutrition Clinic (n = 5) and/or the Chronic Pain Clinic (n = 5), and most were using cannabis for chronic pain (n = 5) and/or anxiety (n = 5).

Medically Supervised Cannabis Use

For most patients, medically supervised cannabis use began after 2015 (Table 2). Slightly more than half were seen only as outpatients (n = 17). For half of these patients (n = 15), the source of cannabis was not documented in the patient chart. Fourteen patients obtained their cannabis from a licensed producer (Table 4). All 30 patients with medically supervised cannabis use had used an oil. For some of these patients, the oil was additional to other forms of cannabis. Of those using cannabis under medical supervision, 27 took it orally. Fourteen patients discontinued use during the period of the chart review. The most common reason for discontinuation was an increase in seizure frequency (n = 5;

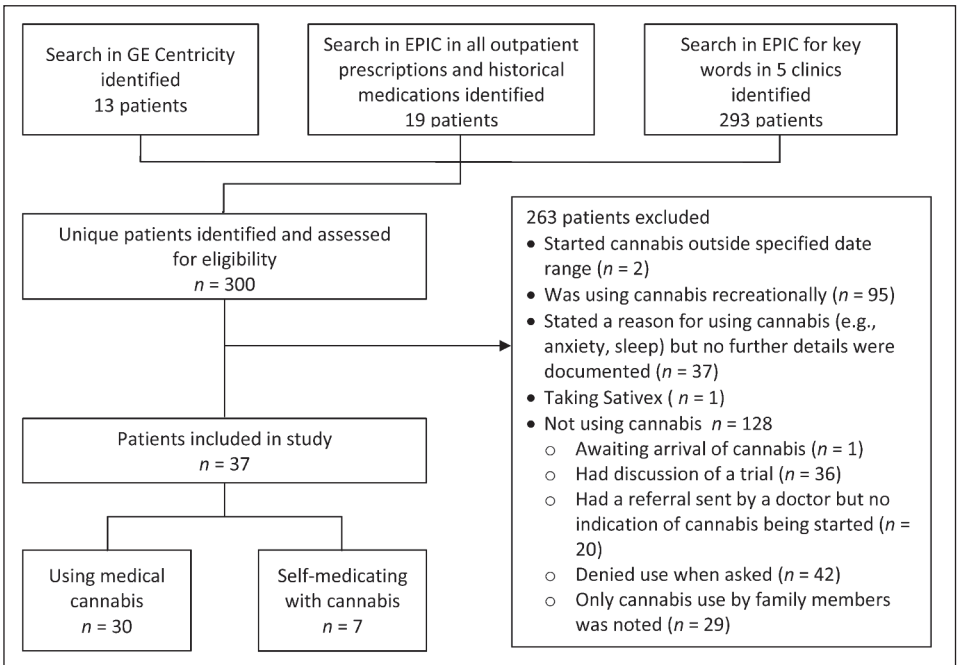

Figure 1. Patient selection.

Table 2. Characteristics of Patients Included in the Study*

Characteristic	Medical Cannabis (*n* = 30)	Self-Medication with Cannabis (*n* = 7)
Age at initiation of cannabis (years) (mean ± SD)	8.1 ± 4.1	15.6 ± 1.8
Sex		
Male	23	2
Female	7	5
Year when patient began cannabis use†		
2013	1	–
2014	4	–
2015	9	–
2016	10	–
2017	6	–
Patient type		
Both inpatient and outpatient	11	0
Inpatient	13	0
Outpatient	28	7
Substance use		
Tobacco	0	2
Other substances	0	4
Services following patient‡		
Neurology	29	0
Complex care	6	0
Palliative care	6	0
Gastroenterology, hepatology, nutrition	4	5
Endocrinology	5	0
Autism program	2	0
Ear, nose, and throat	2	0
Nephrology	2	0
Mental health	1	4
Cardiology	1	0
Urology	1	1
Oncology	1	0
Chronic pain	0	5
Adolescent health	0	2
ADHD/behavioural	0	1
Outpatient observation period (days) (mean ± SD)	1443.5 ± 593.4	753 ± 432.9

ADHD = attention deficit hyperactivity disorder, SD = standard deviation.
*Data are presented as number of patients, except where indicated otherwise.
†For patients who were self-medicating with cannabis, data concerning start date were not available (indicated by dashes).
‡Each patient could be followed by more than one service.

Table 4). Among cases for which the ratio of CBD to THC was recorded (*n* = 17), more than half reported using more than one unique formulation. Whereas 8 of these patients (47%) reported using a single formulation, 6 patients (35%) reported the use of 2 formulations, 2 patients (12%) reported the use of 3 formulations, and 1 patient (6%) reported the use of 5 different formulations.

Symptom Control

The presence of symptom control was based on a physician's documentation indicating that the patients' symptoms were controlled. According to this definition, only 5 patients with medically supervised cannabis use achieved control over their symptoms during the observation period (Table 5). Among those who were using cannabis for seizure control and who were experiencing seizures at initiation of medical cannabis (*n* = 27), 21 had documentation of an initial decrease in seizure frequency (although this decrease was not characterized as "seizure control" in the patients' charts). Most of these patients (*n* = 16) experienced a transient decrease in seizure frequency, with the decrease lasting, on average, 130.4 (SD 99.1) days. The average number of antiepileptic medications taken concurrently with cannabis was 3.7 (SD 1.9), with a range from 0 to 8. For patients with seizures described as refractory, the average number of antiepileptic medications taken concurrently with cannabis was 4.1 (SD 1.8), with a range from 1 to 8.

Side Effects

For the 30 patients using medically supervised cannabis, the most commonly documented negative side effects were worsening of seizures (*n* = 19), onset of a new type of seizure (*n* = 7), drooling (*n* = 6), and fatigue (*n* = 6) (Figure 2). The most commonly documented positive side effects were being more engaged (*n* = 5),

Table 3. Indications for Which Cannabis Use Was Documented*

Indication	Medical Cannabis (*n* = 30)	Self-Medication with Cannabis† (*n* = 7)
Seizures	28	0
Type of seizure		
Dravet syndrome	7	
Idiopathic	5	
Hypoxic damage	4	
Lennox-Gastaut syndrome	2	
Infantile spasms that progressed with new seizure types	2	
Febrile infection-related epilepsy syndrome (FIRES)	2	
Other	6	
Documentation that ketogenic diet was tried	18	
Seizures described as intractable/refractory	23	
No. of medications tried by patients described as having intractable/refractory seizures (mean ± SD, range)	7.1 ± 2.7 3–16	
No. of medications tried for seizures before cannabis (mean ± SD, range)	6.4 ± 2.9 2–16	
Spasticity or dystonia	2	0
No. of medications tried before cannabis	3	
Chronic pain	0	5
Abdominal pain		2
Myofascial pain syndrome		2
Other		1
Anxiety	0	5
For sleep	0	2
Nausea	0	1

SD = standard deviation.
*Data are presented as number of patients, except where indicated otherwise.
†Patients who self-medicated used cannabis for multiple indications.

improved mood/feeling brighter (*n* = 5), increased alertness (*n* = 5), and improved motor skills (*n* = 4) (Figure 3).

Self-Medication with Cannabis

For the 7 patients who were self-medicating, all obtained cannabis without authorization as a dried flower, and most (*n* = 6) inhaled the product by smoking (Table 4). For all of these patients, there was a failure to achieve symptom control (Table 5). Among these patients, the most common negative side effects were emesis (*n* = 6), decreased appetite (*n* = 2), constipation (*n* = 2), and sleeping difficulties (*n* = 2). The positive side effects noted in this group were increased appetite (*n* = 2) and improved sleep quality (*n* = 1).

DISCUSSION

Medically Supervised Cannabis Use

Over the 3-year period of the chart review, there were 30 patients with documentation of medically supervised cannabis use. The majority were using cannabis for seizures, which were most often described in the chart as intractable or refractory. This finding is consistent with the recent and rapid increase in research studies investigating the use of medical cannabis in the treatment of epilepsy.[20] Most patients in this study were male, and many were followed by the neurology, complex care, and palliative care services at CHEO. No use of tobacco or other substances was noted among patients using cannabis under medical supervision. None of the patients were using medical cannabis for control of chemotherapy-induced nausea and vomiting. This is not surprising, because although there is strong evidence for the use of synthetic cannabinoids in the treatment of chemotherapy-induced nausea and vomiting, evidence for plant-based cannabis in this context is lacking.[20]

All of the patients with medically supervised cannabis use were using an oil. We observed that details of this form of medical cannabis usage were not documented consistently for outpatients. It was frequently unclear whether the oil was purchased as a premade product or if the patient's parents had purchased cannabis as a dried flower and prepared the oil at home. Other details, such as the source of the cannabis, were not documented for half of the patients. Such documentation is an important aspect of verifying authorization. Furthermore, for many patients, the ratio of CBD to THC was not documented. For those who did have documentation of this ratio, the range was relatively wide, from as high as 50:1 to as low as 1:1.

Of the 28 patients who were using medical cannabis for seizure control, 27 had active seizures at the time of initiation, and 21 of these had documentation of decreased seizure frequency after initiation of cannabis. Porter and Jacobson[10] completed a

Table 4. Description of Cannabis Use*

Cannabis-Related Information	Medical Cannabis† (*n* = 30)	Self-Medication with Cannabis† (*n* = 7)
Source of cannabis		
Canadian licensed producer	14	0
Clinical trial	1	0
Unauthorized acquisition	0	7
Not documented	15	0
Dosage form		
Oil	30	0
Purchased as oil	16	
Purchased as dried flower and made into oil	5	
Not specified	9	
Capsules	1	0
Powder	1	0
Dried flower	0	7
Dried flower in cookies	1	0
Route of administration		
Oral	27	0
Gastrostomy tube or nasojejunal tube	3	0
Inhaled, vaporization	0	2
Inhaled, smoking	0	6
Concerns expressed over cost of cannabis	6	2
No. of doses documented per patient (mean ± SD)	5.4 ± 4.6	4.5 ± 3.8
Patients who discontinued cannabis	14	1
Increase in seizures	5	0
Not seeing a benefit	4	1
Death	2	0
No longer having seizures	1	0
Cost	1	0
Learning difficulties	1	0
Behavioural problems	1	0
EEG worsening	1	0
Emesis	1	0

EEG = electroencephalography, SD = standard deviation.
*Data are presented as number of patients, except where indicated otherwise.
†For each section, more than one category could apply to each patient.

survey of parents whose children were using cannabidiol-enriched cannabis for epilepsy. Parents of 19 patients completed the survey, with 84% reporting decreases in seizure frequency.[10] The range of CBD–THC ratios in that study was similar to what was found in the current study. A recent open-label trial of high-ratio therapy (50:1) for Dravet syndrome produced reductions in seizure frequencies for 79% of patients with daily doses ranging from 7 to 16 mg/kg of CBD and 0.14 to 0.32 mg/kg of THC.[33] In our chart review, only 1 patient for whom information on formulation was available was using a cannabis oil formulation with a CBD–THC ratio as high as 50:1, yet the percentage of patients reporting seizure reductions was similar.

Different formulations and concentrations will likely affect outcomes in terms of both efficacy and side effects. In the current chart review, roughly half of the patients for whom we had information on formulation used more than one formulation during the period of the chart review. It is unclear what effect switching between cannabis products with different concentrations of CBD and THC might have on seizure control. Although approximately three-quarters of the patients in the current study experienced a decrease in seizure frequency, the magnitude of the decrease was unclear because there was no standardized method of documenting seizure control in patient charts. For a small number of patients with documentation of a decrease in seizure frequency, the decrease was maintained over the chart review period (*n* = 5), but it is possible that the decrease in frequency did not continue beyond the review period. For the remaining 16 patients, the frequency of seizures was documented to have decreased initially with a later return to baseline or increase above baseline. For 5 of these patients with a transient decrease in seizure frequency, the parents opted to withdraw and then reinitiate cannabis. For 3 of these 5 patients, a second transient decrease in seizure frequency was noted.

These results provide insight into the course of symptoms in seizure disorders among patients with medically supervised cannabis use. Maa and Figi[29] documented cases of children using cannabis who had a persistent decrease in seizures over 20 months and were able to wean off their antiepileptic drugs. Given this finding, some parents may be hopeful that an initial decrease in seizure frequency will be maintained. On the basis of our

Table 5. Relation between Cannabis Use and Symptom Control

Efficacy	Medical Cannabis (*n* = 29)*	Self-Medication with Cannabis (*n* = 7)
Symptom control achieved†		
Yes	5	0
No	24	7
Initial decrease in seizures (*n* = 27 patients with seizures upon initiation of cannabis)*		
Yes	21	NA
No	6	NA
Patients with decrease in seizures	*n* = 21	
Decrease in seizure frequency was *maintained*	*n* = 5	
Duration of decrease (days) (mean ± SD)	267.0 ± 301.7	
Decrease in seizure frequency was *transient*		
First attempt using cannabis	*n* = 16	
Duration of decrease (days) (mean ± SD)	130.4 ± 99.1	
Second attempt using cannabis after stopping (*n* = 5)	*n* = 3	
Duration of decrease (days) (mean ± SD)	150.3 ± 44.1	
Third attempt using cannabis after stopping (*n* = 1)	*n* = 1	
Duration of decrease (days)	39	

NA = not applicable, SD = standard deviation.
*Overall sample size was 29 patients using medical cannabis, with 27 of these patients using medical cannabis for seizures (instead of 30 and 28, respectively), because 1 of the 28 patients using medical cannabis for seizures had not actually had any seizures for several months before initiation of cannabis, and symptom/seizure control was therefore not a relevant outcome measure.
†Symptom control was defined as presence of physician documentation that symptoms were controlled while patient was using cannabis.

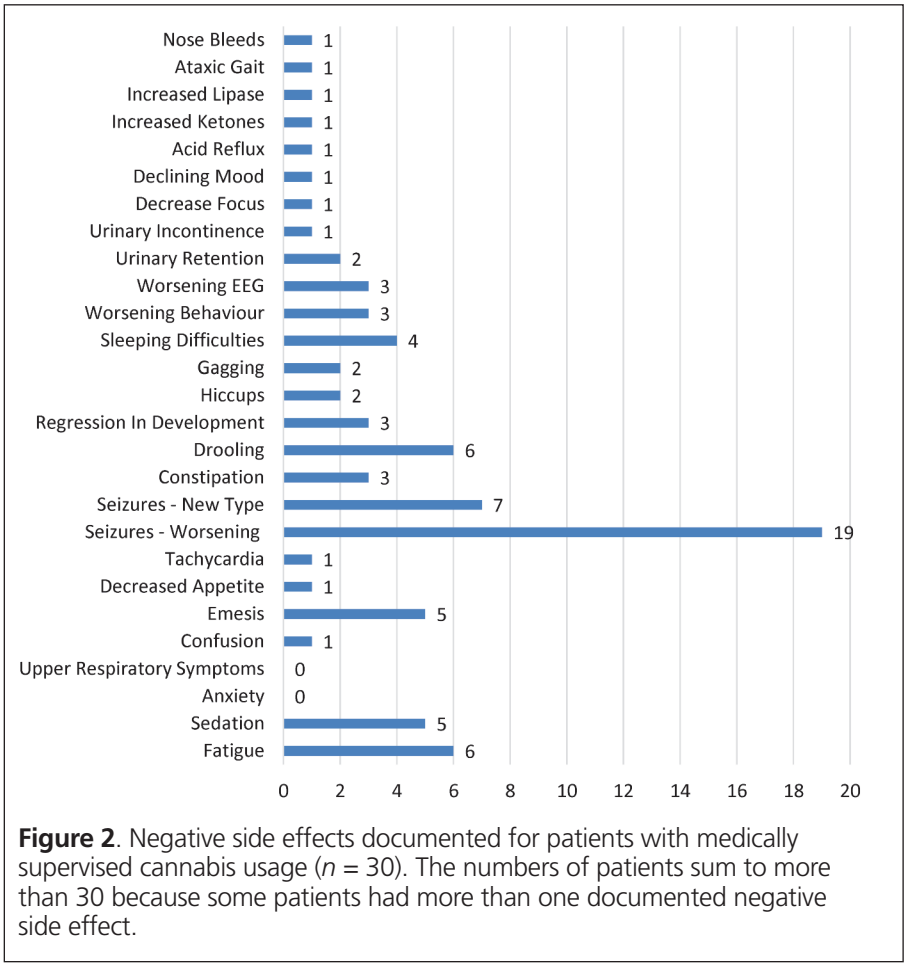

Figure 2. Negative side effects documented for patients with medically supervised cannabis usage (*n* = 30). The numbers of patients sum to more than 30 because some patients had more than one documented negative side effect.

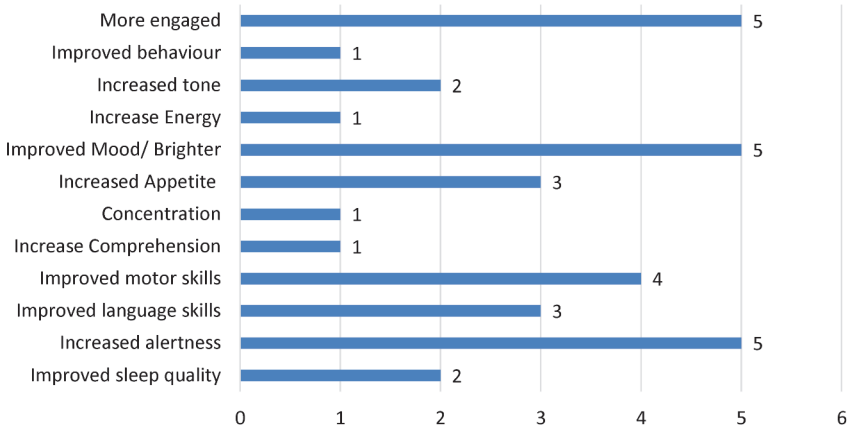

Figure 3. Positive side effects documented for patients with medically supervised cannabis usage (n = 30). The numbers of patients sum to more than 30 because some patients had more than one documented positive side effect.

observations, we recommend that parents should be informed of the possibility that cannabis use may not be associated with long-term seizure control. Furthermore, an alternative (and counterintuitive) explanation for any observed decrease in seizure frequency may be weaning off existing antiepileptic drugs, as there have been instances where polypharmacy has worsened seizures.[34]

The most frequent negative side effect noted in the current study was worsening of seizures. Notably, 5 patients discontinued cannabis because of an increase in seizure frequency. This observation is consistent with previous reports of worsening of seizures associated with use of cannabis.[6,8] The percentage of patients experiencing an increase in seizure frequency following medically supervised cannabis use was higher in the current study than that observed by Tzadok and others,[6] who reported seizure aggravation for 7% of patients. The rate may have been higher in the current study because many patients experienced concurrent changes to their antiepileptic medications.

Positive side effects were also noted, such as improved alertness, improved or brighter mood, and being more engaged. These positive side effects can also be important to parents and may factor into the decision to continue medically supervised cannabis use, even if long-term symptom control is not achieved. Again, these positive side effects could be due to concurrently weaning off antiepileptic medications.[35]

Self-Medication with Cannabis

In this study, there were 7 outpatients who were self-medicating with cannabis obtained from unauthorized sources. The average age in this group was 15.6 years, and most of the patients were female. The majority reported using cannabis for a chronic pain condition and/or anxiety. These findings are consistent with a recent survey by the Canadian Centre on Substance Abuse,[36] in which adolescents reported doing their own research and "self-medicating" with cannabis without consulting a doctor. Similar cases of adolescents using cannabis for pain were described by Harrison and others,[13] who noted that full pain control was not achieved with cannabis use. Similarly, none of the patients in our study who were self-medicating with cannabis achieved control of their symptoms. Although some parents expressed concern about their children's use of cannabis, others had accepted it and allowed them to use it regularly. As explained by Harrison and others,[13] parents may allow the use of cannabis when their child's symptoms are not well controlled by other means.

The Lower-Risk Cannabis Use Guidelines, developed by the Canadian Research Initiative in Substance Misuse, explain that smoking cannabis can have negative effects on respiratory health.[37] The adolescents in our study were mostly smoking cannabis. Other side effects, such as emesis, can occur when cannabis is smoked. In the group of patients who smoked cannabis, there was some concurrent tobacco and substance use. This finding is consistent with information in the Canadian Paediatric Society position statement,[38] which states that use of cannabis can lead to use of tobacco and other substances. As mentioned in that position statement, health care professionals should screen for cannabis use and discuss the risks of using cannabis regularly.[38] Even if a child uses cannabis through self-medication, these discussions should still take place. The Lower-Risk Cannabis Use Guidelines also recommend abstinence and avoidance of initiation of cannabis at a young age,[37] guidance that should be communicated to parents.

Limitations

This study was a retrospective chart review, and we acknowledge that the data collected are limited to the documentation

available in the patients' medical records. For example, we were not able to describe the specific weight-based dosage of CBD (as milligrams per kilogram), which would be useful for understanding observed outcomes of CBD use in pediatric practice. In addition, we were unable to extract detailed information about the onset of efficacy. Furthermore, a relatively large number of patients (n = 37) had documentation of cannabis use for therapeutic purposes, but the information available was insufficient to characterize this use, and these patients were excluded. Therefore, the results of this study may not be generalizable to all pediatric patients who are using cannabis for therapeutic purposes. Cannabis was often authorized by physicians outside of CHEO, and information concerning authorization could only be obtained if it was well documented in the chart. There may have been instances in which a patient was using cannabis, but it was not documented or there was lack of detail because a CHEO physician was not the authorizing health care provider. Furthermore, the families of some outpatients may not have disclosed use of cannabis during their clinic visit for fear of stigma. Another limitation was our inability to objectively quantify seizure frequency because information for the study was limited to documentation in the patient chart, which was in turn based on parental characterization of seizure frequency. As such, these outcomes were limited by parental report and any bias that might have entailed.

Implications

According to the results of this study, we propose improving documentation of cannabis use for therapeutic purposes by integrating a template for documentation into the electronic medical record. Such a template would allow for more structured and standardized documentation of cannabis use. It could also facilitate future studies on the use of cannabis for therapeutic purposes. We propose that the elements required to effectively document the use of cannabis for therapeutic purposes, and thus improve understanding of its use in the pediatric population, are the following: start date; confirmation of authorization for cannabis, including name of the authorizing health care practitioner and expiry date of the certificate; brand name and source of cannabis (e.g.,. licensed producer); CBD–THC ratio; concentration of CBD for oils (e.g., as milligrams per millilitre [mg/mL]); route of administration; dose; and frequency of administration.

This information could be gathered by referring to both the medical document of authorization and the label of the product. In all cases of medical use of cannabis, a document provided by a health care practitioner is required to access the product.[39] This document contains the authorizing practitioner's information and the period of use authorized. The labelling requirements for medical cannabis specify that the name of the licensed producer should be displayed along with the brand name. The THC and CBD content must also appear on the label for both oil and fresh/dried cannabis, and the label for any oil product must show the concentration.[39]

CONCLUSION

In this single-institution retrospective chart review, medically supervised cannabis use was documented most frequently for children with seizures described as refractory. Documented decreases in seizure frequency associated with cannabis use were transient for many patients. There was limited variation in the ratios of CBD to THC. All prospective studies evaluating efficacy for seizure control have used pure CBD preparations or oils with high CBD concentrations. It is unclear whether other compounds contained within cannabis-derived oils could contribute to the documented decrease in seizure frequency observed in this chart review. In the case of patients self-medicating with cannabis, a discussion of risks and benefits should take place between health care professionals and the patients and their families. This study has identified the need for development of a standardized care record, to ensure greater consistency and rigour in the conduct of prospective research in cannabis treatment and thus to generate better-quality research on the therapeutic effects of medical cannabis. We have proposed a template suitable for adoption by other hospitals that allows for a more structured documentation process, thereby facilitating the capture of more robust data on cannabis use in hospital settings. Overall, there continues to be a need for further research and for well-designed clinical trials of the use of cannabis for therapeutic purposes in pediatrics.

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RECHERCHE ORIGINALE

Surveillance des substances contrôlées en établissements de santé : une contribution à la gestion de la crise des opioïdes au Canada

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

RÉSUMÉ

Contexte : La consommation des substances contrôlées et plus particulièrement des opioïdes est un enjeu de santé publique. Le Canada se situe au deuxième rang des plus gros consommateurs d'opioïdes dans le monde. L'utilisation de ces substances est associée à des problèmes de mésusage. À preuve, une crise des opioïdes sévit en Amérique du Nord.

Objectifs : Décrire et analyser les tendances de consommation des substances contrôlées au sein d'un établissement de santé de 2003-2004 à 2017-2018. Proposer un outil de surveillance de la consommation des substances contrôlées dans un établissement de santé.

Methodologie : Étude descriptive rétrospective. À partir du logiciel de gestion des approvisionnements, nous avons extrait les données de consommation de toutes les substances contrôlées du 1er avril 2003 au 31 mars 2018. Les données ont été exprimées selon l'index de la classification *Anatomical Therapeutic Chemical* en nombre de doses définies journalières (DDJ) pour 1000 jours-présence avec les valeurs de DDJ proposées par l'Organisation mondiale de la santé. Seules des statistiques descriptives ont été effectuées.

Resultats : Durant les 15 dernières années, la consommation des substances contrôlées a diminué de 43 % au sein de notre établissement (min. : 739; max. : 1292 DDJ/1000 jours-présence par année). De 2003-2004 à 2017-2018, les principales classes thérapeutiques consommées par ordre décroissant étaient : opioïdes, hypnotiques et sédatifs, anxiolytiques et anesthésiques généraux. Les principales molécules opioïdes consommées en 2017-2018 sont l'hydromorphone et la morphine injectable.

Conclusions : Cette étude descriptive rétrospective montre une diminution de la consommation des substances contrôlées au sein de notre établissement de 2003-2004 à 2017-2018. Elle démontre la faisabilité de développer un outil de surveillance de la consommation des substances contrôlées en établissement de santé. Une telle approche pourrait être implantée à large échelle afin de favoriser les comparaisons entre les établissements.

Mots clés : consommation, substances contrôlées, substances désignées, opioïdes, dose définie journalière, gouvernance des substances contrôlées

ABSTRACT

Background: The use of controlled substances, especially opioids, is a public health concern. Canada is the country with the second greatest opioid use in the world. The use of these substances is associated with problems of misuse, as evidenced by North America's opioid crisis.

Objectives: To describe and analyze usage patterns for controlled substances in a health care facility from 2003/04 to 2017/18, and to propose a tool for monitoring the use of controlled substances in this setting.

Method: In this retrospective descriptive study, usage data for all controlled substances were extracted from the institution's supply management software for the period April 1, 2003, to March 31, 2018. The data are presented according to the *Anatomical Therapeutic Chemical* classification in terms of number of Defined Daily Doses (DDD) per 1000 inpatient-days, using the DDD values proposed by the World Health Organization. Only descriptive statistics were determined.

Results: During the last 15 years, use of controlled substances at the study facility dropped by 43% (min. 739 and max. 1292 DDD/1000 inpatient-days per year). From 2003/04 to 2017/18, the main therapeutic classes consumed (in decreasing order) were opioids, hypnotics and sedatives, anxiolytics, and general anesthetics. The main opioid molecules consumed in 2017/18 were hydromorphone and injectable morphine.

Conclusions: This retrospective descriptive study showed a decrease in the consumption of controlled substances in the study facility from 2003/04 to 2017/18. It also demonstrated the feasibility of developing a tool for monitoring the use of controlled substances in a health care facility. This approach could be implemented at a larger scale to foster comparisons between facilities.

Keywords: consumption, controlled substances, designated substances, opioids, defined daily dose, controlled substances stewardship

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INTRODUCTION

Au Canada, on entend par substances contrôlées (aussi appelées substances désignées), toute substance inscrite à l'une ou l'autre des annexes I, II, III, IV ou VI de la Loi règlementant certaines drogues et autres substances (LRCDAS)[1]. Cette loi concerne les stupéfiants, les drogues contrôlées, les substances ciblées, les benzodiazépines et les précurseurs. Ces drogues sont divisées en catégories basées sur le potentiel d'abus ou d'accoutumance. Les substances contrôlées comprennent autant les drogues illicites en vente libre que les médicaments prescrits[2].

Utilisés depuis plusieurs décennies pour le traitement des douleurs aigües, postopératoires et palliatives, les opioïdes ont vu leur usage s'élargir avec la prise en charge de la douleur chronique non cancéreuse. Ainsi, on observe depuis les années 2000 une augmentation du nombre de prescriptions d'opioïdes aux États-Unis[3]. Parallèlement, 70 237 décès par surdose ont été dénombrés aux États-Unis en 2017, dont les deux tiers étaient liés aux opioïdes[4]. Pour la même année, on a dénombré 4 034 décès apparemment liés aux opioïdes au Canada[5]. Selon l'Organisme international de contrôle des stupéfiants, le Canada et les États-Unis sont les deux principaux pays consommateurs d'opioïdes sur ordonnance dans le monde[6]. Ainsi, l'augmentation croissante de l'utilisation d'opioïdes, avec ou sans ordonnance, est associée à une augmentation du nombre de décès par surdosage dans le contexte de ce qu'on appelle désormais la « crise des opioïdes »[7]. Cette crise constitue un problème de santé publique majeur en Amérique du Nord.

Divers organismes ont mis en place des programmes pour sensibiliser les professionnels de la santé et les patients aux risques liés à l'utilisation des substances contrôlées. Aux États-Unis, la Joint Commission dispose de critères précis pour juger des mesures d'évaluation de la douleur mises en place et de la prescription des opioïdes dans les hôpitaux américains et elle encourage la mise en place de programmes de gestion des opioïdes (*opioid stewardship*)[8-10].

Au Canada, ISMP Canada (Institute for Safe Medication Practices Canada) soutient un programme semblable, qui se définit comme un ensemble d'interventions coordonnées pour améliorer, monitorer et évaluer l'utilisation des opioïdes dans le but de supporter et de protéger la vie humaine (traduction libre)[11].

Les prescripteurs qui exercent dans les hôpitaux sont à l'origine de la mise en œuvre de nombreux traitements aux opioïdes, tant pour les soins aigus (p. ex. après une opération chirurgicale) que pour les soins chroniques (p. ex. douleurs chroniques réévaluées après l'hospitalisation, congé donné en soins palliatifs à domicile). Les substances contrôlées inscrites à la liste locale d'un établissement, les protocoles et feuilles d'ordonnances prérédigées mises en place ont un impact considérable sur la pratique, le choix et les quantités des substances contrôlées prescrites.

En outre, on reconnaît les risques d'abus et de mésusage par les professionnels de la santé[12]. En effet, l'accès des professionnels de la santé aux substances contrôlées dans le cadre de leur pratique facilite le détournement potentiel de ces substances pour une utilisation personnelle ou même du trafic. Ce risque de détournement de substances contrôlées peut influencer l'utilisation et il représente également un risque de sécurité pour les patients, étant donné que des doses de ces médicaments peuvent être enregistrées au nom des patients sans leur être réellement administrées[13]. Ainsi les établissements de santé sont confrontés à d'importants enjeux en termes de respect des exigences règlementaires, d'amélioration continue de la qualité des soins et de prévention du détournement des substances contrôlées. C'est dans ce contexte que la Société canadienne des pharmaciens d'hôpitaux a récemment publié des recommandations entourant la gestion et la prévention du détournement des substances contrôlées en établissement de santé[14].

L'objectif principal de cette étude vise à décrire et à analyser les tendances de consommation des substances contrôlées au sein d'un établissement de santé de 2003-2004 à 2017-2018. L'objectif secondaire consiste à proposer un outil de surveillance de la consommation des substances contrôlées dans un établissement de santé, qui devrait être jumelé à des mesures d'encadrement des prescriptions et de formation données aux prescripteurs et aux usagers.

MÉTHODES

Conception de l'étude

Il s'agit d'une étude descriptive rétrospective se déroulant au CHU Sainte-Justine, un centre hospitalier universitaire mère-enfant de 500 lits situé à Montréal, Québec, Canada. L'établissement offre l'ensemble des soins généraux et spécialisés groupés dans les disciplines suivantes : médecine (y compris médecine interne et hémato-oncologie), chirurgie, gynéco-obstétrique, soins intensifs, psychiatrie, néonatologie et pouponnière, urgence.

Origine des données

Les données de consommation des substances contrôlées ont été extraites par année financière entre le 1er avril 2003 et le 31 mars 2018 à partir du logiciel de gestion des approvisionnements (GRM Espresso^{MD}, Logibec, Montréal, Canada). Une année financière débute le 1er avril d'une année et se termine le 31 mars de l'année suivante. Ces données correspondent aux sorties unitaires annuelles réalisées sur le logiciel de gestion des stocks de la pharmacie. Le nombre d'admissions et de jours-présence par année financière a également été recueilli pour décrire les volumes d'activités d'hospitalisation de courte durée.

Les substances contrôlées ont été déterminées à partir du cadre législatif en vigueur[15-17]. Les substances marquées de la lettre « N » correspondent aux stupéfiants, médicaments régis par le

règlement sur les stupéfiants (p. ex. morphine, codéine, oxycodone, hydromorphone); les substances marquées de la lettre « C » correspondent aux drogues contrôlées, médicaments régis par le règlement sur les aliments et les drogues (p. ex. amphétamine, méthylphenidate, phénobarbital); les substances marquées des lettres « T/C » correspondent aux médicaments régis par le *Règlement sur les benzodiazépines et autres substances ciblées* (p. ex. alprazolam, diazépam)[15-17].

Analyses

Les données de chaque substance contrôlée sont exprimées selon l'index de la classification anatomique, thérapeutique et chimique (ATC) et la formulation des médicaments. Les quantités dispensées sont exprimées en milligrammes par année et en nombre de doses définies journalières (DDJ) pour 1000 jours-présence par année. Les données sont également exprimées en équivalent en milligrammes de morphine (EMM) orale pour 1000 jours-présence par année pour la classe des opioïdes (N02A), des alcaloïdes de l'opium et dérivés (R05D) et des anesthésiques généraux (N01A); enfin, les données sont exprimées en équivalent en milligrammes de diazépam (EMD) oral pour 1000 jours-présence par année pour les classes des anxiolytiques (N05B), des hypnotiques et des sédatifs (N05C).

Dose définie journalière (DDJ)

La dose définie journalière correspond à la dose d'entretien moyenne par jour pour l'indication principale d'un médicament pour l'adulte (70 kg). Définie par l'Organisation mondiale de la santé (OMS), cette norme de mesure permet de convertir les quantités physiques des médicaments (p. ex. comprimés, fioles, inhalateurs) en une unité de mesure standardisée et permet ainsi d'évaluer les tendances d'utilisation des médicaments.

Lorsque cela était possible, les investigateurs ont utilisé les valeurs de DDJ proposées par l'OMS (tableau 1)[14,15,18,19]. Les DDJ des associations de produits ont été considérées comme la DDJ de la substance principale, selon les lignes directrices de l'OMS. Le calcul des données s'effectue comme suit : nombre total de milligrammes consommés par année / ratio DDJ en mg divisé par le nombre total de jours-présence × 1000.

Toutefois, l'OMS n'a pas établi de DDJ pour les formes topiques et pour les anesthésiques généraux et locaux. Compte tenu de la consommation marginale de cocaïne ophtalmique et topique, d'hydroxyamphétamine ophtalmique et de nabilone, nous avons exclu ces médicaments de l'analyse. Ainsi, nous nous sommes basés sur les règles générales utilisées par l'OMS pour établir une DDJ par médicament des produits suivants : kétamine, rémifentanil, sufentanil, etomidate et hydroxyamphetamine[20,21].

Tableau 1 (partie 1 de 2). DDJ et ratio d'équivalent en milligrammes de morphine ou de diazépam utilisés pour les calculs

Médicament et voie d'administration*	1 DDJ (mg)	Équivalent en milligrammes de morphine orale†	Équivalent en milligrammes de diazépam oral‡
Opioïdes (N02A)			
Buprenorphine INJ	1,2	75	NA
Codeine INJ	240	0,3	NA′
Codeine PO	100	0,1	NA
Fentanyl INJ	0,6	200	NA
Fentanyl PO	0,6	100	NA
Fentanyl TOPI	1,2	100	NA
Hydromorphone INJ	4	17,5	NA
Hydromorphone PO	20	5	NA
Hydromorphone R	4	5	NA
Methadone INJ	25	13,5	NA
Methadone PO	25	4,7	NA
Morphine INJ	30	3	NA
Morphine PO	100	1	NA
Morphine R	30	1,5	NA
Nalbuphine INJ	80	3	NA
Oxycodone PO	75	1,5	NA
Tramadol PO	300	0,2	NA
Alcaloïdes de l'opium et dérivés (R05D)			
Normethadone PO	25	4,7	NA
Antagonistes des récepteurs opioïdes périphériques (A06A)			
Methylnaltrexone INJ	6	NA	NA
Anesthésiques généraux (N01A)			
Etomidate INJ	21	NA	NA
Ketamine INJ	350	NA	NA
Ketamine PO	120	NA	NA
Remifentanil INJ	0.6	100	NA
Sufentanil INJ	0.06	2000	NA

suite à la page 119

Tableau 1 (partie 2 de 2). DDJ et ratio d'équivalent en milligrammes de morphine ou de diazépam utilisés pour les calculs

Médicament et voie d'administration*	1 DDJ (mg)	Équivalent en milligrammes de morphine orale†	Équivalent en milligrammes de diazépam oral‡
Anxiolytiques (N05B)			
Alprazolam PO	1	NA	2
Clobazam PO	20	NA	1
Diazepam INJ	10	NA	1
Diazepam PO	10	NA	1
Diazepam R	10	NA	1
Lorazepam INJ	2,5	NA	2.5
Lorazepam PO	2,5	NA	2.5
Oxazepam PO	50	NA	2.5
Hypnotiques et sédatifs (N05C)			
Amobarbital INJ	100	NA	NA
Chloral PO	1000	NA	NA
Chloral R	1000	NA	NA
Midazolam INJ	15	NA	3
Midazolam PO	15	NA	3
Nitrazepam PO	5	NA	0.5
Pentobarbital INJ	100	NA	NA
Pentobarbital PO	100	NA	NA
Phenobarbital PO	100	NA	NA
Secobarbital PO	100	NA	NA
Temazepam PO	20	NA	1
Zolpidem PO	10	NA	0.5
Psychostimulants (N06B)			
Amphetamine PO	15	NA	NA
Dexamphetamine PO	15	NA	NA
Hydroxyamphetamine PO	15	NA	NA
Lisdexamphetamine INJ	30	NA	NA
Methylphenidate PO	30	NA	NA
Androgènes (G03B)			
Methyltestosterone PO	25	NA	NA
Testosterone INJ	18	NA	NA
Testosterone PO	120	NA	NA
Testosterone TOPI	50	NA	NA

*DDJ = doses définies journalières, INJ = injectable, NA = non applicable, PO = *per os,* R = rectal, TOPI = topique
†D'après Nielsen et collab.[18]
‡D'après la table du Ashton.[19]

L'utilisation des DDJ permet la présentation et la comparaison statistique de la consommation de médicaments, mais elle ne reflète pas l'exposition réelle de patients aux substances contrôlées. En effet, il existe une importante différence entre la dose utilisée en pratique clinique de beaucoup d'opioïdes et les DDJ de l'OMS[22]. L'interprétation des études d'utilisation d'opioïdes par la population reposant sur les DDJ doit se faire avec précaution[22]. Ainsi, en complément des DDJ, on recommande l'analyse en équivalent en milligrammes de morphine orale, car la morphine est le médicament de référence pour le traitement de la douleur[18,23-25]. Il en est de même pour les benzodiazépines, étant donné que les DDJ reflètent mal l'exposition clinique, car elles ne prennent pas en compte la puissance de ces molécules. Ainsi, les investigateurs ont réalisé une analyse en équivalent en milligrammes de diazépam en complément des DDJ[25]. Cette unité permet une estimation de l'exposition pharmacologique de la population et une meilleure estimation de la puissance sédative[25].

Équivalent en milligrammes de morphine orale (EMM)

À partir des données de la littérature, des ratios d'équivalent en milligrammes de morphine orale par principe actif et par voie d'administration ont été établis pour les molécules de la classe des opioïdes (N02A), des alcaloïdes de l'opium et dérivés (R05D) et des anesthésiques généraux (N01A) (tableau 1)[18,20-25]. Les ratios ont par la suite été approuvés par un anesthésiste et un pharmacien. Les données ont été calculées comme suit : nombre total de DDJ du médicament considéré × le ratio d'équivalent de morphine × le ratio DDJ en mg divisé par le nombre total de jours-présence × 1000.

Équivalent en milligrammes de diazépam (EMD)

À partir du tableau d'équivalence des benzodiazépines proposé par Ashton[19] et des données de la littérature, des ratios d'équivalent en milligrammes de diazépam ont été déterminés pour les substances de la classe des anxiolytiques (N05B) et des hypnotiques et sédatifs (N05C) (tableau 1). Les données ont été calculées comme suit : DDJ/1000 jours-présence de la molécule × le nombre de milligrammes d'équivalent de diazépam.

RÉSULTATS

De 2003-2004 à 2017-2018, la consommation globale des substances contrôlées a diminué de 43 % au sein de notre établissement (min. 739 DDJ par 1000 jours-présence en 2017-2018; max. 1292 DDJ par 1000 jours-présence en 2003-2004).

Au cours de cette période, les principales classes thérapeutiques consommées sont par ordre décroissant : la classe des opioïdes (N02A), les hypnotiques et sédatifs (N05C), les anxiolytiques (N05B) et les anesthésiques généraux (N01A) (figure 1).

Les opioïdes

De 2003-2004 à 2017-2018, la consommation des opioïdes a diminué de 46 % avec un maximum en 2012-2013 (610 DDJ par 1000 jours-présence) et un minimum en 2017-2018 (314 DDJ par 1000 jours-présence).

En 2017-2018, les principales molécules consommées sont l'hydromorphone injectable (100 DDJ par 1000 jours-présence), suivie par la morphine injectable (70 DDJ par 1000 jours-présence), la codéine orale (58 DDJ par 1000 jours-présence) et le fentanyl injectable (45 DDJ par 1000 jours-présence) (figure 2A). Des résultats similaires sont observés en équivalent en milligrammes de morphine (R^2 = 0,98). Ainsi, l'hydromorphone injectable (7029 EMM par 1000 jours-présence) est la principale molécule consommée, suivie de la morphine injectable (6307 EMM par 1000 jours-présence) et du fentanyl injectable (5454 EMM par 1000 jours-présence). Toutefois, la codéine, dont la puissance est plus faible que celle de la morphine, se retrouve loin derrière la morphine injectable et le fentanyl injectable (583 EMM par 1000 jours-présence) (figure 3A).

Les hypnotiques et sédatifs

De 2003-2004 à 2017-2018, la consommation des hypnotiques et des sédatifs a diminué de 76 % avec un maximum en 2005-2006 (283 DDJ par 1000 jours-présence) et un minimum en 2017-2018 (65 DDJ par 1000 jours-présence). En 2017-2018, la principale molécule consommée est le midazolam injectable (58 DDJ par 1000 jours-présence). La principale modification observée est l'abandon du nitrazépam oral en 2015-2016 (figure 2B). Des résultats similaires sont observés en équivalent en milligrammes de diazépam (R^2 = 0,91) (figure 3B). On note 174 EMD par 1000 jours-présence pour le midazolam injectable.

Les anxiolytiques

De 2003-2004 à 2017-2018, la consommation des anxiolytiques a diminué de 24 % avec un maximum de 292 DDJ par 1000 jours-présence en 2007-2008 et un minimum de 184 DDJ par 1000 jours-présence en 2015-2016. Les principales variations observées sont la diminution de la consommation de lorazépam injectable depuis 2013 et l'augmentation de clobazam oral depuis 2014 (figure 2C). Des données similaires sont retrouvées en EMD (R^2 = 0,96) (figure 3C).

Les anesthésiques généraux

De 2003-2004 à 2017-2018, la consommation des anesthésiques généraux a augmenté de 7 %, avec un maximum

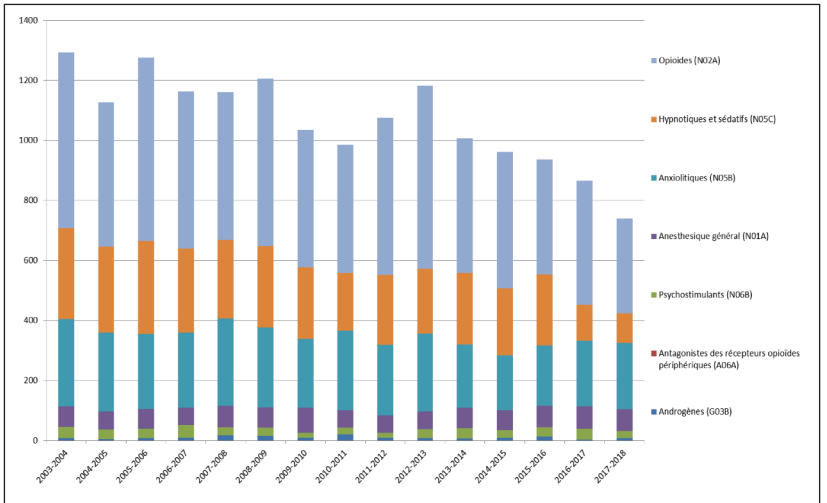

Figure 1. Profil des doses définies journalières (DDJ) par 1000 jours-présence par classe thérapeutique du 1er avril 2003 au 31 mars 2018.

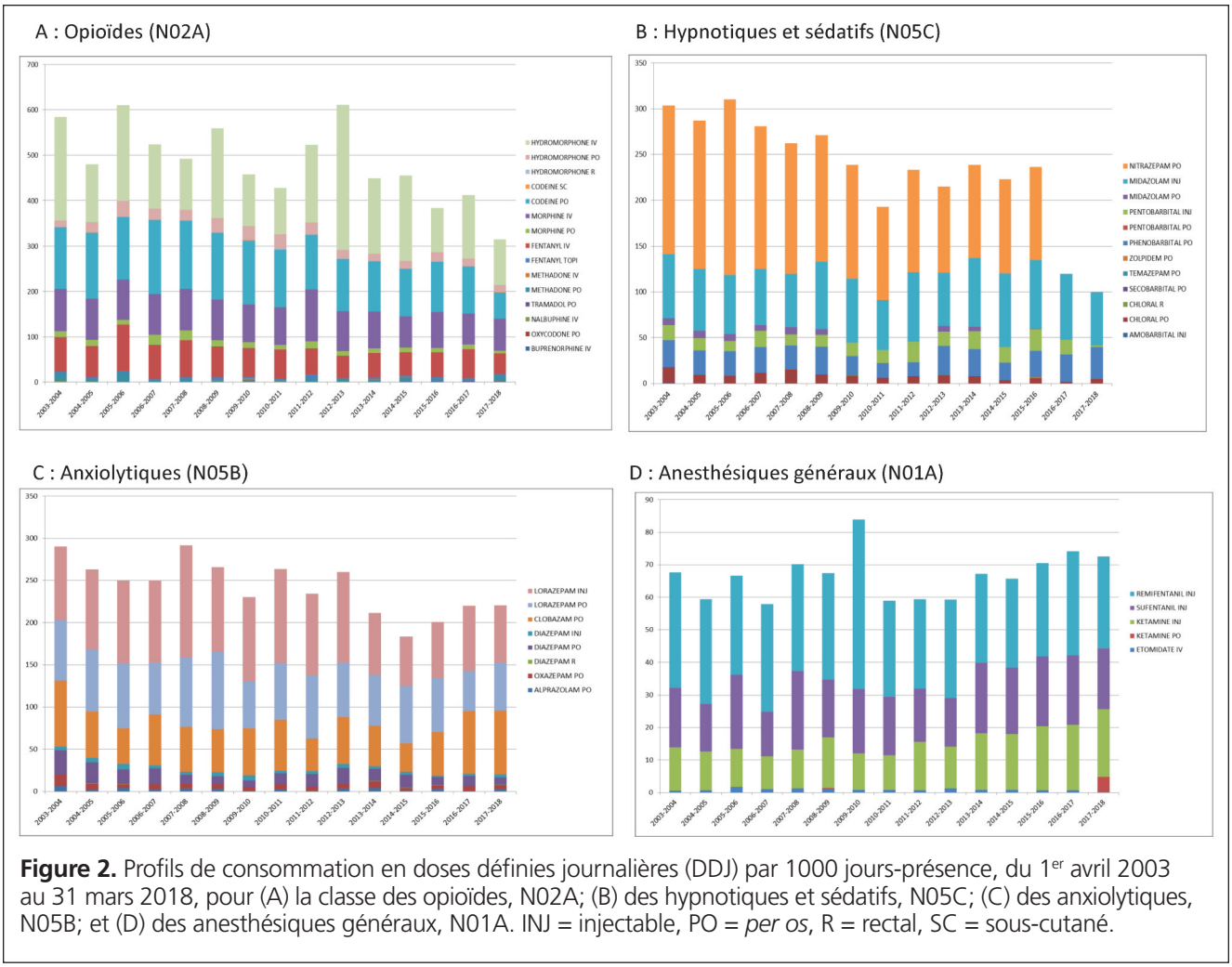

Figure 2. Profils de consommation en doses définies journalières (DDJ) par 1000 jours-présence, du 1er avril 2003 au 31 mars 2018, pour (A) la classe des opioïdes, N02A; (B) des hypnotiques et sédatifs, N05C; (C) des anxiolytiques, N05B; et (D) des anesthésiques généraux, N01A. INJ = injectable, PO = *per os*, R = rectal, SC = sous-cutané.

de 84 DDJ par 1000 jours-présence en 2009-2010 et un minimum de 58 DDJ par 1000 jours-présence en 2006-2007. Les principales molécules consommées en 2017-2018 sont le remifentanil injectable (28 DDJ par 1000 jours-présence), la kétamine injectable (21 DDJ par 1000 jours-présence) et le sufentanil injectable (19 DDJ par 1000 jours-présence) (figure 2D). Des données similaires sont retrouvées en EMM (R^2 = 0,86) (figure 3D).

Autres

En ce qui concerne les psychostimulants, la principale molécule consommée en 2017-2018 est le méthylphenidate oral (23 DDJ par 1000 jours-présence) (annexe 1, disponible au https://www.cjhp-online.ca/index.php/cjhp/issue/view/196/showToc). La testostérone injectable est le principal androgène consommé en 2017-2018 (annexe 2, disponible au https://www.cjhp-online.ca/index.php/cjhp/issue/view/196/showToc).

DISCUSSION

Cette étude originale présente l'évolution de la consommation des substances contrôlées sur une période de 15 ans au sein d'un établissement hospitalier mère-enfant canadien. Des travaux similaires sur les benzodiazépines ont notamment été effectués en Australie[26].

Notre étude propose une approche similaire à celle utilisée dans la gestion des antimicrobiens[27]. Afin de réduire les risques de résistance associés à la surutilisation des antimicrobiens, plusieurs autorités conseillent de surveiller le nombre de DDJ et le nombre de jours de traitement aux antimicrobiens afin de déterminer des changements de pratique qui ne respectent pas les règles d'utilisation[28-30]. Cette approche est associée à un meilleur contrôle d'utilisation en permettant une analyse des tendances[31]. Dans le cas des antimicrobiens, les établissements de santé ont développé des outils facilitant l'extraction des données et la production de rapports synthèses, ce qui n'est pas forcément le cas pour d'autres classes thérapeutiques de médicaments, comme les substances contrôlées.

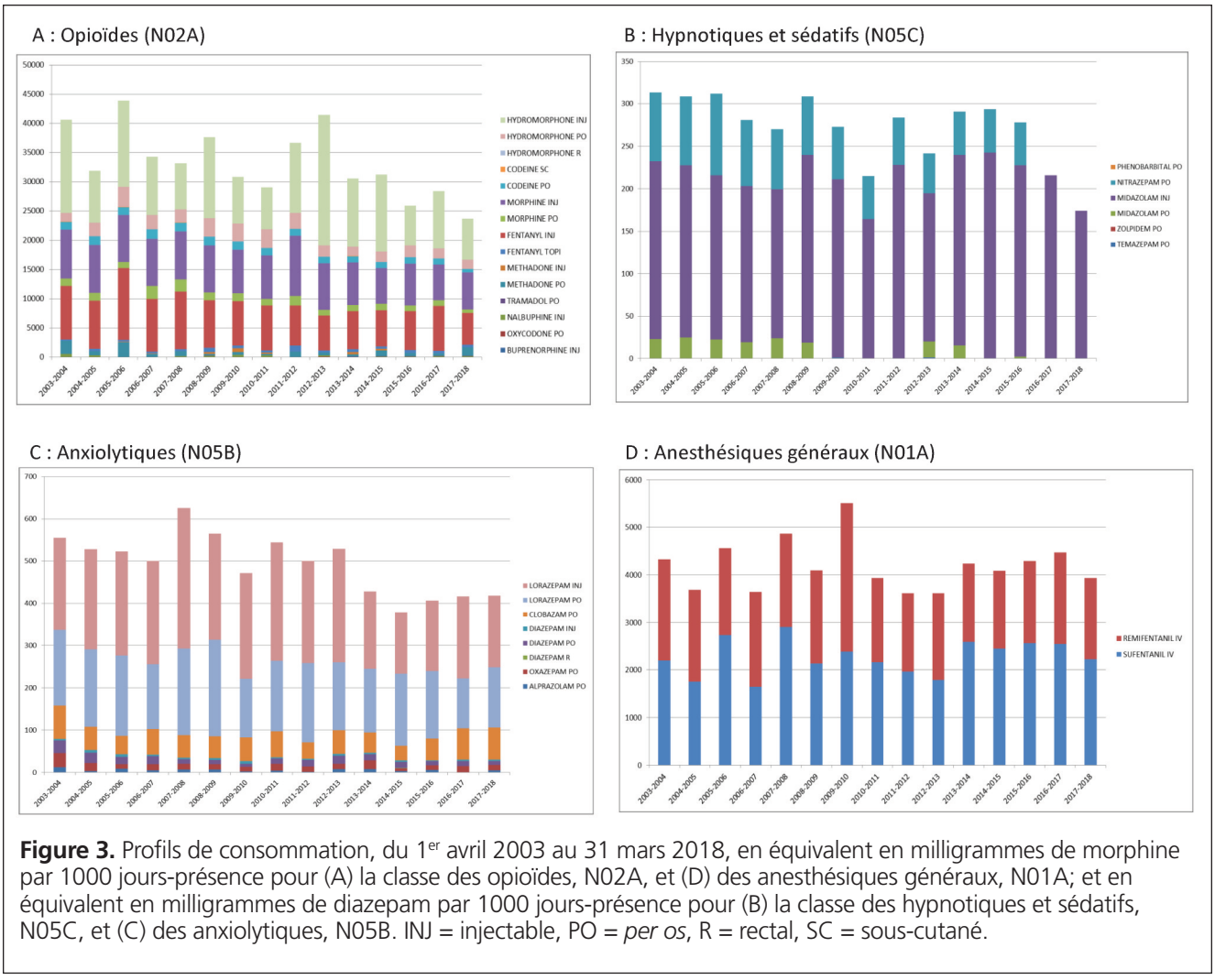

Figure 3. Profils de consommation, du 1er avril 2003 au 31 mars 2018, en équivalent en milligrammes de morphine par 1000 jours-présence pour (A) la classe des opioïdes, N02A, et (D) des anesthésiques généraux, N01A; et en équivalent en milligrammes de diazepam par 1000 jours-présence pour (B) la classe des hypnotiques et sédatifs, N05C, et (C) des anxiolytiques, N05B. INJ = injectable, PO = *per os*, R = rectal, SC = sous-cutané.

Nous observons une diminution de 43 % de la consommation globale des substances contrôlées de 2003-2004 à 2017-2018 ainsi qu'une diminution de la plupart des sous-classes évaluées, à l'exception des anesthésiques généraux. Plusieurs facteurs sont associés à cette diminution, notamment le virage ambulatoire en chirurgie, qui déplace de l'hôpital au domicile la prise de certaines doses par le patient, le recours à de nouvelles techniques chirurgicales moins invasives (p. ex. laparoscopie), la pénurie de certains médicaments (p. ex. opioïdes fabriqués par Sandoz en 2012, lorazépam à quelques reprises), le recours à l'anesthésie sans opioïdes (c.-à-d. kétamine, dexmédétomidine, lidocaine, etc.[32]), le retrait de la codéine comme analgésique postopératoire au profit d'anti-inflammatoires non stéroïdiens et de morphine ainsi que le retrait de la codéine orale des trousses d'automédication en obstétrique. En 2013, Santé Canada a recommandé que la codéine ne soit administrée qu'aux patients d'âge égal ou supérieur à 12 ans[33]. En 2016, un nouvel avis a été publié afin de préciser les situations cliniques où la codéine ne devrait pas être utilisée[34]. En 2019, un autre avis a été publié, déconseillant l'utilisation de produits contre la toux et le rhume contenant des opioïdes pour les enfants et les adolescents[35]. À l'échelle du Canada, l'Institut canadien d'information sur la santé a noté une diminution de la quantité globale de 4,9 % des opioïdes dispensés entre 2012 et 2016, soit 238 millions de DDJ en 2012 contre 226 millions de DDJ d'opioïdes en 2016[36]. Cette réduction nationale et locale n'est pas étrangère à la crise des opioïdes qui sévit au Canada et aux différentes initiatives de sensibilisation et d'actions mises en place au cours de la dernière décennie[37].

Bien que la diminution de la consommation d'opioïdes semble nécessaire au Canada, elle ne doit pas se faire au détriment de la prise en charge de la douleur des patients. En effet, l'augmentation de la consommation des opioïdes a longtemps été considérée comme un signe de meilleure prise en charge de la douleur (lien avec le PIB des pays et indicateur de développement humain élevé). Il existe donc un équilibre précaire entre une prise en charge optimale de la douleur et les prescriptions excessives, ces dernières pouvant conduire au mésusage, au détournement et à la dépendance[38].

En établissement de santé, la gestion des substances contrôlées est généralement bien encadrée compte tenu des exigences législatives et normatives et du circuit du médicament[15-17]. Par exemple, l'acquisition de substances contrôlées requiert une signature électronique de la part d'un pharmacien lors de l'achat et de la confirmation de la réception. L'entreposage à la pharmacie est sécurisé dans une voûte verrouillée sous surveillance avec la présence de caméras de surveillance. La dispensation et l'administration de doses de substances contrôlées aux patients requièrent la signature d'un soignant et d'un témoin et le processus repose sur l'utilisation de registres détaillés pour chaque étape applicable. En outre, des armoires sécurisées et parfois automatisées sont utilisées pour l'entreposage et la dispensation dans les unités de soins et les cliniques externes des établissements de santé. Toutefois, en dépit de toutes ces mesures de gestion, il n'existe pas de bonnes pratiques standardisées déterminant les modalités de surveillance de l'utilisation des substances contrôlées en établissement de santé, y compris les rapports de consommation.

Notre étude met en évidence l'intérêt de développer un programme de gestion des substances contrôlées, sur le même principe que la gestion des antimicrobiens. Par exemple, un sous-comité du comité de pharmacologie pourrait consulter périodiquement le profil de consommation des substances contrôlées en utilisant les DDJ, les EMM et les EMD, s'intéresser aux demandes de modifications de la liste locale, proposer des rétroactions aux grands prescripteurs de ces substances, encourager la tenue d'audits ciblés afin de réévaluer la pertinence de la prescription d'opioïdes. Dans la foulée des pratiques organisationnelles requises et de la norme sur la gestion des médicaments proposées par Agrément Canada, un critère explicite pourrait favoriser la gestion des substances contrôlées.

Limites

Cette étude comporte des limites. Les données recueillies correspondent à celles de la distribution (c.-à-d. quantités dispensées par la pharmacie au moyen des armoires automatisées ou de la distribution unitaire quotidienne au nom des patients) et incluent toutes les quantités mises au rebut ou détruites (doses partielles, expirées, etc.). L'analyse macro proposée ne permet pas de déterminer les situations avérées de vols ou de chapardage, compte tenu qu'elles sont limitées en occurrences et en quantités. Une analyse des données de consommation réelle par patient, par pathologie ou par parcours de soins pourrait apporter un éclairage complémentaire aux risques de mésusage. Le concept de DDJ a été élaboré dans un contexte de soins aux adultes. En gestion des antimicrobiens, nous utilisons plutôt le concept de nombre de jours de traitement, lequel serait moins pertinent pour décrire l'utilisation des substances contrôlées. À la différence des antimicrobiens, la dose des substances contrôlées varie selon l'indication, l'état clinique, la tolérance et l'exposition préalable.

CONCLUSION

La consommation des substances contrôlées et plus particulièrement des opioïdes est un enjeu de santé publique. Il y a une diminution de la consommation des substances contrôlées au sein de notre établissement de 2003-2004 à 2017-2018. Cette étude démontre la faisabilité de développer un outil de surveillance de la consommation des substances contrôlées en établissement de santé. Une telle approche pourrait être implantée à large échelle afin de favoriser les comparaisons entre les établissements.

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Sedative Medications for Critically Ill Children during and after Mechanical Ventilation: A Retrospective Observational Study

Deanna Caldwell, Jonathan Wong, and Mark Duffett

ABSTRACT

Background: Providing safe and effective sedation to critically ill children is challenging. The assessment, prevention, and treatment of symptoms of iatrogenic withdrawal are critical aspects of sedation practice.

Objective: To describe the use of sedative medications in critically ill children at McMaster Children's Hospital.

Methods: This retrospective observational study included children admitted over a 12-month period who survived their illness and who received sedation and at least 48 h of invasive ventilation. We collected data from the time of admission to the pediatric intensive care unit to 3 days after discontinuation of sedation.

Results: We included 67 children. The median age was 1.6 (interquartile range [IQR] 0.2–6.2) years, and respiratory illnesses were the most common reason for admission (41 [61%]). The children received invasive ventilation for a median of 7 (IQR 4–11) days and sedation for a median of 12 (IQR 6–20) days. Sixty-six children (99%) received an opioid, and all received a benzodiazepine, with median cumulative doses of 14 (IQR 5–27) mg/kg morphine equivalents and 15 (IQR 6–32) mg/kg midazolam equivalents. Dexmedetomidine was given to 31 children (46%), for a median of 8 (IQR 4–12) days. Most children (67%) received sedation after extubation (median duration 7 [IQR 4–14] days). In addition, 32 children (48%) continued to receive sedative medications after transfer to the ward, for a median of 6 (IQR 4–13) days. Forty-two children (63%) had at least one Withdrawal Assessment Tool-1 (WAT-1) score indicative of iatrogenic withdrawal. Children who experienced withdrawal were exposed to more opioids and more benzodiazepines, both per day and overall, and for longer periods.

Conclusions: The children in this study were exposed to multiple sedatives, and many continued to receive these medications for an extended period after discontinuation of mechanical ventilation. Iatrogenic withdrawal was common and represents an important opportunity to improve children's recovery after critical illness.

Keywords: pediatrics, sedation, withdrawal

RÉSUMÉ

Contexte : Il est difficile d'offrir une sédation sûre et efficace aux enfants gravement malades. L'évaluation, la prévention et le traitement des symptômes du sevrage iatrogène sont des aspects critiques de la pratique de la sédation.

Objectif : Décrire l'usage de sédatifs pour les enfants gravement malades à l'Hôpital pour enfants McMaster.

Méthodes : Cette étude observationnelle rétrospective comprenait des enfants admis sur une période de 12 mois, ayant survécu à leur maladie et ayant reçu une sédation ainsi qu'une ventilation effractive d'au moins 48 h. Nous avons recueilli des données à partir du moment de leur admission à l'unité de soins pédiatriques intensifs et jusqu'à trois jours après l'arrêt de la sédation.

Résultats : Nous avons inclus 67 enfants. L'âge moyen était 1,6 an (écart interquartile [IQR] 0,2–6,2), et les maladies respiratoires étaient la raison la plus fréquente (41 [61 %]). Les enfants ont reçu une ventilation effractive pendant 7 jours en moyenne (IQR 4–11) et une sédation pendant 12 jours en moyenne (IQR 6–20). Soixante-six (99 %) enfants ont reçu un opiacé et ils ont tous reçu une benzodiazépine, avec des doses moyennes cumulées équivalentes à 14 mg/kg (IQR 5–27) de morphine et des doses moyennes cumulées équivalentes à 15 (IQR 6–32) mg/kg de midazolam. Trente et un (46 %) enfants ont reçu de la dexmédétomidine pendant huit jours en moyenne (IQR 4–12). La plupart (67 %) des enfants ont reçu une sédation après l'extubation (durée moyenne 7 [IQR 4–14] jours). De plus, 32 (48 %) enfants ont continué de recevoir des sédatifs après leur transfert dans leur chambre, et cela pendant six jours en moyenne (IQR 4–13). Les scores de quarante-deux (63 %) des enfants obtenus grâce à l'Outil d'évaluation du sevrage, version 1 [WAT-1], révèlent un sevrage iatrogène. Les enfants ayant ressenti des symptômes de sevrage ont été exposés à davantage d'opiacés et de benzodiazépines, aussi bien chaque jour que de manière globale, mais également pendant des périodes prolongées.

Conclusions : Les enfants de cette étude ont été exposés à plusieurs sédatifs et bon nombre d'entre eux ont continué à recevoir ces médicaments pendant une période prolongée après l'arrêt de la ventilation mécanique. Le sevrage iatrogène se pratiquait couramment; il s'agit d'une belle occasion d'améliorer la convalescence des enfants après une maladie grave.

Mots-clés : pédiatrie, sédation, sevrage

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INTRODUCTION

Balancing the benefits and harms of sedatives in critically ill children is challenging. Sedatives are commonly used to reduce agitation and facilitate mechanical ventilation, but prolonged exposure to these medications is associated with poorer outcomes, including prolonged duration of mechanical ventilation, pediatric intensive care (PICU) stay, and iatrogenic withdrawal.[1-3] Despite the almost universal use of sedatives, the best approach for sedation liberation—the weaning and discontinuation of sedative medications, and the assessment, prevention, and treatment of iatrogenic withdrawal—remains unclear.

Withdrawal after prolonged exposure to sedatives is common in children, with estimates ranging from 45% to 86%.[4] This variation may be due to differences in patient populations, sedative exposure, and assessment methods among studies. The assessment of withdrawal is based on a combination of central nervous system symptoms (e.g., anxiety or agitation), gastrointestinal symptoms (e.g., vomiting or diarrhea), and autonomic symptoms (e.g., sweating or tachycardia) according to validated scores, such as the Withdrawal Assessment Tool version 1 (WAT-1)[5] or the Sophia Observation Withdrawal Symptoms Scale.[6] Two general approaches have been studied to reduce rates of withdrawal. The first of these are strategies to reduce sedative exposure, given that withdrawal has been associated with increased dose and duration of opioid and benzodiazepine exposure.[3,7] Both protocol-based sedation and the addition of an α-agonist have been studied, but without any difference in rates of withdrawal.[8-12] The second general approach involves various methods of weaning sedatives after extubation. It has been hypothesized that a slower rate of weaning may prevent withdrawal, but this has not been proven in studies to date. Two randomized controlled trials enrolling a total of 115 children compared methadone weaning schedules and found that different doses or durations of tapering were not associated with reduced incidence of withdrawal.[13,14] Unfortunately, children experiencing withdrawal generally require additional monitoring, additional sedative medications (including prolonged tapering), and longer stays in the PICU and in hospital than children not experiencing withdrawal.[2,3] In addition, the effects of withdrawal on the children themselves, on their families, and on clinicians have not been well studied.

The objective of this study was to describe the use of sedative medications in critically ill children at McMaster Children's Hospital, in Hamilton, Ontario, specifically the exposure to sedation (during and after mechanical ventilation), the incidence and duration of iatrogenic withdrawal, and the association between patient characteristics and medication exposure and withdrawal. Our ultimate goals were to inform local efforts to improve the management of sedation and to allow centres to compare their practices. This study also provides a foundation for future research on interventions to improve sedation-related outcomes and research to identify the most appropriate and efficient metrics to measure the process of liberating children from sedatives.

METHODS

Study Design

This retrospective observational study was conducted in a 12-bed, medical-surgical PICU at a tertiary academic centre that does not perform cardiac surgery. Sedation, including weaning of sedatives and management of withdrawal, is at the discretion of individual physicians, without set protocols. WAT-1 scoring is performed at the discretion of the clinical team when patients are thought to be at high risk of withdrawal or withdrawal is clinically suspected. We included all children who required invasive ventilation for a minimum of 48 h and who received at least 1 dose of any sedative between July 1, 2016, and June 30, 2017. We hypothesized that children receiving sedation for less than 48 h would be very unlikely to have sedation weaned or to experience withdrawal. We excluded children who were admitted for status epilepticus and those who did not survive to discharge from hospital. For children with multiple eligible PICU admissions, we selected 1 admission at random. This study was approved by the Hamilton Integrated Research Ethics Board, which waived the need for consent.

Data Collection and Outcomes

We extracted data from each child's medical records, including age, sex, weight, home use of opioids or benzodiazepines, and admission diagnosis, and we used the Pediatric Index of Mortality[15] and Pediatric Logistic Organ Dysfunction[16] scores to assess severity of illness. We also collected the WAT-1 scores documented by bedside nurses and the doses, routes, and modes of administration of all sedative and analgesic medications, from PICU admission to 72 h after discontinuation of sedation, or to hospital transfer or discharge, whichever occurred first.[5]

Data Analysis and Reporting

We converted all opioids to parenteral morphine equivalents (fentanyl 0.015 mg/kg and hydromorphone 0.15 mg/kg = morphine 1 mg/kg) and benzodiazepines to midazolam equivalents (lorazepam 0.3 mg/kg = midazolam 1 mg/kg).[8] For enterally administered drugs, we assumed bioavailability of 33% for opioids and 100% for lorazepam. To describe patterns of medication usage, we considered 3 phases of sedation: early mechanical ventilation (less than or equal to the first quartile of the overall duration of mechanical ventilation in this study), late mechanical ventilation (greater than the first quartile), and after extubation. We considered a WAT-1 score of 3 or more as indicating iatrogenic withdrawal on that day and assumed that a patient was not experiencing withdrawal if no WAT-1 scores were documented. We reported the data as medians (with interquartile ranges [IQRs]) or counts (with percentages). We used the Mann-Whitney *U* test and the Fisher exact test to compare those with

and without withdrawal. We used R software, version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria), to perform the analyses and $p < 0.05$ as the criterion for statistical significance.

RESULTS

Included Children

We included 67 children between 3 days and 16 years of age (median 1.6 [IQR 0.2–6.2] years). Figure 1 shows the study flow diagram, and Table 1 shows the characteristics of the included children. The most common type of reason for admission was respiratory illness (41 [61%]). The children received invasive mechanical ventilation for a median of 7 (IQR 4–11) days and were admitted to the PICU for a median of 10 (IQR 6–14) days.

Exposure to Sedatives

Overall, children in this study received 11 different sedatives and received sedation for a median of 12 (IQR 6–20) days. Table 2 lists the sedatives received along with their respective durations of exposure. All children received a benzodiazepine, and 66 (99%) received an opioid, for a median duration of 9 (IQR 4–15) and 10 (IQR 5–19) days, respectively (Table 2). The median day on which children reached their peak opioid and benzodiazepine dose was day 3 (IQR 2–6) and day 4 (IQR 2–6), respectively. Sixty-two children (93%) received sedative agents other than opioids and benzodiazepines, with dexmedetomidine and propofol being the most common. Similar to opioids and benzodiazepines, dexmedetomidine was used for a median of 8 (IQR 4–12) days, but the peak dose occurred later, at a median of day 7 (IQR 6–10) days. The children were exposed to a median cumulative dose of 14 (IQR 5–27) mg/kg morphine equivalents and 15 (IQR 6–32) mg/kg midazolam equivalents. Doses given on an as-needed basis contributed to 25% and 30% of the total doses of opioids and benzodiazepines, respectively.

Almost all children (66 [99%]) received multiple sedatives (maximum 7) from multiple drug classes. Figure 2 shows the patterns of drug choice and combinations for the early (days 1 to 4) and late (day 5 to extubation) phases of mechanical ventilation and after extubation. After extubation, 45 children (67%) received sedative medications for a median of 7 (IQR 4–14) days. Twenty-five children (37%) continued to receive sedatives by continuous infusion for a median of 3 (IQR 1–3) days, and 36 (54%) received oral medications for a median of 9 (IQR 4–14) days. Additionally, 32 children (48%) received sedative medication after transfer to the ward, for a median of 6 (IQR 4–13) days.

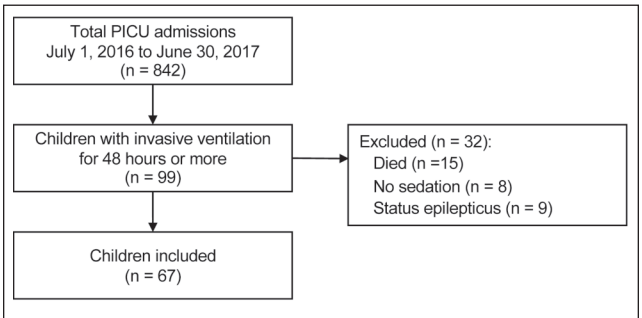

Figure 1. Study flow diagram.
PICU = pediatric intensive care unit.

Table 1. Characteristics of Included Children

Characteristic	No. (%) of Children* (*n* = 67)
Age	
< 1 month	6 (9%)
1–12 months	25 (37%)
1–5 years	19 (28%)
6–12 years	10 (15%)
> 12 years	7 (10%)
Sex, male	43 (64%)
Weight (kg) (median and IQR)	10 (5–21)
Opioid or benzodiazepine use before PICU admission	4 (6%)
Predicted risk of death†	
Median (IQR)	1.1% (0.8%–3.7%)
Maximum	33%
PELOD score (maximum per patient)	
Median (IQR)	12 (2–21)
Maximum	32
Reason for PICU admission	
Medical	56 (84%)
Bronchiolitis	24 (36%)
Pneumonia	9 (13%)
Sepsis or septic shock	5 (7%)
Neurologic	6 (9%)
Other medical	12 (18%)
Surgical	9 (13%)
Trauma	2 (3%)
Duration of admission (days)	
PICU	
Median (IQR)	10 (6–14)
Maximum	68
Hospital	
Median (IQR)	17 (11–29)
Maximum	152
Duration of invasive ventilation (days)	
Median (IQR)	7 (4–11)
Maximum	35
Disposition on PICU discharge	
Ward	59 (88%)
Home	6 (9%)
Another PICU	2 (3%)

IQR = interquartile range, PELOD = Pediatric Logistic Organ Dysfunction, PICU = pediatric intensive care unit.
*Except where indicated otherwise.
†Based on the Pediatric Index of Mortality score.[15]

Table 2. Sedatives Used

Medication	Duration of Therapy (Days) Median (IQR)	Timing; No. (%) of Children Receiving Medication (*n* = 67)			
		Any Time	Early (Days 1–4)	Late (Day 5 to Extubation)*	After Extubation
Opioids					
Any opioid	10 (5–19)	66 (99%)	62 (93%)	50 (98%)	40 (60%)
Continuous infusion	7 (3–10)	60 (90%)	54 (81%)	41 (80%)	20 (30%)
Fentanyl	6 (2–9)	60 (90%)	55 (82%)	39 (76%)	14 (21%)
Continuous infusion	6 (3–9)	51 (76%)	45 (67%)	35 (69%)	11 (16%)
Hydromorphone	10 (5–16)	32 (48%)	12 (18%)	22 (43%)	26 (39%)
Continuous infusion	7 (3–11)	10 (15%)	6 (9%)	5 (10%)	8 (12%)
Morphine	2 (1–6)	43 (64%)	27 (40%)	18 (35%)	17 (25%)
Continuous infusion	3 (2–3)	15 (22%)	10 (15%)	8 (16%)	2 (3%)
Remifentanil	1 (1–1)	0	0	1 (2%)	0
Benzodiazepines					
Any benzodiazepine	9 (4–15)	67 (100%)	63 (94%)	49 (96%)	35 (52%)
Lorazepam	4 (2–10)	50 (75%)	23 (34%)	31 (61%)	32 (48%)
Midazolam	6 (4–9)	65 (97%)	61 (91%)	46 (90%)	16 (24%)
Continuous infusion	6 (3–9)	62 (93%)	57 (85%)	43 (84%)	15 (22%)
Alpha agonists					
Any α-agonist	16 (7–28)	35 (52%)	19 (28%)	31 (61%)	28 (42%)
Clonidine	9 (7–16)	26 (39%)	1 (1%)	7 (14%)	26 (39%)
Dexmedetomidine	8 (4–12)	31 (46%)	18 (27%)	27 (53%)	21 (31%)
Other sedatives					
Any other sedative	6 (2–10)	62 (93%)	53 (79%)	43 (84%)	13 (19%)
Chloral hydrate	3 (2–6)	28 (42%)	17 (25%)	21 (41%)	7 (10%)
Ketamine	1 (1–1)	23 (34%)	14 (21%)	10 (20%)	2 (3%)
Continuous infusion	3 (2–4)	3 (4%)	2 (3%)	1 (2%)	0
Propofol	3 (2–6)	60 (90%)	47 (70%)	43 (84%)	8 (12%)
Continuous infusion	2 (1–2)	39 (58%)	16 (24%)	28 (55%)	3 (4%)

*The denominator for this column is the 51 children who were ventilated for 5 days or more.

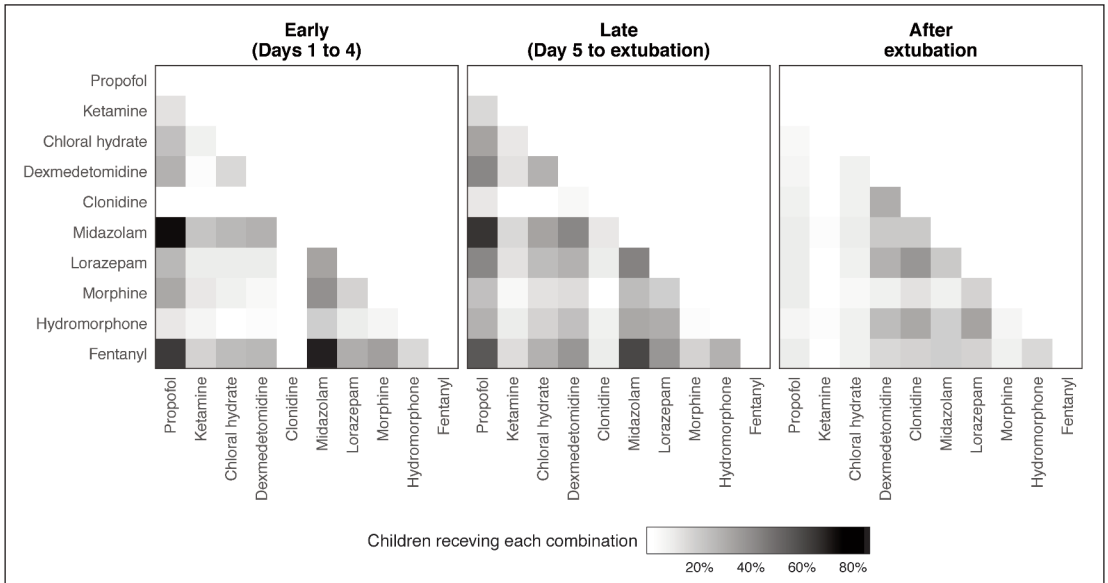

Figure 2. Medication combinations used for early sedation (days 1 to 4), for late sedation (day 5 to extubation), and after extubation. The shading of each square is proportional to the percentage of children who received that combination. This figure excludes remifentanil, of which 2 bolus doses were given to 1 patient for a single procedure.

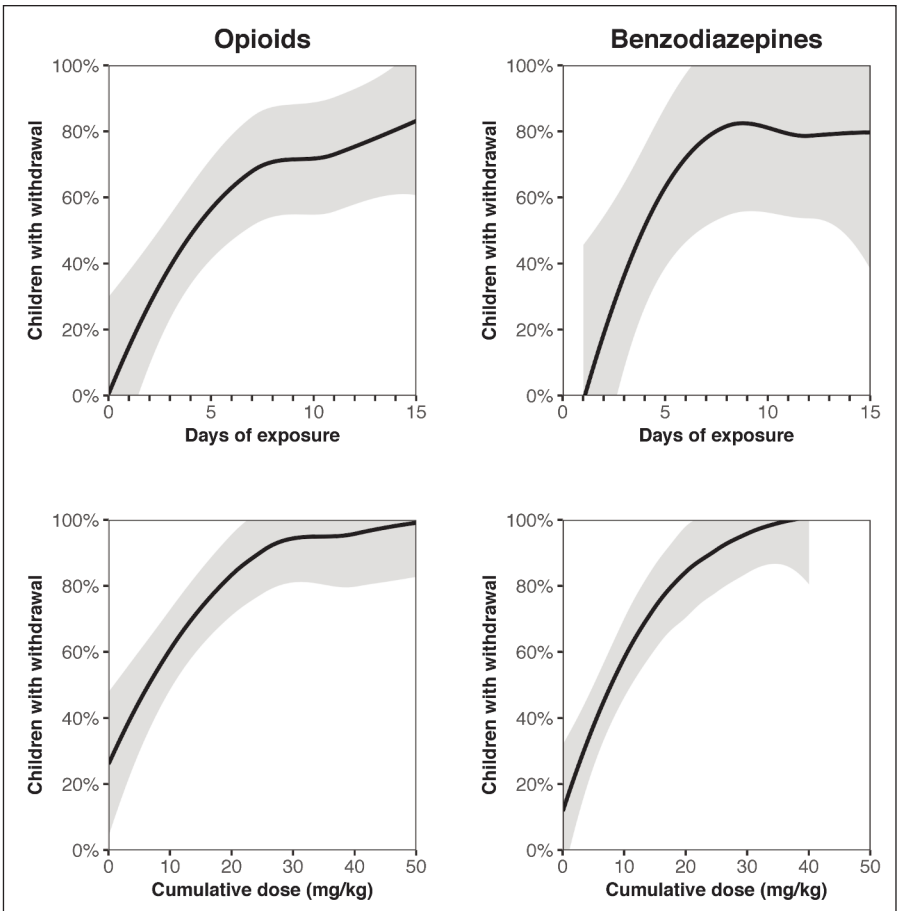

Figure 3. Occurrence of withdrawal in relation to duration and cumulative dose of opioids and benzodiazepines. The black line shows the percentage of children who experienced withdrawal according to the duration of exposure or cumulative dose before the first recorded instance of withdrawal. The shaded area shows the 95% confidence interval.

Iatrogenic Withdrawal

WAT-1 scores were documented for 47 children (70%). These children were assessed a median of 41 (IQR 21–82) times in total on a median of 9 (IQR 5–16) days each. The median number of scores documented per day was 5 (IQR 4–5). Forty-two (63%) of the 67 children had at least one WAT-1 score of 3 or more, indicating iatrogenic withdrawal. Withdrawal first occurred at a median of 5 (IQR 7–11) days after PICU admission. The median duration of withdrawal was 4 (IQR 2–8) days, and 18 children (43% of those in withdrawal and 27% of all children in the study) experienced withdrawal on the ward after discharge from the PICU. Figure 3 shows the association between the occurrence of withdrawal and the duration and cumulative dose of opioids and benzodiazepines. There were no differences in age or severity of illness, but compared with children who did not experience withdrawal, those who did experience withdrawal were exposed to higher total doses of opioids, benzodiazepines, and dexmedetomidine before their first recorded instance of withdrawal (Table 3, Figure 4). In addition, they required more days of ventilation and stayed longer in the PICU and in hospital.

DISCUSSION

In this retrospective observational study, we found that children were exposed to many different sedatives and that the patterns of use changed over the course of their illness and recovery. Many continued to receive sedatives for an extended period after discontinuation of mechanical ventilation and after transfer to the ward. Iatrogenic withdrawal was common, and the frequency of withdrawal was greater with higher doses and longer duration of sedation.

Our overall findings with respect to sedation exposure and withdrawal are consistent with those from other centres in North America. In a randomized controlled trial (RCT), Curley and others[8] compared protocol-based sedation with usual care in 2449 children in 31 PICUs in the United States. The patients at our centre, when compared with the usual care group in the RCT,[8] had similar duration of ventilation (median 7 versus

Table 3. Characteristics of Children Who Did and Did Not Experience Withdrawal

Characteristic	Group; Median (IQR)*		*p* Value†
	Withdrawal (*n* = 42)	No Withdrawal (*n* = 25)	
Age (years)	1.3 (0.4–4.5)	2.3 (0.1–7.6)	0.71
Sex, male, no. (%) of children	32 (76%)	11 (44%)	0.002
No. (%) with opioid or benzodiazepine use before PICU admission	3 (7%)	1 (4%)	> 0.99
Predicted risk of death‡	1.0% (0.6%–2.9%)	2.8% (0.9%–4.2%)	0.11
Opioids§			
Total dose (mg/kg morphine equivalents)	8 (13–25)	4 (1–7)	< 0.001
Dose per day (mg/kg morphine equivalents)¶	2.5 (1.5–3.2)	0.6 (0.3–1.2)	< 0.001
Days of therapy	7 (6–8)	5 (3–8)	< 0.001
Benzodiazepines§			
Total dose (mg/kg midazolam equivalents)	20 (14–31)	5 (2–8)	< 0.001
Dose per day (mg/kg midazolam equivalents) ¶	2.7 (1.8–3.6)	1.2 (0.4–1.9)	< 0.001
Days of therapy	7 (6–8)	4 (2–6)	< 0.001
Dexmedetomidine§			
Total dose (mg/kg)	62 (0–136)	0 (0–0)	< 0.001
Dose per day (mg/kg)¶	18 (9–20)	15 (10–16)	0.32
Days of therapy	4 (0–6)	0 (0–0)	< 0.001
Clinical outcomes			
Invasive ventilation (days)	8 (6–11)	4 (3–5)	< 0.001
PICU stay (days)	11 (8–15)	5.5 (3–10)	< 0.001
Hospital stay (days)	19 (14–33)	11 (6–17)	0.002

IQR = interquartile range, PICU = pediatric intensive care unit.
*Except where indicated otherwise.
†Mann-Whitney *U* test or the Fisher exact test.
‡Using the Pediatric Index of Mortality score.[15]
§For the withdrawal group, these data include only drugs given before the first day of withdrawal.
¶Dose administered on days that the patient was exposed to the drug.

7 days), similar duration of opioid therapy (median 10 versus 10 days), similar total doses of opioids (14 versus 18 mg/kg) and benzodiazepines (15 versus 14 mg/kg), and similar incidence of withdrawal (63% versus 68%), respectively. There were also some differences, particularly with respect to the medications used after extubation. None of the children at our centre received methadone, and 39% received clonidine, whereas in the usual care group of Curley and others[8] these rates were 30% and 13%, respectively. In our study, increased dose and duration of opioids, benzodiazepines, and dexmedetomidine were all associated with withdrawal. Although opioids and benzodiazepines are well-established risk factors for withdrawal, we hypothesize that the effect of dexmedetomidine represents confounding by indication, whereby this drug was selectively used for children at high risk of withdrawal.

The results of this study highlight the importance of sedation liberation and the need for quality improvement and further research. We observed a high incidence of iatrogenic withdrawal, which affected the majority of children ventilated for longer than 48 h. In addition, we observed prolonged administration of sedatives after extubation, for a median of 7 days, which was similar to the median duration of ventilation. We hypothesize that withdrawal and the sedation liberation process may have important effects on quality of life for both children and their parents, as well as on clinician workload. We were unable to measure such effects in our study, but if present, they could be due to withdrawal symptoms, adverse effects of medications, and delay of children's return to normal functioning after their critical illness (through prolongation of the need for IV access, increased acuity of care, and need for additional monitoring). The results of this study also highlight the importance of a system-wide approach to managing care for these children and improving their recovery from critical illness. After transfer to the ward, almost one-third of the children (29%) continued to experience withdrawal, and nearly half (48%) continued to receive sedative medications. Clearly, weaning and discontinuation of sedation and iatrogenic withdrawal are challenges for clinicians on pediatric and surgical wards, not just within the PICU.

To facilitate quality improvement and research studies of interventions to improve this process, future studies should focus on defining the most appropriate and efficient metrics to measure the process of liberating children from sedatives. Such studies should investigate methods to describe children's sedative exposure, given that almost all critically ill children receive multiple medications and given that the dose, duration, timing, and choice of drugs, as well as the duration and complexity of the weaning process, are all potentially relevant factors. Additionally, the effects of score-based diagnosis, including use of the WAT-1

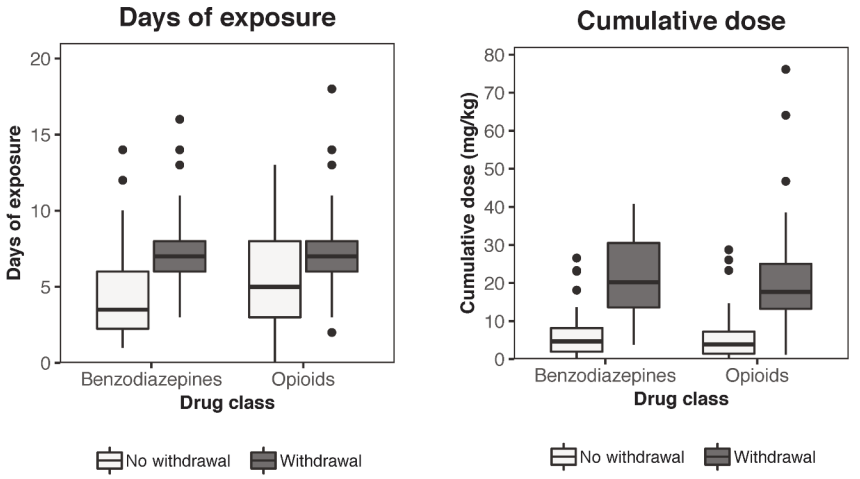

Figure 4. Duration and cumulative dose of opioids and benzodiazepines in children with and without withdrawal. This figure shows the duration of exposure and cumulative dose before the first recorded instance of withdrawal. The line in each box indicates the median, the edges of each box indicate the first and third quartiles, and the whiskers extend to 1.5 × interquartile range. Data beyond the end of the whiskers are plotted individually. $p < 0.001$ for all comparisons.

score, on clinical, patient, and parental outcomes should be assessed. We defined withdrawal as a single score of 3 or more; other criteria may be more specific. Throughout the course of each child's illness and recovery, medication doses were frequently titrated and sedation targets and medication choices were changed; as a result, we were unable to determine, as we had intended, when the sedation weaning process for each child began. Finally, insight into the priorities and preferences of patients, families, and clinicians with regard to sedation, weaning, and withdrawal are critical to selecting outcomes for future studies of interventions to improve the sedation liberation process.

The strengths of this study included its broad inclusion criteria and granular, daily data collection. In addition, we collected data from before and after extubation and from both the PICU and the ward, to capture the full trajectory of each child's illness and recovery. We included all eligible children admitted to the PICU during a complete calendar year to minimize the effect of seasonal variation and differences among prescribers. This study also had some limitations. We were unable to measure some aspects of the process of discontinuing sedation, such as the clinical rationale for drug choices and dosing, nor could we measure clinician workload. We could not distinguish medications given for sedation or withdrawal from those that were administered for analgesia or procedures. Not all children were assessed for withdrawal with the WAT-1 score. Because this scoring was completed according to clinical suspicion, it is possible that the true incidence of withdrawal was higher. In addition, delirium scores were not routinely used at the time of this study. We were also unable to fully assess the risk factors for withdrawal because of the small number of children, both overall and among those who did not experience withdrawal. Finally, although our results were consistent with those of other studies, the extent to which our local practice is generalizable to other centres is uncertain because of differences in patient population, sedation protocols, and sedative agents of choice.

CONCLUSION

In this retrospective observational study, we found that children were exposed to many different sedatives and that patterns of use changed over the course of their illness and recovery. Many of the children continued to receive sedatives for an extended period after mechanical ventilation was discontinued. Iatrogenic withdrawal remained common and represents an important opportunity to improve children's recovery after critical illness.

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Compounded Topical Amitriptyline for Neuropathic Pain: In Vitro Release from Compounding Bases and Potential Correlation with Clinical Efficacy

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ABSTRACT

Background: Topical amitriptyline has been described as having mixed clinical efficacy for neuropathic pain. A few case reports using higher concentrations of this compound found clinical benefit, but many of these studies did not describe the components used in formulating the amitriptyline preparations.

Objective: To generate reproducible clinical measures of the characteristics of amitriptyline diffusion from selected compounding bases, to support a scientific approach to base selection when compounding this drug for neuropathic pain.

Methods: Amitriptyline hydrochloride (1%, 5%, and 10%) was compounded with 3 proprietary compounding bases: Lipoderm base, Emollient Cream, and Mediflo 30 pluronic lecithin organogel (PLO) gel. In vitro release of the drug from each base and subsequent permeation across artificial human skin were investigated with the Franz diffusion system. Amitriptyline release mechanisms were determined with kinetic models. How quickly and to what extent the drug leaves each base to diffuse through the skin were characterized by determining steady-state flux, cumulative permeation, and lag times.

Results: Release of amitriptyline was significantly higher from the Mediflo PLO gel than from the Lipoderm base or Emollient Cream ($p < 0.05$). Mean cumulative drug release after 24 h, from the 10% formulation, was 23.9% (standard deviation [SD] 4.1%) for Lipoderm base, 41.8% (SD 3.1%) for Emollient Cream, and 53.2% (SD 7.7%) for Mediflo PLO gel. A high percentage of amitriptyline was retained in all 3 bases. Although amitriptyline release was highest with Mediflo PLO gel, this base resulted in significantly lower cumulative permeation relative to Lipoderm base and Emollient Cream ($p < 0.05$). There was a strong overall correlation between amitriptyline concentration, lag time, and flux. Higher concentrations were associated with significantly lower lag times and increased flux. The highest lag time and flux were observed for Mediflo PLO gel.

Conclusion: These data indicate that the therapeutic effectiveness of compounded amitriptyline for neuropathic pain depends on its diffusion out of the compounding bases and penetration through the skin.

RÉSUMÉ

Contexte : L'efficacité clinique de l'amitriptyline topique contre les douleurs neuropathiques a été décrite comme étant variable. Quelques rapports utilisant des concentrations plus élevées de cette base indiquent des avantages cliniques, mais bon nombre d'entre eux ne décrivent pas les composants des préparations d'amitriptyline.

Objectif : Établir des mesures cliniques reproductibles des caractéristiques de la diffusion de l'amitriptyline selon une approche scientifique de la sélection des bases pour la préparation de ce médicament contre les douleurs neuropathiques.

Méthodes : Le chlorohydrate d'amitriptyline (1 %, 5 % et 10 %) a été mélangé à trois bases de préparations magistrales brevetées : la base Lipoderm, la crème émolliente et le gel Mediflo PLO 30. La libération *in vitro* du médicament de chaque base et la perméation qui s'en est suivie dans la peau humaine artificielle ont été étudiées à l'aide du système de diffusion Franz. La définition des mécanismes de libération de l'amitriptyline repose sur des modèles cinétiques. La rapidité et la durée de libération du médicament de chaque base pour se diffuser dans la peau ont été caractérisées par la détermination du flux constant, de la perméation cumulée et des temps de latence.

Résultats : La libération de l'amitriptyline était sensiblement plus élevée quand le produit était mélangé au gel Mediflo PLO plutôt qu'à la base Lipoderm ou à la crème émolliente ($p < 0,05$). La libération cumulée du médicament, formule 10 %, après 24 h était de 23,9 % (écart type [É.T.] ± 4,1 %) avec la base Lipoderm; 41,8 % (É.T. ± 3,1 %) avec la crème émolliente et 53,2 % (É.T. ± 7,7 %) avec le gel Mediflo PLO. Les trois bases retenaient un pourcentage élevé d'amitriptyline. Bien que la libération d'amitriptyline était plus élevée en présence du gel Mediflo PLO, la perméation cumulée de cette base par rapport à celle de la base Lipoderm et de la crème émolliente était sensiblement moins élevée ($p < 0,05$). L'observation a révélé une forte corrélation générale entre la concentration d'amitriptyline, le temps de latence et le flux. Les concentrations plus élevées étaient associées à des temps de latence sensiblement moins élevés. C'est le gel Mediflo PLO qui a démontré une supériorité du temps de latence et du flux.

Keywords: neuropathic pain, compounding, amitriptyline, compounding bases, transdermal drug absorption

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Conclusion : Ces données indiquent que l'efficacité thérapeutique de la préparation d'amitriptyline contre les douleurs neuropathiques dépend de sa diffusion hors des bases dans les préparations magistrales et de sa pénétration dans la peau.

Mots-clés : douleurs neuropathiques, base, amitriptyline, bases pour préparations magistrales, absorption transdermique de médicaments

INTRODUCTION

According to the International Association for the Study of Pain, neuropathic pain is "pain caused by a lesion or disease of the somatosensory nervous system".[1] This means that the mechanisms leading to the pain involve the brain, spinal cord, and descending modulation systems.[2] Amitriptyline produces analgesia in neuropathic pain by inhibiting voltage-gated sodium channels in the peripheral nerves.[3] This mechanism is comparable to the effect of local anesthetics (e.g., lidocaine) that block sodium channels, leading to anesthesia, which is the rationale for their effectiveness as topical analgesics.[4] Amitriptyline, a tricyclic antidepressant, is often used for neuropathic pain.[5] It has a relatively high logP value[6,7] and low molecular weight (313.86 g/mol),[8] important attributes that facilitate its permeation across the skin.

Topical application of a medication has the advantage of circumventing many adverse effects associated with oral formulations (e.g., dizziness, drowsiness, dry mouth, blurred vision, urinary retention, weight gain, and tachycardia).[9] However, there is limited information on the stability of compounded products, release of the medication from compounding bases, and permeation across the skin. In the literature, evidence for efficacy is mixed, partly because of the relatively low amitriptyline concentrations in tested topical preparations.[9] Lynch and others[10] conducted a double-blind, randomized, placebo-controlled 3-week study evaluating the efficacy of topical 2% amitriptyline, 1% ketamine, and a combination of the 2 medications. They found no significant difference in pain scores among the 3 groups and no systemic absorption. Other controlled trials using low concentrations (≤ 5% amitriptyline) had similar outcomes.[11-13] Limited information exists regarding the types of bases used and the formulation/compounding methods. For studies involving higher drug concentrations, more consistent results have been obtained. For instance, according to case reports, patients experienced significant pain relief with amitriptyline concentrations ranging from 5% to 10%.[14-16] In their literature review, Kopsky and Hesselink[14] found that among patients who received topical amitriptyline, 10% had a better pain response; however, one patient had trouble concentrating. More recently, a high concentration (10%) of topical amitriptyline was reported to be effective for chemotherapy-induced peripheral neuropathy, which allowed chemotherapy to be administered at effective doses.[17] However, a previously published systematic review found no evidence to support the use of low-dose amitriptyline (2%) for this condition,[18] an indication that strength of the formulation is important for topical use of amitriptyline in the management of chemotherapy-induced peripheral neuropathy.

Drug release from formulation excipients and subsequent permeation through the stratum corneum of the skin are highly dependent on physicochemical properties, drug concentration, and properties of the vehicle.[19] Many studies that have examined the efficacy of topical amitriptyline alone either have used pluronic lecithin organogel (PLO) or have not identified the compounding bases. For those that used PLO, no rationale was given to justify this choice.[20] Amitriptyline is a highly lipophilic, small-molecular-weight compound, which means that the physicochemical characteristics of the compounding base must be considered when studying the rate and extent of amitriptyline release. The stability of the drug in the selected base and the absorption enhancement characteristics of that base are other important considerations.

The current study aimed to generate reproducible clinical measures of the characteristics of amitriptyline diffusion from selected compounding bases, to support a scientific approach to base selection when pharmacists are compounding the drug for topical application. To achieve this aim, we compared the in vitro release characteristics of amitriptyline compounded with 3 proprietary compounding bases: Lipoderm base, Emollient Cream, and Mediflo 30 PLO gel. The permeation of 1%, 5%, and 10% formulations across synthetic human skin was used to estimate skin permeation. The compounding bases were selected because of their popularity and frequency of use for compounding topical drugs in many pharmacies.

MATERIALS AND METHODS

Materials

Amitriptyline hydrochloride, Lipoderm base, and Emollient Cream were obtained from Professional Compounding Centers of America (Houston, Texas). Mediflo 30 PLO gel was purchased from Medisca Inc (Saint-Laurent, Quebec). Ethoxy diglycol was

purchased from Galenova Inc (Saint-Hyacinthe, Quebec). Monobasic sodium phosphate monohydrate and phosphoric acid were obtained from Sigma-Aldrich (Oakville, Ontario), while analytical grade acetonitrile was from Fisher Scientific (New Jersey). Deionized water was processed using a Nanopure II filtering system (Barnstead Lab Water Products). Phosphate-buffered saline (PBS) 10× was bought from Sigma-Aldrich. Strat-M membrane was acquired from EMD Millipore (Billerica, Massachusetts). The coarse cellulose filter paper was purchased from Fisher Scientific (Ottawa, Ontario). Cellulose acetate membranes with a pore size of 0.47 µm were obtained from Geotech Environmental Equipment Inc (Denver, Colorado). Tuffryn membrane filters with a pore size of 0.45 µm were obtained from Pall Corporation (Ann Arbor, Michigan).

Instrumentation

Franz cells and a V-series stirrer were purchased from Perme-Gear, Inc (Hellertown, Pennsylvania). An Ecoline E100 heated water bath circulator (Lauda-Brinkmann, Lauda-Koenigshofen, Germany) was used to maintain the cells at a specific temperature. A Varian-920 liquid chromatograph with a quaternary gradient pump, autosampler with 50-µL sample loop, an ultraviolet-visible detector, and Galaxie chromatographic software (Varian Inc, Walnut Creek, California) was used for sample analysis. Chromatographic separation was performed with a µBondapack 125 Å (3.9 mm × 300 mm; 10 µm) C18 column (Waters Corporation, Milford, Massachusetts).

Quantification of Amitriptyline

Spectrophotometric methods for amitriptyline are complicated and result in low sensitivity.[21-23] Therefore, the *United States Pharmacopoeia* (USP) high-performance liquid chromatography method was used.[24] The mobile phase was prepared by combining phosphate buffer and acetonitrile in a 58:42 ratio v/v, vacuum-filtering through a 0.22-µm nylon filter, and degassing for 20 min. The chromatographic method was previously validated for specificity, linearity, range, accuracy, precision, limit of detection, and limit of quantification, in accordance with the International Conference on Harmonization guidelines.[25]

Preparation of Compounded Amitriptyline

Amitriptyline HCl was compounded with Lipoderm base, Emollient Cream, and Mediflo 30 PLO gel. Three different concentrations (1%, 5%, and 10%) were made with each base. To prepare the formulations, an appropriate amount of amitriptyline was weighed and triturated to produce a fine powder using mortar and pestle. The required amount of ethoxy diglycol was added to the fine powder and levitated to produce a smooth paste. Each base was added to the prepared paste using the principles of geometric dilution. The cream was transferred to a jar, mixed using an Unguator electronic mortar and pestle (Gako, Norman, Oklahoma), and processed once through an Exakt 50 ointment mill (Exakt Technologies Inc, Oklahoma City, Oklahoma). The resulting amitriptyline formulations in Lipoderm base, Emollient Cream, and Mediflo 30 PLO gel were placed in Ecolo-Jar ointment jars (EcoloPharm, Chambly, Quebec).

In Vitro Drug Release and Permeation Studies

To characterize the release rate of amitriptyline from the various topical formulations, the in vitro Franz diffusion cell system was used (diffusion area 0.64 cm^2 and receptor medium capacity 5 mL). The system was maintained at a constant temperature of 32 ± 0.5 °C with the heated water bath circulator. A 5-mL volume of PBS (pH 7.4) was added slowly from a pipette to each Franz cell through the receptor chamber orifice. Small magnetic stir bars were placed into the receptor chambers of each cell, and the system was equilibrated for a minimum of 60 min.

To investigate amitriptyline release, cellulose membranes were soaked in PBS for 30 min. Each wetted membrane was placed on top of one receptor chamber with the Teflon O-ring and donor chamber placed over the membrane and secured with a metal clamp. Each compounded amitriptyline formulation (100 ± 0.5 mg) was applied on the membrane with a glass rod. The mass of the glass rod was recorded before and after each application to determine the exact quantity applied. One cell, containing the base with ethoxy diglycol only, was reserved as a blank. Both the sampling port opening and the donor chamber chimney were covered with Parafilm. Samples (0.5 mL) were drawn at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h. The volume of receptor medium taken during each sampling was replaced with fresh PBS. Cumulative drug release was calculated using a standard equation[26]:

$$Q = (\mathrm{C_n V} + \sum_{i=1}^{n-1} Ci\ S)$$

where C_n is the concentration of drug determined at the nth sampling interval, V is the volume of the Franz diffusion cell, $\sum_{i=1}^{n-1} Ci$ is the sum of concentrations of drug determined at sampling intervals 1 through $n - 1$, and S is the surface area of the sample membrane.

To determine the mechanism of drug release from each of the formulations, the data were analyzed with the first-order, second-order, Higuchi, Korsmeyer-Peppas, and Hixon-Crowell kinetic models.

Amitriptyline permeation studies were conducted identically to the drug release studies except a different membrane was used and neither the receptor nor the sampling port was covered during the experiments. Strat-M membrane, which is an in vitro membrane model that functionally simulates drug permeation through human skin, was placed on the receptor. Each topical formulation was tested in triplicate, and flux and lag times were calculated. The steady-state flux was the slope divided by the diffusional area from the linear portion of the cumulative drug

permeation graph, whereas lag time was the *x*-intercept. Additionally, after the permeation experiments were completed, the Strat-M membrane and the diffusion cell were rinsed with deionized water, which was then used to determine overall drug recovery.

Statistical Analysis

Differences between mean cumulative amitriptyline release or permeation at each time point were determined using 2-way statistical analysis of variance with Tukey multiple-comparison post hoc tests using GraphPad Prism software version 7.0 (GraphPad Software Inc, San Diego, California) with 95% confidence intervals.

RESULTS

In Vitro Amitriptyline Release from Compounding Bases

Cumulative release of amitriptyline from the 10% formulation in each of the 3 bases is shown in Figure 1A. There was no significant difference in amitriptyline release from Lipoderm base and Emollient Cream in the first 4 h ($p < 0.05$). However, after 4 h, significantly more amitriptyline was released from the Emollient Cream than from the Lipoderm base ($p < 0.05$). At all time points after 3 h, release of drug from Mediflo PLO gel was significantly higher than release from the other 2 bases ($p < 0.05$). Mean cumulative drug release after 24 h was 23.9% (standard deviation [SD] 4.1%) for Lipoderm base, 41.8% (SD 3.1%) for Emollient Cream, and 53.2% (SD 7.7%) for Mediflo PLO gel. A high percentage of amitriptyline was retained in all 3 bases.

Cumulative release of amitriptyline from the 5% formulation in each of the 3 bases (Figure 1B) followed a similar pattern, except that no significant difference was observed between Mediflo PLO gel and Emollient Cream beyond 6 h ($p > 0.05$). However, there was no difference among the 3 bases in the first 2 h ($p > 0.05$). As for the 10% formulation, there was significantly less amitriptyline release from the Lipoderm base at all time points after 4 h ($p < 0.05$). Mean cumulative drug release after 24 h was 23.6% (SD 4.1%) for Lipoderm base, 40.8% (SD 3.1%) for Emollient Cream, and 39.7% (SD 2.8%) for Mediflo PLO gel. Figure 1C shows significant differences in cumulative amitriptyline release from the 1% formulation in all 3 bases. After 2 h, more amitriptyline was released from Mediflo PLO gel than from the other 2 bases ($p < 0.05$). Also, significantly more drug was released from the Emollient Cream than from the Lipoderm base ($p < 0.05$). Mean drug release after 24 h was 35.5% (SD 4.6%) for Emollient Cream and 64.0% (SD 13.8%) for Mediflo PLO gel; release from Lipoderm base was much lower, at about 10%. Consistently less amitriptyline was released from Lipoderm base than from any other base, regardless of drug concentration.

The fact that a significant amount of drug was retained in all 3 bases compelled us to explore potential amitriptyline release

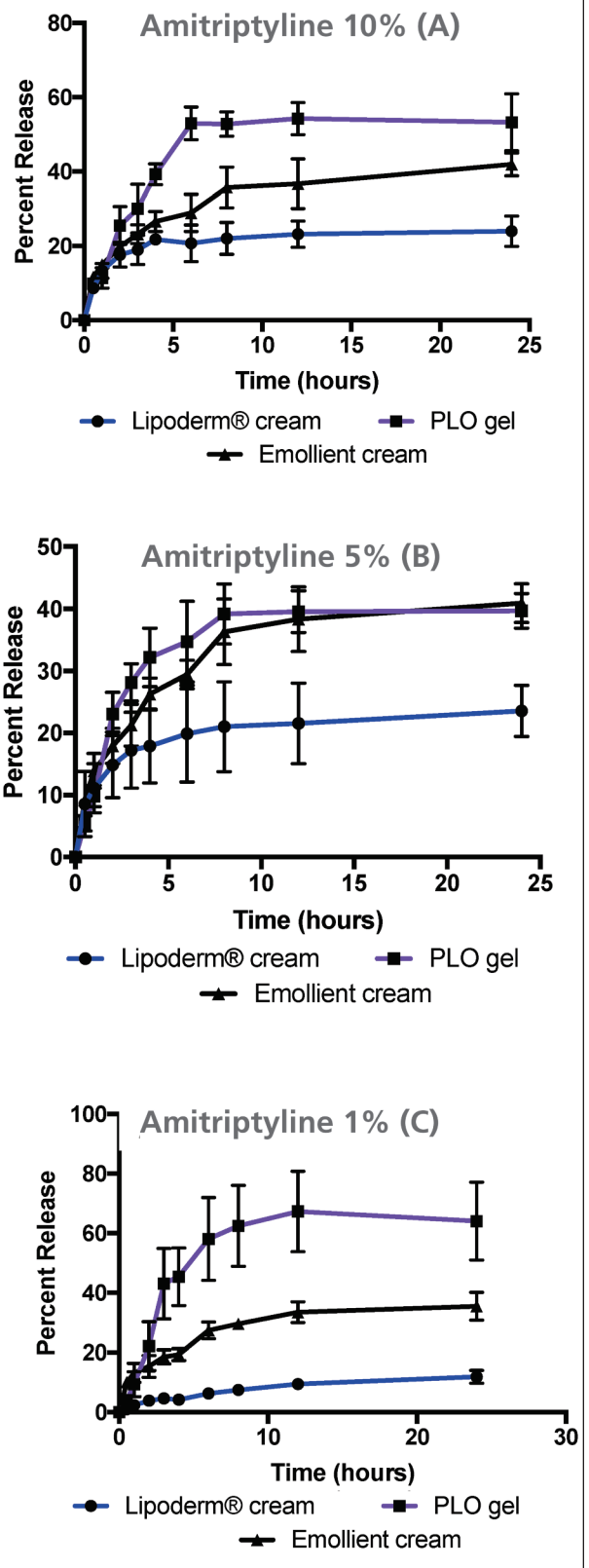


Figure 1. Cumulative release of amitriptyline from each of the 3 bases. (A) 10% formulation of amitriptyline; (B) 5% formulation of amitriptyline; (C) 1% formulation of amitriptyline.

mechanisms (Table 1). The R^2 values for amitriptyline compounded with Lipoderm base, Emollient Cream, and Mediflo PLO gel were highest with the Higuchi model, which implies that the drug was released from the bases according to this model. However, the R^2 values for the Korsmeyer-Peppas model were also relatively high, which suggests drug release by multiple mechanisms. The slope of the linear regression equations for the Korsmeyer-Peppas model was used to confirm whether other release mechanisms contributed to amitriptyline release from the bases. All slopes for release of amitriptyline (1%, 5%, and 10% formulations) from Lipoderm base and Mediflo PLO gel were between 0.5 and 1, which suggests anomalous release. However, release of amitriptyline (1%, 5%, and 10% formulations) from Emollient Cream had slopes below 0.5, which implies release by Fickian diffusion.

In Vitro Amitriptyline Permeation across Simulated Skin

Permeation of 10% amitriptyline through Strat-M membrane varied with the base used (Figure 2A). Although the highest amitriptyline release occurred with Mediflo PLO gel, this base resulted in significantly lower cumulative permeation at all time points relative to Lipoderm base and Emollient Cream ($p < 0.05$).

The cumulative permeation of 5% amitriptyline through Strat-M synthetic skin is illustrated in Figure 2B. At this concentration, no significant difference in permeation was observed between Lipoderm base and Emollient Cream ($p > 0.05$). Surprisingly, when the amitriptyline concentration in Mediflo PLO gel was reduced from 10% to 5%, no drug permeation occurred. Decreased and erratic permeation was observed when amitriptyline concentration was reduced from 5% to 1%. For the most part, there was no permeation, although in some instances unreliable, up-and-down, nonpredictable permeation occurred (Figure 2C). For instance, the mean 4-h permeation of amitriptyline 1% was 0.43% (SD 0.04%) in Lipoderm base and 0.37% (SD 0.24%) in Emollient Cream, with no further permeation beyond that time point.

The total quantity of amitriptyline that permeated the membrane over 24 h (expressed as a percentage relative to the amount applied) is summarized in Figure 3. At 10% amitriptyline, mean permeation through Strat-M membrane was 16.8% (SD 0.9%) for Lipoderm base, 15.4% (SD 1.5%) for Emollient Cream, and 9.3% (SD 1.5%) for Mediflo PLO gel. Significantly lower permeation occurred with Mediflo PLO gel ($p < 0.05$), but no difference was observed between Lipoderm base and Emollient Cream ($p > 0.05$). At 5% amitriptyline, mean permeation was 10.9% (SD 0.9%) for Lipoderm base, 9.7% (SD 0.5%) for Emollient Cream, and 0% for Mediflo PLO gel. Significantly less permeation occurred with Mediflo PLO gel ($p < 0.05$), but no difference between Lipoderm base and Emollient Cream ($p > 0.05$) was observed. Decreasing the amitriptyline strength from 10% to 5%, and further from 5% to 1%, resulted in significant differences in the total percent permeation ($p < 0.05$). Total amitriptyline recovery from Strat-M membrane, the receptor medium, and equipment was within acceptable limits (90%–110%).

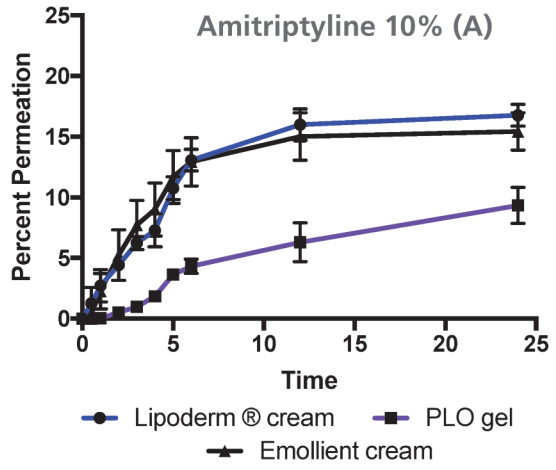
Lag time refers to the time needed for a drug to start passing through the skin, which may signify its onset of action. At 5% and 10% strengths, amitriptyline compounded with Lipoderm base permeated the skin rapidly, with the flux of 10% strength almost double that of the 5% preparation (Table 2). For amitriptyline in Emollient Cream, permeation began after about 45 min for the 5% formulation and after about 7 min for the 10% formulation. There was a strong overall correlation among amitriptyline concentration, lag time, and flux. Higher concentrations were associated with significantly reduced lag times and increased flux. The highest lag time and flux were observed for Mediflo PLO gel.

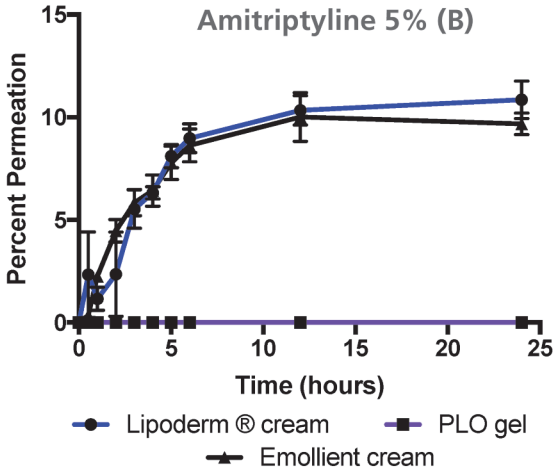
DISCUSSION

In vitro drug release testing and the subsequent investigation of active ingredient permeation through the skin from semisolid

Table 1. Modelling of Mean Amitriptyline Release

	Model; R^2 Value				
% Amitriptyline in Vehicle	**Higuchi**	**First-Order**	**Second-Order**	**Hixon-Crowell**	**Korsmeyer-Peppas**
Lipoderm base					
10%	0.9801	0.4059	0.4319	0.4232	0.8302
5%	0.9621	0.5404	0.5369	0.5260	0.8168
1%	0.9809	0.856	0.8687	0.8645	0.7179
Emollient Cream					
10%	0.9843	0.6709	0.7371	0.7155	0.9521
5%	0.9944	0.6616	0.7141	0.6974	0.9558
1%	0.9771	0.6793	0.7252	0.7104	0.8732
Mediflo 30 PLO gel					
10%	0.9745	0.4724	0.5136	0.5005	0.7939
5%	0.9452	0.4961	0.5337	0.5212	0.824
1%	0.9819	0.543	0.6015	0.3441	0.844





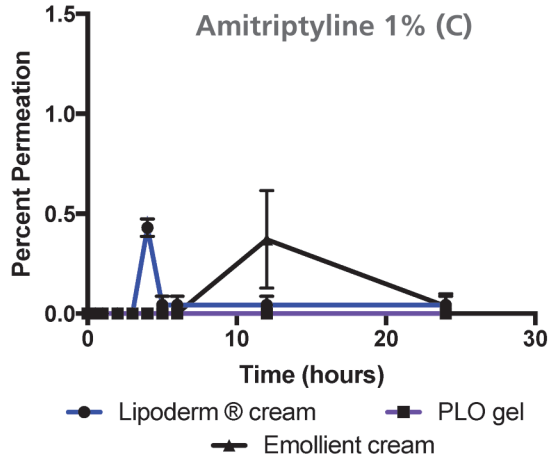


Figure 2. Permeation of amitriptyline through Strat-M membrane. (A) 10% formulation of amitriptyline; (B) 5% formulation of amitriptyline; (C) 1% formulation of amitriptyline.

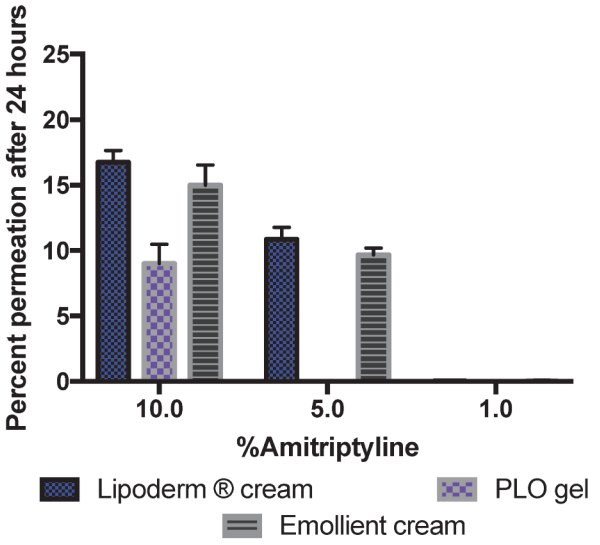


Figure 3. Total quantity of amitriptyline that permeated Strat-M membrane over 24 h, as percentage relative to the amount applied.

Table 2. Lag Times and Flux of Amitriptyline Permeation Through Strat-M Synthetic Human Skin

% Amitriptyline in Vehicle	Lag Time (min)	Flux (mg/h per cm²)
Lipoderm base		
10%	0	0.2601
5%	0	0.1458
Emollient Cream		
10%	6.8	0.3878
5%	46.3	0.1459
Mediflo 30 PLO gel		
10%	47.6	0.0913

preparations are essential in formulation development, quality control procedures, and prediction of in vivo performance of a product.[27]

In addition to aiding in formulation development, in vitro drug release testing serves to compare the performance of different noncommercial compounded medications with various bases and excipients.[26] According to the USP, "The vertical diffusion cell (VDC) system is a simple, reliable, and reproducible means of measuring drug release from semisolid dosage forms".[28] In this system, topical formulations are placed on a membrane support in the donor chamber, and the released drug diffuses to the acceptor chamber, from where samples are collected at specific intervals for analysis with a suitable analytical method.

The selection and composition of the vehicle play a critical role in drug release and permeation behaviour, which ultimately hinders or enhances clinical response.[26]

In this study, the compounding of amitriptyline with various bases was investigated for release of the drug from the compound-

ing bases and subsequent permeation across Strat-M, a synthetic membrane that mimics the morphology of human skin.[29,30] The Strat-M product was selected for this study because of its high in vitro – in vivo correlation for a variety of active pharmaceutical ingredients. It also offers lower sample variability than human skin.[29-31]

Several patient case reports and controlled trials have used topical amitriptyline for treating peripheral neuropathic pain. However, there is a surprising absence of vehicle description, as well as release and permeation data. In trials that did show evidence for efficacy, higher concentrations (> 5%) were used, whereas studies that used lower strengths and cases in which the compounding bases were described as "PLO" resulted in no benefits.[14-16] Our data may shed some light on these reported observations. The release of amitriptyline from all formulations most closely followed the Higuchi kinetic model, which suggests that its release was controlled mainly by its rate of diffusion from the upper areas of the vehicles toward the surface exposed to the membrane.[32] However, relatively high R^2 values were calculated with the Korsmeyer-Peppas model, which implies the possible involvement of other release mechanisms.[33] Amitriptyline release from Emollient Cream (1%, 5%, and 10% formulations) had slopes under 0.5, implying release by Fickian diffusion. All of the slopes for amitriptyline release from Lipoderm base and Mediflo PLO gel (1%, 5%, and 10% formulations) were between 0.5 and 1. The mechanism, in this case, follows non-Fickian or anomalous transport, meaning that vehicle swelling and/or erosion contributed to drug release.[33]

Despite these potential mechanisms of amitriptyline release, we found that amitriptyline compounded with Mediflo PLO gel at 1% and 5% strengths did not permeate through the artificial skin membrane. The result was similar with the 1% formulation in Emollient Cream and Lipoderm base, where a minimal quantity of the drug was detected at the 12- and 4-h time points, respectively. Low lag time and high flux are important characteristics of topical analgesics because, with typical patient use, the topical formulation may be rubbed or washed off in a short period. As shown in Table 2, amitriptyline 5% in Lipoderm base had high flux, whereas amitriptyline 10% in Emollient Cream had low lag time. The lack of clinical efficacy in formulations containing less than 5% amitriptyline makes sense given poor permeation at that concentration. Overall, amitriptyline 5% or 10% compounded in Lipoderm base or Emollient Cream resulted in the highest drug permeation and low lag times.

On the basis of our data, it was evident that substantial amounts of amitriptyline remained in the bases and were unavailable for diffusion across the skin. Ironically, the vehicle that resulted in the highest overall amitriptyline release (Mediflo PLO gel) had the highest lag time and the least permeation over a 24-h period. Theoretically, for this base, more amitriptyline was available to permeate through the skin,[34] but its comparatively lower flux suggests that drug release and permeation should be optimized for individual drugs before choosing a particular base for compounding specific drugs for patient use. The in vitro data generated through the permeation experiments with the Strat-M membrane reflects the most absorption that could potentially occur, given that in vitro methods tend to overestimate in vivo absorption in human subjects.[35] For instance, topically applied drugs are often rubbed or washed off after a relatively short period, which was not the case during the in vitro permeation studies.

CONCLUSION

Our in vitro drug release and permeation data for amitriptyline revealed that roughly half of the active drug was retained in all 3 formulations after 24 h. This ultimately affected drug permeation in compounded formulations with less than 5% amitriptyline. These data indicate that the ability of amitriptyline to diffuse from various compounding bases and the absorption-enhancing properties of these bases are essential in ensuring optimal drug release, permeation through the skin, and perhaps therapeutic effectiveness. Pharmacists should, therefore, ask the suppliers of compounding bases to provide drug release and possibly permeation data that justify the use of a specific base for compounding topical pain medications.

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Stability of Methadone Hydrochloride for Injection in Saline Solution

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ABSTRACT

Background: Until October 2014, methadone hydrochloride for injection (10 mg/mL) was available in Canada through Health Canada's Special Access Programme. Diluted to 5 mg/mL in saline, it was used in pediatrics for acute and cancer-related pain. More recently, the department of pharmacy of the Centre hospitalier universitaire Sainte-Justine in Montréal, Quebec, proposed compounding a solution of methadone hydrochloride for injection (5 mg/mL) from bulk powder and saline solution for pediatric administration.

Objective: To assess the stability of the proposed compounded preparation.

Methods: Solutions of methadone hydrochloride in saline were prepared from bulk powder and stored in clear glass vials for up to 180 days at room temperature (25 °C) or with refrigeration (5 °C), with testing on days 0, 7, 14, 30, 60, 90, and 180. The appearance of the solutions and presence of particulate matter were assessed. A stability-indicating high-performance liquid chromatography (HPLC) method was developed to assay the concentration of methadone over time.

Results: No notable changes in appearance of the methadone solution were observed, particle counts did not exceed limits specified by the *United States Pharmacopeia*, and no microbial growth was observed. The HPLC analysis showed that the concentration of methadone remained above 90% on all study days.

Conclusions: Methadone hydrochloride for injection prepared from bulk powder in saline solution at a concentration of 5 mg/mL remained chemically stable for at least 180 days when stored in clear glass vials at 5 °C and at 25 °C.

Keywords: methadone, powder, injection, stability

RÉSUMÉ

Contexte : Jusqu'en octobre 2014, le chlorhydrate de méthadone pour injection (10 mg/mL) était disponible au Canada à l'aide du Programme d'accès spécial de Santé Canada. Dilué à 5 mg/mL dans une solution saline, il était utilisé en pédiatrie contre les douleurs aigües et celles liées au cancer. Plus récemment, le département de pharmacie du Centre hospitalier universitaire Sainte-Justine de Montréal au Québec a proposé de préparer une solution de chlorhydrate de méthadone pour injection (5 mg/mL) à partir d'une poudre en vrac et d'une solution saline en vue de l'administrer en pédiatrie.

Objectif : Évaluer la stabilité de la préparation proposée.

Méthodes : Les préparations de chlorhydrate de méthadone diluées dans une solution saline se font à partir d'une poudre en vrac, elles sont stockées dans des fioles en verre transparent pendant180 jours à la température ambiante (25 °C) ou réfrigérées (5 °C) et sont soumises à des tests les jours 0, 7, 14, 30, 60, 90 et 180. L'apparence des solutions et la présence de substances particulaires ont fait l'objet d'une évaluation. Une méthode de chromatographie liquide à haute performance (CLHP) indiquant la stabilité a été développée pour tester la concentration de méthadone dans le temps.

Résultats : Aucun changement notable de l'apparence de la solution de méthadone n'a été observé, le nombre de particules ne dépassait pas les limites précisées par l'*United States Pharmacopeia* et aucune croissance microbienne n'a été observée. L'analyse CLHP a indiqué que la concentration de méthadone était demeurée au-delà de 90% durant toute la durée de l'étude.

Conclusions : Le chlorhydrate de méthadone pour injection préparé à partir de poudre en vrac dans une solution saline à une concentration de 5 mg/mL est resté chimiquement stable pendant au moins 180 jours lorsqu'il était stocké dans des fioles en verre transparent à 5 °C et à 25 °C.

Mots-clés : méthadone, poudre, injection, stabilité

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INTRODUCTION

Methadone is a long-acting opiate analgesic with μ-receptor agonist activity.[1] It is approved for the treatment of severe chronic pain and opiate addiction in adult patients. It can be administered orally or intravenously in its salt form, methadone hydrochloride.[2] The dosage is individualized according to many factors, including the severity of the pain and the patient's tolerance of opioid analgesic.[3]

In the pediatric setting, methadone can be used in palliative care, for severe and chronic cancer-related nociceptive and neuropathic pain, for refractory noncancer pain, and for weaning from opioid therapy.[4-6] In the hospital care setting, it is important to have access to an IV formulation of methadone as an alternative opioid therapy for pain that is refractory to conventional opioid treatment or to avoid treatment interruption for patients who are already receiving methadone and are unable to take medications by mouth. It has been proposed that methadone hydrochloride for injection (5 mg/mL) be compounded from bulk powder and saline solution for the purpose of pediatric administration. This study was undertaken to determine the stability of the proposed compounded preparation.

METHODS

A compounded formulation of methadone hydrochloride (5 mg/mL) was prepared aseptically from bulk powder dissolved in saline solution on October 27, 2016. More specifically, methadone hydrochloride USP powder (10 g, lot 12766-5313, expiry January 2017; Galenova Inc, Saint-Hyacinthe, Quebec) was dissolved in saline solution (2 L, 0.9%, lot w6i06ml, expiry March 2018; Baxter, Mississauga, Ontario) and then filtered through a sterile 0.22-μm membrane into 10-mL clear sterile glass vials (100 vials per batch, 2 batches in total). Twelve vials were used for the initial analyses, 50 vials were stored at 5 °C ± 2 °C, and the remaining 50 vials were stored at 25 °C ± 2 °C. At predetermined time points (0, 7, 14, 30, 60, and 90), 3 vials from each temperature condition were retrieved for analysis. At the end of the study (180 days), 9 vials from each temperature condition were retrieved for analysis. Unused vials and residual volumes of solution were destroyed at the end of the study or were used for microbial testing.

On each study day, each vial was inspected for visual appearance against a white and black background, and the concentration of methadone in the solution was assayed using a stability-indicating high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection. At the beginning and the end of the study, a particle count was obtained using a light obscuration method (LS-20 particle counter, Lighthouse Worldwide Solutions, Fremont, California).

The particle count was performed initially and at the end of the study (180 days) using combined solutions from 2 vials (total volume 20 mL), repeated 3 times (i.e., total of 6 vials). To count the particles in each 20-mL sample, a first fraction (4 mL) was used to flush the instrument, then 3 counts (using 5 mL each) were performed; the remaining solution was discarded. The specification was based on test 1.B of General Chapter <788> in the *United States Pharmacopeia–National Formulary*, for solutions intended for injection supplied in containers smaller than 100 mL: "The preparation complies with the test if the average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10 μm and does not exceed 600 per container equal to or greater than 25 μm."[7]

For the HPLC analyses, each test sample (20 μL) was placed in an HPLC injection vial, diluted with a 20:80 mixture of methanol and water (1000 μL), and mixed with a vortex mixer (20 s). Solutions for HPLC analysis (nominal concentration 98 μg/mL) were analyzed immediately after preparation using an HPLC system (Prominence UFLC, Shimadzu, Laval, Quebec) equipped with an LC-20AD binary pump, a DGU-20A5 solvent degasser, a SPD-M20A multiple-wavelength photodiode array detector set at 220 nm, an SIL-20AC HT refrigerated autosampler set at 5 °C, a CTO-20AC column oven set at 40 °C, and a Kinetex XB-C18 column (4.6 × 100 mm, 5 μm, Phenomenex, Torrance, California). An isocratic method (1:1 methanol: phosphate buffer, 20 mmol/L, pH 3) with a flow rate of 0.9 mL/min was used. The methadone peak eluted at approximately 5.5 min; the peak area was used to perform the quantification. Six test samples were prepared for the initial analysis, whereas 3 test samples were prepared for each condition of the stability study. Each test sample (10 μL) was injected in duplicate ($n = 6 \times 2$ at time zero and $n = 3 \times 2$ for each time point during the stability study). The HPLC analysis of collected samples was performed at each study time point.

To perform the calibration, a stock solution of methadone base in methanol (1 mg/mL, lot FE06221502, expiry July 2020; Cerilliant Corporation, Round Rock, Texas) was diluted to concentrations of 80, 90, 100, 110, and 120 μg/mL using a methanol-water mixture (20:80) and analyzed by HPLC (r^2 not less than 0.999; $n = 3$). The 100 μg/mL standard was also injected after every 24 sample injections to ensure system stability ($n = 3$). The highest intraday coefficient of variation observed was 0.4% ($n = 3$, all concentrations) and the highest interday coefficient of variation was 1.57% (3 consecutive days, $n = 3 \times 3$, target concentration).

Aliquots (0.5 mL) of a methadone stock solution prepared at 5 mg/mL in saline solution were mixed with water (0.5 mL), aqueous solution of 3% hydrogen peroxide (0.5 mL), hydrochloric acid 1 mol/L (0.5 mL), and sodium hydroxide 1 mol/L (0.5 mL) and then submitted to forced degradation by heating at 60 °C for 4 h. After cooling, aliquots (40 μL) of these solutions were diluted with the 20:80 mixture of methanol and water (960 μL) and assayed by HPLC.

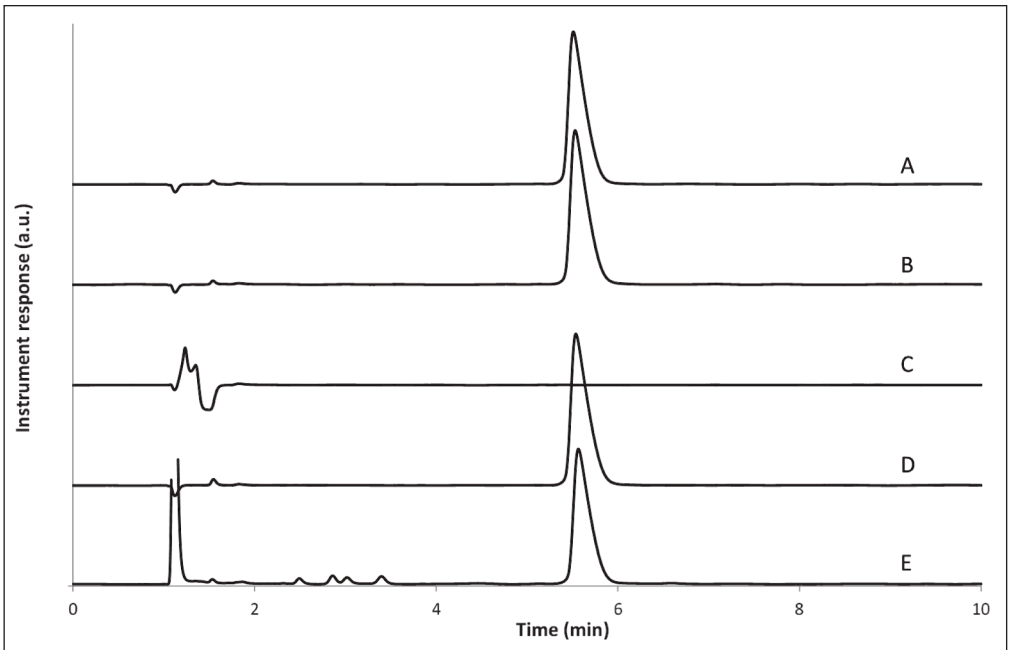

Figure 1. A: Representative chromatogram of methadone injectable solution in water (1:1) after storage at 5 °C for 4 h. B–E: Representative chromatograms of methadone injectable solution submitted to forced degradation at 60 °C for 4 h in (B) water, (C) sodium hydroxide 1 mol/L, (D) hydrochloric acid 1 mol/L, and (E) hydrogen peroxide 3%.

RESULTS

After forced degradation, recovery of methadone hydrochloride was variable: 102% after heating at 60 °C for 4 h in one volume of purified water, 0% after addition of sodium hydroxide 1 mol/L, 101% after addition of hydrochloric acid 1 mol/L, and 87% after addition of hydrogen peroxide 3% (Figure 1). These results suggest that methadone precipitates in alkaline conditions and is prone to oxidation. No peak overlap of methadone with impurities or degradation products was observed. Similarity of the UV spectra at all of the sampling points on the peak was compared using the HPLC system software (LabSolution version 5.54; Shimadzu, Laval, Quebec) to compute a similarity index and determine the presence of multiple components within the peak. With this system, the similarity index can vary between –1 (dissimilar) and 1 (identical).[8] Here, the methadone peak purity index calculated between 190 and 250 nm was not less than 0.9999 in all cases.

At the beginning of the stability study, the study preparation was clear, and the concentration of methadone hydrochloride was 5.02 (standard deviation 0.01) mg/mL. No notable changes in appearance were observed after storage at either temperature for up to 180 days. Over the study period, the concentration of methadone hydrochloride in solution stored at either temperature remained not less than 90.0% of the initial concentration at all time points (Table 1). The particle count complied with *United States Pharmacopeia–National Formulary* specifications at the start and end of the study under both storage conditions (Table 2). No microbial growth was noted in samples tested at the end of the study.

Table 1. Concentration of Methadone Hydrochloride Remaining after Storage

Storage Time	Storage at 5 °C		Storage at 25 °C	
	Concentration* (mg/mL)	% of Original	Concentration* (mg/mL)	% of Original
Initial solution	5.02 ± 0.01		5.02 ± 0.01	
7 days	5.03 ± 0.01	100.3	5.01 ± 0.01	99.9
14 days	4.99 ± 0.01	99.4	5.02 ± 0.03	100.1
30 days	4.98 ± 0.02	99.2	4.97 ± 0.01	99.0
60 days	5.00 ± 0.01	99.6	4.98 ± 0.02	99.3
90 days	4.61 ± 0.03	92.0	4.71 ± 0.08	93.9
180 days	4.92 ± 0.01	98.0	4.90 ± 0.01	97.8

*Mean ± standard deviation of duplicate measurement of 6 samples for original solution (n = 12) and duplicate measurement of 3 samples for all subsequent storage times (n = 6).

Table 2. Particulate Matter Observed in Samples

Condition	Particle Size; No. of Particles/mL (Mean ± SD)*	
	> 10 µm	> 25 µm
Initial solution	7.6 ± 8.4	1.3 ± 1.5
5 °C, 180 days	5.2 ± 1.9	3.0 ± 0.8
25 °C, 180 days	2.9 ± 0.9	0.6 ± 0.3

SD = standard deviation.
*Each data point is based on triplicate measurements.

DISCUSSION

Methadone hydrochloride injection USP (Synastone 10 mg/mL, Auden Mckenzie Group, Ruislip, England) was available in Canada through Health Canada's Special Access Programme until production of this drug was discontinued in October 2014. The stability of methadone hydrochloride in aqueous solutions is good.[9,10] Methadone hydrochloride for injection diluted in saline solutions (at 1, 2, or 5 mg/mL) was reported to be stable for at least 4 weeks at room temperature.[9] Solutions of methadone hydrochloride prepared in orange-flavoured Tang® drink mix for oral administration were stable for 91 days at room temperature or under refrigeration.[10] With methadone hydrochloride injection USP no longer available, this study proposes a compounded methadone hydrochloride solution for injection (5 mg/mL) prepared from bulk powder and saline solution as an alternative for pediatric administration.

CONCLUSION

This study demonstrated that methadone hydrochloride for injection prepared from bulk powder in saline solution at a concentration of 5 mg/mL remained chemically stable and conformed to the specifications for particulate matter in solutions intended for injection for at least 180 days when stored in clear glass vials at 5 °C and at 25 °C.

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Conformité du circuit du médicament dans les unités de soins et les cliniques externes : étude observationnelle transversale au sein d'un établissement universitaire de 500 lits

par Amélie Chabrier, Pauline Rault, Suzanne Atkinson et Jean-François Bussières

RÉSUMÉ

Contexte : En établissement de santé, le circuit du médicament est complexe, puisqu'il compte plus de 50 étapes. Pour évaluer la conformité du circuit du médicament de notre établissement, nous avons mis en place un processus annuel d'audit.

Objectifs : L'objectif principal vise à décrire la conformité de certaines étapes du circuit du médicament (principalement la gestion des médicaments) aux unités de soins et dans les cliniques externes d'un centre hospitalier universitaire mère-enfant. L'objectif secondaire consiste à comparer les résultats à ceux des audits précédents.

Méthodes : Il s'agit d'une étude descriptive observationnelle transversale réalisée à l'été 2018 dans les unités de soins (n = 34) et les cliniques externes (n = 28) de l'établissement. Les données ont été recueillies à partir d'une grille d'audit.

Résultats : En 2018, le taux de conformité de l'ensemble des unités de soins aux critères mentionnés dans la grille d'audit variait de 32 % à 100 %. Par rapport à l'année précédente, le taux de conformité à 30 critères est demeuré inchangé et celui à quatre critères s'est détérioré. La conformité à 35 % des critères (12/34) était totale à plus de 85 %. En 2018, le taux de conformité de l'ensemble des cliniques externes aux critères mentionnés dans la grille d'audit variait de 0 % à 100 %. Le taux de conformité à un critère s'est amélioré, celui à 21 critères est demeuré inchangé et celui à deux critères s'est détérioré. La conformité à 32 % des critères (9/28) était totale à plus de 85 %. Trente-cinq recommandations ont été formulées au comité pharmacie-soins infirmiers et un rapport personnalisé a été transmis aux gestionnaires.

Conclusions : Cette étude descriptive observationnelle transversale décrit le degré de conformité du circuit du médicament relatif à la gestion des médicaments, principalement dans les unités de soins et les cliniques externes. Cette démarche originale à l'initiative du Département de pharmacie a abouti à la formulation de 35 recommandations au comité pharmacie-soins infirmiers, ce qui a permis d'améliorer la sécurité du circuit du médicament dans les unités de soins et les cliniques externes.

Mots clés : circuit du médicament, audit, pharmacie, unités de soins, cliniques externes

ABSTRACT

Background: In the hospital setting, the medication-use system is complex, having more than 50 steps. To assess the compliance of the study organization's medication-use system with established criteria, an annual audit process was developed.

Objectives: The primary objective was to describe the compliance of certain steps in the medication-use system (mainly medication management) in care units and outpatient clinics of a mother and child university hospital centre. The secondary objective was to compare the current results with those of previous audits.

Methods: This cross-sectional descriptive observational study was carried out in summer 2018 in patient care units (n = 34) and outpatient clinics (n = 28) of the study hospital. Data were collected according to an audit matrix.

Results: In 2018, the rate of compliance with audit criteria varied between 32% and 100% for the patient care units. Relative to the previous year, the compliance rate remained unchanged for 30 criteria and worsened for 4 criteria. For 35% of the criteria (12/34), compliance was greater than 85%. In 2018, the rate of compliance with audit criteria varied between 0% and 100% for the outpatient clinics. The compliance rate increased for one criterion, remained unchanged for 21 criteria, and worsened for 2 criteria. For 32% of the criteria (9/28), compliance was more than 85%. Thirty-five recommendations were made to the pharmacy and nursing care committee, and a personalized report was sent to managers.

Conclusions: This cross-sectional descriptive observational study reports the degree to which the medication-use system complies with medication management criteria, mainly in patient care units and outpatients' clinics. This original approach from the Pharmacy Department led to the formulation of 35 recommendations to the pharmacy and nursing care committee, which helped to improve the safety of the medication-use system in patient care units and outpatient clinics.

Keywords: medication-use system, audit, pharmacy, patient care units, outpatient clinics

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INTRODUCTION

En établissement de santé, le circuit du médicament est complexe et il comporte plus de 50 étapes, de la sélection d'un médicament à sa prescription, à sa préparation, à sa validation pharmaceutique, à l'administration aux patients et à l'élimination des quantités résiduelles[1]. Ce circuit est encadré par des lois fédérales et provinciales et de nombreux documents provenant de différents organismes (p. ex. Santé Canada, Agrément Canada, Ordre des pharmaciens du Québec).

De nombreux intervenants participent au circuit du médicament, dont les prescripteurs (p. ex. médecins, pharmaciens, infirmières praticiennes spécialisées), les personnes responsables de la validation et les préparateurs (p. ex. pharmaciens, assistants techniques en pharmacie, infirmières), les administrateurs de doses (p. ex. infirmières, infirmières auxiliaires, inhalothérapeutes), les personnes responsables de l'élimination des doses (p. ex. préposé, personnel de l'hygiène et salubrité)[1].

Chaque dose de médicament utilisée pour un patient comporte un risque de survenue d'événements indésirables (c.-à-d. effet indésirable ou erreur médicamenteuse). Afin de limiter les risques d'événements indésirables prévisibles, plusieurs organismes d'agrément proposent un cadre normatif visant à sécuriser le circuit du médicament[2-4]. Ce cadre normatif comporte des pratiques organisationnelles requises et plusieurs normes. Les critères concernés par ce cadre requièrent la mise en place d'un circuit du médicament bien défini, avec des politiques et des procédures écrites, des rôles explicites, un processus sécuritaire et de bons outils permettant d'assurer la traçabilité des gestes posés.

Bien que le circuit du médicament concerne le Département de pharmacie, une portion importante de ce circuit se déroule dans les unités de soins et dans les cliniques externes des établissements de santé. Afin de promouvoir la conformité du circuit du médicament au sein de son institution, un établissement de santé a mis en place un processus annuel d'audit de ce circuit[1].

MÉTHODE

Il s'agit d'une étude descriptive observationnelle transversale.

Objectifs

L'objectif principal de cette étude vise à décrire la conformité d'une sélection d'étapes du circuit du médicament (principalement la gestion du médicament) applicable aux unités de soins et aux cliniques externes d'un centre hospitalier universitaire mère-enfant. L'objectif secondaire de cette étude consiste à comparer les résultats des audits des unités de soins et des cliniques externes à ceux de l'année précédente.

Lieu et critères d'inclusion

L'étude s'est déroulée dans un centre hospitalier universitaire mère-enfant de 500 lits durant l'été 2018. Deux assistantes de recherche ont procédé à l'évaluation de la conformité du circuit du médicament par observation directe complétée d'un court entretien avec l'assistante-infirmière-chef de chaque unité de soins ou de clinique externe. Toutes les unités de soins (n = 22) et toutes les cliniques externes qui ont des médicaments en réserve (n = 22) ont été incluses dans l'étude.

Grille de critères de conformité

En 2012, une équipe d'un département de pharmacie a conçu une grille de critères de conformité du circuit du médicament (n = 25 critères) pour la tenue d'un audit annuel à partir du cadre juridique et normatif en vigueur complété d'une revue documentaire[5]. Au fil des années, cette grille s'est adaptée à l'évolution du cadre juridique et normatif et des besoins de l'établissement[6]. Durant l'audit du 9 juillet au 10 août 2018, la grille des unités de soins comportait 34 critères et celle des cliniques externes, 28 critères. La grille était divisée en trois thèmes : a) entreposage, réfrigération et gestion des déchets (n = 12 critères) b) chariots unidoses et cabinets (n = 6 critères) et c) documentation (n = 11 critères). L'annexe 1 (disponible au https://www.cjhp-online.ca/index.php/cjhp/issue/view/196/showToc) présente la grille de critères et les tests de conformité.

Tenue de l'audit

Les deux assistantes de recherche se sont présentées ensemble dans chaque unité de soins ou clinique externe pour procéder à l'audit. Le personnel des différentes unités et cliniques n'avait pas été averti de la réalisation de l'audit. La première partie de l'audit reposait sur une observation directe des différentes zones de stockage des médicaments. La seconde partie de l'audit reposait sur un entretien avec l'assistante-infirmière-chef de chaque unité afin de vérifier ses connaissances des outils développés par la pharmacie et de sa pratique. L'ensemble des réponses ont été recueillies par écrit à partir de la grille de collecte des données. De plus, la durée de la réalisation de l'audit et de l'analyse avec les assistantes de recherche et les pharmaciens concernés a été prise en compte.

Rapport personnalisé par unité de soins ou clinique externe

Les résultats ont ensuite été retranscrits dans un rapport de synthèse destiné à chaque gestionnaire de l'unité de soins ou de la clinique externe. Le rapport a été revu par la chef adjointe aux services pharmaceutiques et discuté avec les pharmaciens cliniciens de chaque lieu avant d'être remis au gestionnaire infirmier. Chaque rapport était personnalisé et comportait une suggestion d'actions correctrices à mettre en place.

Analyse des résultats

Les données ont été saisies dans un chiffrier (Excel, Microsoft, Seattle [Washington]) et analysées dans le logiciel SPSS (IBM SPSS Statistics for Windows, version 24.0, publié en 2016;

IBM Corporation, Armonk [New York]). Les deux assistantes de recherche devaient indiquer la cote qui correspondait à chaque critère : C (Conforme), Cr (Conforme avec recommandations), NC (Non conforme avec recommandations), NA (Non applicable). La conformité à un critère était considérée comme totale lorsque 100 % des observations faites étaient conformes ; la conformité à un critère était considérée comme presque totale avec recommandations lorsque plus de 85 % des observations étaient conformes (il s'agit généralement d'un oubli, d'un comportement isolé, d'un élément portant à interprétation) ; la non-conformité à un critère correspondait à une conformité inférieure à 85 % des observations. Les cotes et commentaires ont ensuite été révisés par la chef adjointe aux services pharmaceutiques. Ils prenaient en compte l'activité des unités de soins ou des cliniques externes et de l'ensemble du processus.

Le taux de conformité à chaque critère a été calculé comme suit : nombre total de critères portant la mention « conforme » + nombre total de critères portant la mention « conforme avec recommandations » / nombre total de critères observés. La mesure de l'évolution de la conformité a été obtenue par comparaison des taux de conformité de 2017 à ceux de 2018 à l'aide d'un test de χ^2 (test exact de Fisher). De plus, pour chaque année, nous avons calculé le nombre de critères auxquels le taux de conformité était supérieur ou égal à 85 %, seuil défini arbitrairement.

Une valeur de *p* inférieure à 0,05 était considérée statistiquement significative.

RÉSULTATS

Les assistantes de recherche ont reçu 88 heures de formation ventilées de la manière suivante : formation des assistantes de recherche à l'audit (5 heures), tenue de l'audit (64 heures), rédaction des rapports (10 heures), analyse (3 heures) et rétroaction au personnel soignant (6 heures). La grille d'évaluation étant reprise des années précédentes, son temps de conception n'est donc pas pris en compte.

De façon globale, en 2018, le taux de conformité à 12 des 34 critères applicables aux unités de soins était égal ou supérieur à 85 % et à 9 des 28 critères applicables aux cliniques externes. Entre 2017 à 2018, on note une différence de conformité significative à seulement quatre des 34 critères dans les unités de soins et à seulement trois des 28 critères dans les cliniques externes. Le taux de conformité à une majorité de critères est demeuré inchangé.

Le tableau 1 présente le profil du taux de conformité à chaque critère de l'« Entreposage » dans les unités de soins et les cliniques externes de 2017 à 2018.

Tableau 1. Profil du taux de conformité à chaque critère de l'« Entreposage » dans les unités de soins et les cliniques externes de 2017 à 2018

Thèmes et critères	Unités de soins auditées			Cliniques externes auditées		
	2017 (*n* = 21)	2018 (*n* = 22)	Valeur de *p**	2017 (*n* = 21)	2018 (*n* = 22)	Valeur de *p**
Entreposage						
Toutes les zones d'entreposage et de préparation sont propres	86 %	95 %	0,61	93 %	92 %	> 0,99
Absence de médicaments non autorisés	91 %	77 %	0,41	94 %	100 %	> 0,99
Absence d'électrolytes concentrés sauf exception selon pol/pro	100 %	77 %	0,048	100 %	96 %	> 0,99
Absence d'échantillons de médicaments	100 %	100 %	> 0,99	83 %	63 %	0,18
Absence de médicaments périmés	82 %	32 %	0,002	75 %	57 %	0,34
Présence d'un bac de retour des médicaments	100 %	67 %	0,004	NA	4 %	NA
Aucun patient ne peut se servir dans le stock de médicaments	91 %	100 %	0,49	100 %	87 %	0,24
Réfrigérateur						
Présence d'un thermomètre conforme dans le réfrigérateur	95 %	94 %	> 0,99	63 %	92 %	0,09
Registre des valeurs de températures du réfrigérateur disponible et à jour	45 %	33 %	0,52	27 %	46 %	0,43
Présence de médicaments uniquement dans le réfrigérateur	71 %	78 %	0,73	80 %	77 %	> 0,99
Réanimation						
Présence d'un plateau de réanimation conforme, sans médicaments périmés	95 %	95 %	> 0,99	86 %	100 %	0,17
Déchets						
Présence d'une poubelle adaptée aux pol/pro	86 %	67 %	0,16	75 %	26 %	0,002
Proportion (nombre) de situations conformes aux critères à plus de 85 %	9/12 (75 %)	5/12 (42 %)	NA	5/11 (45 %)	6/12 (50 %)	NA

NA = non applicable, pol/pro = politiques et procédure.

Le tableau 2 présente le profil du taux de conformité à chaque critère de « Chariots et cabinets » aux unités de soins seulement, de 2017 à 2018. Ces critères ne s'appliquent qu'aux unités de soins.

Le tableau 3 présente le profil du taux de conformité à chaque critère de « Documentation » aux unités de soins et aux cliniques externes de 2017 à 2018.

À la lumière de l'audit mené en 2018, 35 recommandations ont été formulées et transmises au comité pharmacie-soins infirmiers. Les recommandations types suivantes ont été formulées à chaque unité de soins ou clinique externe seulement lorsque cela était applicable. Le tableau 4 présente le profil des recommandations générales découlant de l'audit mené en 2018.

Les rapports personnalisés ont été validés avec les pharmaciens et transmis aux gestionnaires dans les 14 semaines après l'audit. L'annexe 2 (disponible au https://www.cjhp-online.ca/index.php/cjhp/issue/view/196/showToc) présente un exemple de rapport personnalisé pour une unité de soins.

DISCUSSION

Cette étude décrit un exemple concret de la mise en place d'un processus structuré et annuel d'évaluation de la conformité d'une partie du circuit du médicament au sein d'un établissement de santé. On trouve peu d'exemples d'audits similaires dans la littérature scientifique[7-11]. Des équipes de recherche ont également mené des travaux similaires au bloc opératoire[12,13]. Selon les études recensées, les grilles de conformité proposées comportent un nombre variable de thèmes (de 5 à 21) et de critères (de 12 à 164)[10,11]. Il est difficile de comparer nos résultats à ceux de ces études, compte tenu des différents critères utilisés, des particularités propres à chaque circuit du médicament spécifique à chaque établissement de santé (p. ex. aménagement, rôles, façons de travailler) et approches d'audit utilisées. De façon générale, le taux de conformité varie beaucoup d'un critère à l'autre et d'une étude à l'autre.

En vertu de la norme sur la gestion des médicaments publiée par Agrément Canada, « un comité interdisciplinaire est responsable de la gestion du système des médicaments »[4]. En vertu des Standards de pratique de l'Ordre des pharmaciens du Québec, « le pharmacien s'assure de l'efficience et de la sécurité du circuit du médicament »[14]. Nous pensons que le pharmacien est le mieux placé pour assurer la bonne gouverne du circuit du médicament dans son ensemble, compte tenu des obligations juridiques et normatives, de son expertise, de sa vision globale du circuit du médicament et de sa présence au sein de l'établissement. Cette étude décrit une initiative pharmaceutique originale, arrimée au travail du personnel infirmier, dans le but de sécuriser le circuit du médicament et d'offrir un outil de rétroaction structuré et pérenne. Le résultat de cet audit est notamment utilisé comme preuve d'évaluation et de suivi lors des visites d'Agrément Canada.

De 2017 à 2018, on note très peu de différence statistiquement significative du taux de conformité à chaque critère (c.-à-d. détérioration de la conformité à trois critères dans les unités de soins et à deux critères dans les cliniques externes et amélioration de la conformité à un critère dans les cliniques externes).

En ce qui concerne l'entreposage entre 2017 et 2018, la conformité aux critères d'au moins 85 % est passée de 9/12 à 5/12 dans les unités de soins (trois différences statistiquement significatives incluant l'absence d'électrolytes concentrés) et de 5/12 à 6/12 dans les cliniques externes (une seule différence statistiquement significative concerne la présence de poubelle adaptée aux politiques et procédures). Les électrolytes concentrés examinés avaient été servis au nom des patients selon les règles d'exception en vigueur, mais ils n'avaient pas été remisés dans un endroit conforme. Notons aussi que, de 2017 à 2018, des changements de fournisseur et de type de poubelles à déchets pharmaceutiques avaient lieu pendant la tenue de l'audit.

En ce qui concerne les chariots et cabinets, la conformité aux critères, qui était d'au moins 85 %, est passée de 3/6 à 1/6 dans les unités de soins (aucune différence statistiquement significative) de 2017 à 2018.

Tableau 2. Profil du taux de conformité à chaque critère de « Chariots et cabinets » aux unités de soins de 2017 à 2018

Thèmes et critères	Unités de soins auditées		Valeur de *p**
	2017 (*n* = 21)	2018 (*n* = 22)	
Chariots de médicaments unidoses			
Toute la documentation disponible est conforme	100 %	76 %	0,39
Tous les chariots sont propres	71 %	64 %	0,44
Tous les médicaments des tiroirs communs sont sur liste des communs de l'unité de soins	93 %	64 %	0,13
Tous les médicaments dans le tiroir multidose servis par la pharmacie sont nominatifs et destinés à un patient hospitalisé	38 %	55 %	0,68
Cabinets			
Toute la documentation disponible est conforme	70 %	45 %	0,55
Tous les cabinets sont propres	94 %	94 %	>0,99
Proportion (nombre) de situations conformes aux critères à plus de 85 %	50 % (3/6)	17 % (1/6)	NA

NA = non applicable.

Tableau 3. Profil du taux de conformité à chaque critère de « Documentation » aux unités de soins et aux cliniques externes de 2017 à 2018

Thèmes et critères	Unités de soins auditées			Cliniques externes auditées		
	2017 (*n* = 21)	2018 (*n* = 22)	Valeur de *p**	2017 (*n* = 21)	2018 (*n* = 22)	Valeur de *p**
Substances contrôlées						
Toutes les feuilles de contrôle sont actives	100 %	100 %	> 0,99	100 %	100 %	> 0,99
Absence d'opiacés concentrés sauf exceptions selon pol/pro	100 %	100 %	> 0,99	100 %	100 %	> 0,99
BCM						
Toutes les admissions comportent un BCM	91 %	73 %	0,30	NA	54 %	NA
Tous les BCM étudiés ont un minimum de conformité	59 %	82 %	0,26	NA	60 %	NA
Documentation						
Aucune FADM préimprimée n'est périmée	90 %	100 %	> 0,99	100 %	63 %	0,07
Réanimation						
Tous les dossiers étudiés ont une FOPR-I conforme	91 %	50 %	0,044	NA	38 %	NA
Utilisation du module de simulation pour autoapprentissage	58 %	64 %	> 0,99	33 %	40 %	0,75
Intranet						
Connaissance de la page d'accès à deux items types sur l'intranet	63 %	73 %	0,70	62 %	15 %	0,002
Détermination des documents et actions à accomplir par l'intranet en cas de panne	68 %	73 %	> 0,99	58 %	50 %	0,74
Utilisation systématique de la feuille de contact pour faire une demande à la pharmacie	69 %	100 %	0,07	6 %	64 %	0,001
Mention de la date de péremption sur l'étiquette générée par la pharmacie	89 %	100 %	0,53	80 %	67 %	0,54
Connaissance de l'outil de déclaration d'un effet indésirable	26 %	45 %	0,42	0 %	47 %	0,52
Connaissance de la liste interne des abréviations interdites	61 %	55 %	> 0,99	55 %	19 %	0,56
Connaissance de la pol/pro et de la liste des médicaments à alerte élevée	61 %	91 %	0,11	57 %	52 %	0,67
Connaissance du feuillet d'utilisation des antimicrobiens	56 %	36 %	0,45	NA	0 %	NA
Connaissance de l'EPP lors de la manipulation des médicaments dangereux	50 %	73 %	0,27	43 %	100 %	0,46
Proportion (nombre) de critères auxquels la conformité est supérieure à 85 %	6/16 (38 %)	6/16 (38 %)	NA	3/12 (25 %)	3/16 (19 %)	NA

BCM = bilan comparatif des médicaments, EPP = équipement de protection personnel, FADM = feuille d'administration des médicaments, FOPR-I = feuille d'ordonnance prérédigée individuelle utilisée en cas de réanimation cardiorespiratoire, NA = non applicable, pol/pro = politiques et procédure.

En ce qui concerne la documentation, la conformité aux critères est restée inchangée, soit 6/16 critères dans les unités de soins (une seule différence statistiquement significative relative à la présence de FOPR-I conforme) et 3/16 critères (deux différences statistiquement significatives relatives à la connaissance de la page d'accès à deux items types sur l'intranet et à l'utilisation systématique de la feuille de contact pour faire une demande à la pharmacie) dans les cliniques externes. Certaines variations du taux de conformité peuvent s'expliquer. Par exemple, la proportion d'admissions comportant un BCM est passée de 91 % à 73 % tandis que la conformité des BCM présents dans les dossiers est passée de 59 % à 82 %. De 2017 à 2018, des efforts ont été faits pour que les BCM soient davantage conformes aux différents éléments normatifs, et le renforcement de ces exigences a pu contribuer à réduire la participation de certains cliniciens à cette démarche. Peut-on s'attendre à un taux de conformité à chaque critère de 100 %? À notre avis, le taux de conformité obtenu à chaque critère est acceptable, compte tenu du grand nombre d'intervenants (c.-à-d. plusieurs gestionnaires, > 1000 infirmières, > 400 médecins, > 40 pharmaciens, des centaines de résidents et d'étudiants en formation dans les disciplines concernées), du grand nombre d'unités de soins et de cliniques

Tableau 4. Profil des recommandations générales découlant de l'audit mené en 2018

1. Respecter la liste établie de médicaments disponibles au commun et éviter les cachettes
2. Retirer les électrolytes concentrés
3. Retirer les opiacés concentrés
4. Retirer les échantillons non autorisés
5. Retirer les médicaments périmés
6. Ajouter un bac de retour
7. Sécuriser l'accès à la pharmacie d'étage (c.-à-d. local, armoire sous clé, cabinets)
8. Demander à la salubrité l'ajout d'une poubelle à déchets pharmaceutiques
9. Vérifier que les feuilles de contrôle sont actives et répondent à un besoin
10. Ajouter un thermomètre au glycol / ou remplacer l'existant par un au glycol
11. Instaurer ou remplir quotidiennement le registre de relevés de température du frigo
12. Éviter de placer des aliments dans le frigo réservé aux médicaments
13. Vérifier la conformité de la documentation disponible sur les chariots unidoses
14. Faire avec le personnel de la salubrité le suivi du nettoyage des chariots de médicaments
15. Assurer le suivi des produits périmés dans les communs des chariots et disposer adéquatement des doses des patients ayant quitté l'établissement
16. Vérifier la conformité de la documentation disponible sur les cabinets
17. Faire avec le personnel de la salubrité et de la pharmacie le suivi du nettoyage de l'extérieur et de l'intérieur des cabinets
18. Vérifier la présence d'un meilleur schéma thérapeutique possible lors de toutes les admissions
19. Remplir adéquatement les meilleurs schémas thérapeutiques possibles et s'assurer de les ajouter aux dossiers
20. Remplir adéquatement les meilleurs schémas thérapeutiques possibles / ordonnances de départ et s'assurer de les ajouter aux dossiers
21. Faire le tri dans les FOPR préimprimées et jeter les versions qui ne sont pas à jour. Éviter la préimpression de grosses quantités de FOPR
22. Faire le tri dans les FADM préimprimées et jeter les versions qui ne sont pas à jour. Éviter la préimpression de grosses quantités de FADM
23. Imprimer les FOPR-I lors de toutes les admissions
24. Vérifier la présence de médicaments non périmés sur le plateau
25. Confirmer avec les assistantes-infirmières-chefs qu'elles sont capables d'utiliser le module d'autoapprentissage des chariots de réanimation
26. Offrir de la formation sur les outils de l'intranet
27. En cas de panne de cabinet, chariot ou FADMe, appeler le service informatique; en cas de panne de frigo, appeler le service technique
28. Instaurer la mise en place de la feuille de contact si nécessaire
29. Informer sur l'interprétation de la date de péremption
30. En cas d'effet indésirable potentiellement lié à un médicament, il faut laisser un message sur la boîte vocale 3636 et un résident ou une résidente en pharmacie assurera la déclaration de cet effet indésirable
31. Diffuser le feuillet sur les abréviations à ne pas utiliser au sein du service
32. Diffuser aux services le feuillet sur les antimicrobiens à usage restreint (disponible sur l'intranet)
33. Diffuser la note sur les habillements / équipements nécessaires à la manipulation des médicaments dangereux
34. Offrir la formation sur les pompes intelligentes
35. Offrir la formation sur les médicaments à alerte élevée

FADM = feuille d'administration des médicaments, FADMe = feuille d'administration des médicaments électronique,
FOPR = feuille d'ordonnance prérédigée, FOPR-I = feuille d'ordonnance prérédigée individuelle utilisée en cas de réanimation cardiorespiratoire.

externes auditées, du grand nombre de critères applicables et du grand nombre de gestes posés (~ trois millions de doses de médicaments données chaque année au sein de notre établissement). Un seul professionnel qui manque de formation, qui a été récemment intégré ou qui est négligent peut contribuer à générer de nombreux éléments non conformes lors d'un audit, même si la majorité des intervenants respectent le cadre normatif en vigueur au quotidien.

Notre démarche repose sur la production d'un rapport ayant abouti à des recommandations personnalisées relatives à chaque unité de soins ou clinique externe. Il a été discuté avec le pharmacien répondant du secteur en question pour ensuite être transmis à l'infirmière responsable. Les recommandations ont également été discutées dans le cadre du comité pharmacie-soins infirmiers, ce qui permet de profiter de l'influence des cadres conseillers et conseillères en soins infirmiers. L'analyse finale montre que le taux de conformité à chaque critère demeure stable. Ivers et collab. ont publié en 2012 une revue systématique sur l'effet des audits suivis de rétroaction sur les pratiques professionnelles[15]. Les auteurs notent qu'un audit est plus efficace lorsqu'il est réalisé par un superviseur ou un collègue respecté, qu'il comporte des objectifs spécifiques et des plans d'action visant à diminuer le comportement ciblé et si le public cible n'est pas constitué de médecins. Ces trois points correspondent à notre démarche de rétroaction avec la diffusion d'un rapport personnalisé au sein de notre établissement. En revanche, d'autres points importants concernant le retour d'information à la suite d'un audit ne sont pas systématiquement réalisés, comme une rétroaction orale au personnel soignant en plus de l'envoi du rapport d'audit, la mention de l'importance du critère évalué et la mise en place d'un plan d'action. De plus, l'efficacité des audits et des rétroactions est également tributaire du degré de conformité au point de départ (c.-à-d. qu'il est plus facile de s'améliorer quand la conformité est très faible).

On peut hésiter à publier des résultats lorsque les changements sont faibles. En revanche, nous pensons que la publication de l'effort qu'a nécessité cet audit dans le circuit du médicament

peut encourager d'autres établissements à faire de même. En faisant connaître ces efforts, nous pensons accroître l'intérêt et la vigilance de tous les intervenants de notre établissement pour un circuit du médicament plus sécuritaire.

En dépit de l'effet plateau observé de 2017 à 2018, nous pensons que la tenue annuelle d'un audit est essentielle et permet d'explorer de nouvelles stratégies de diffusion des résultats (p. ex. en faisant davantage participer le personnel soignant lors de la tenue de l'audit, en organisant une activité structurée sur le thème du circuit du médicament lors d'une journée de formation annuelle). L'audit perpétue une culture d'évaluation pérenne du circuit du médicament.

Cette étude comporte des limites. Bien que les critères soient explicites, leur interprétation peut varier entre les observateurs, malgré l'existence d'un outil expliquant chaque critère. Dans notre étude, les personnes qui auditent varient d'une année à l'autre. Par ailleurs, bien que l'audit soit mené sans préavis, il peut exister un biais d'observation, particulièrement lors de l'entretien avec l'assistante-infirmière-chef. D'ailleurs, l'observation directe de l'utilisation des éléments du circuit (p. ex. chariots, pompes, intranet) par le personnel soignant à l'œuvre pourrait permettre de décrire de façon plus réaliste l'état de la conformité. De plus, l'étude repose sur un entretien avec une seule personne par unité de soins ou par clinique externe. Par conséquent, on ne peut généraliser ces résultats à l'ensemble du personnel infirmier. Toutefois, l'assistante-infirmière-chef représente la personne clé de chaque secteur, elle est censée être à jour et consciente de l'ensemble des critères de conformité et des outils à sa disposition.

CONCLUSION

Cette étude descriptive observationnelle transversale analyse la conformité du circuit du médicament dans les unités de soins et les cliniques externes. De façon globale, les taux de conformité à une majorité de critères sont restés stables aussi bien dans les unités de soins que dans les cliniques externes. Cette démarche originale à l'initiative du Département de pharmacie a mené à la formulation de 35 recommandations transmises au comité pharmacie-soins infirmiers, ce qui permet d'améliorer la sécurité du circuit du médicament dans les unités de soins et les cliniques externes.

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Role of the US Veterans Health Administration Clinical Pharmacy Specialist Provider: Shaping the Future of Comprehensive Medication Management

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INTRODUCTION

Providing access to high-quality care is one of the top priorities of the US Veterans Health Administration (VHA). The VHA is the largest integrated health care system in the United States, providing care at 1255 health care facilities, including 170 VHA medical centres and 1074 outpatient sites for care of varying complexity. However, substantial shortages of primary and specialty care providers exist across the nation, including within the VHA.[1] The deployment of clinical pharmacists in various roles may be one way to address gaps in care. As advanced practice providers, clinical pharmacists have improved medication safety, quality of care, and clinical outcomes for veterans, as well as the general population. Hundreds of studies, many of which were conducted in the VHA setting, have been published in the peer-reviewed literature and have demonstrated benefits of pharmacist-directed patient care.[2,3] For example, in their comprehensive systematic review, Chisholm-Burns and others[4] evaluated 298 studies of the effect of US pharmacists, working as members of care teams, on patient care and found positive results in terms of therapeutic and safety metrics. The most frequently reported therapeutic outcomes included reductions in hemoglobin A1c, low-density lipoprotein, and blood pressure. Clinical pharmacist care has also improved humanistic components of patient care related to patient satisfaction, adherence to therapy, and knowledge of medications. The authors of a 2008 literature review of the economic impact of clinical pharmacist providers endeavoured to quantify the benefit-to-cost ratio.[5] Among studies reporting data suitable for determining the benefit-to-cost ratio (n = 15), the pooled median value revealed that for every dollar invested in a clinical pharmacist, US$4.81 was achieved in cost reductions or other economic benefits.[5]

The current review article highlights the VHA's efforts to utilize pharmacists as direct patient care providers to increase quality of and access to care for the veteran patient in a value-based payment model.

BACKGROUND: VHA Clinical Pharmacy Practice and the Clinical Pharmacy Specialist

Within the VHA, all pharmacists have the professional designation of "clinical pharmacist". In addition, a subset of pharmacists with the title Clinical Pharmacy Specialist (CPS) exist who operate as advanced practice providers, providing comprehensive medication management (CMM), with authority to initiate, discontinue, or modify medication under a defined scope of practice. The scope of practice for VHA CPS providers is similar to a collaborative practice agreement between a pharmacist and a physician provider, as used outside of the VHA; however, the VHA CPS scope of practice is specific to the facility, not with an individual provider. Notably, a scope of practice is not required to perform routine activities, such as dispensing, patient counselling, medication reconciliation, teaching, chart reviews, or the provision of monitoring or assessment recommendations related to a patient's medication therapy. However, only CPS providers with a scope of practice are allowed to perform medication management activities, which include but are not limited to prescribing medications, ordering laboratory assessments, and performing physical examinations. In 2010, the VHA Pharmacy Benefits Management Services created the Clinical

Pharmacy Practice Office (CPPO), which is responsible for developing interventional and proactive approaches to support, sustain, and spread clinical pharmacy practice throughout the VHA. The CPPO targets and supports initiatives to improve veterans' access to care and the quality and cost-effectiveness of care provided, while aligning current VHA clinical pharmacy practice with policy, developing processes to support pharmacy leadership, and ensuring that the VHA's clinical pharmacy workforce is recognized as a foundational necessity. As of August 2019, the VHA employed more than 8517 clinical pharmacists, of whom 4359 (51%) had a scope of practice authorizing them to provide CMM services with autonomous prescriptive authority.

Given the CPPO's transformational strategy for clinical pharmacy practice, VHA policy had to be modernized to accurately reflect the practice roles and settings where CPS providers function. Therefore, in 2015, the *VHA Handbook 1108.11: Clinical Pharmacy Services* was created to provide specific direction, policy, and procedures related to clinical pharmacy.[6] The policy modernized the activities included within the CPS scope of practice, defined the credentialing process for VHA CPS providers, and also defined the procedures for initiation and renewal of the scope of practice, along with the components of peer review (otherwise known as professional practice evaluation), both initial and ongoing, for pharmacists possessing a scope of practice.[7] Prescriptive authority outlined in the scope of practice applies only to noncontrolled substances and is outlined on the basis of VHA policy, rather than by the pharmacy practice legislation for the state where the pharmacist is licensed. If the CPS provider is licensed in a state that allows prescriptive authority for controlled substances and has obtained a DEA (Drug Enforcement Administration) number, the CPS provider's scope of practice may include authority to prescribe controlled substances. Pharmacy practice legislation at the state level typically uses the term "collaborating agreements", "collaborative practice", or "collaborative practice agreement". The VHA CPS scope of practice is the collaborating agreement through which the CPS provider enters into a formal agreement with a facility's medical staff to perform CMM. The scope of practice is overseen by the Executive Committee of the Medical Staff and holds VHA CPS providers to a higher level and frequency of quality review standards than most state-level legislation, as evidenced by the components of professional practice evaluation outlined in the *VHA Handbook 1108.11: Clinical Pharmacy Services*.[6]

VHA CPS providers who possess a scope of practice are highly trained: 73% of VHA CPS providers have advanced residency training (postgraduate year 1 [PGY-1] and/or PGY-2), and 53% have board certification (e.g., Board Certified Pharmacotherapy Specialist, Board Certified Psychiatric Pharmacist, Board Certified Ambulatory Care Pharmacist) or certification in another discipline, such as geriatrics or diabetes care. In total, 84% of VHA CPS providers have advanced residency training and/or certification. VHA CPS providers recorded over 6 million patient care visits in fiscal year 2018 (October 1, 2017, to September 30, 2018). Nationally, CPS provider roles vary in type and setting, including management of complex anticoagulation clinics, treatment of chronic disease states (e.g., diabetes, hypertension, dyslipidemia, chronic obstructive pulmonary disease, heart failure, pain), and acute and chronic management of specialty care conditions in areas such as hepatitis C, mental health, and cardiology.[8]

In the sections below, we review VHA CPS practice and provide an overview of current CMM activities in various clinical areas, based on internal data from the VHA CPPO.

CPS AND DISEASE STATE INTERVENTIONS: The Pharmacists Achieve Results with Medications Documentation (PhARMD) Project

Although in the past the number of CMM patient care visits indicated the breadth of practice across the VHA system, this number did not describe the types of activities performed during these direct care encounters. In response to that need, an electronic tool for documenting interventions was developed, which is now available at all VHA medical centres. This project, known as the Pharmacists Achieve Results with Medications Documentation or PhARMD project, has been described in detail elsewhere.[9]

In fiscal year 2018, a total of 4 070 609 disease state interventions were documented by 5360 CPS providers using the tool. The tool allows evaluation of intervention capture by disease state/condition, as well as by type of intervention. Some of the most common disease state interventions are listed in Table 1. Interventions are further subdivided into those intended for purposes of medication management (e.g., initiating, modifying or changing, discontinuing, or monitoring a medication), those unique to the process of identifying drug-related problems or performing risk evaluation (e.g., suicide risk assessment performed, drug-drug interaction identified, adverse drug event identified, polypharmacy evaluated), and those related to education or referrals for care. Nationwide, in fiscal year 2018 the tool was used during 52% of all CPS patient care visits. Use of the tool was as high as 89% at an individual VHA facility.

CPS PROVIDER ROLES: Current Status and Relevant Evidence

Primary Care

The VHA used the principles of the patient-centred medical home model to design its patient-aligned care team (PACT) for delivery of primary care. The PACT model was introduced within the VHA in 2009 and its implementation across the health care system began in 2010. Each VHA PACT is broken down into 2 components: the core team and the expanded team. The core

Table 1. PhARMD Disease State Interventions, Fiscal Year 2018*

Disease State	No. of PhARMD Interventions
Anticoagulation	1 365 931
Diabetes, type 2	975 154
Mental health	298 544
Hypertension	274 054
Pain management	254 861
Lipids	136 299
Antimicrobial stewardship	127 365
Hepatitis C virus	107 241
Tobacco cessation	95 819
Oncology	66 269
Congestive heart failure	33 911
Anemia	32 316
Chronic obstructive pulmonary disease	14 192
Transplant	12 771
Chronic kidney disease	11 642
Hypothyroidism	11 314

PhARMD = Pharmacists Achieve Results with Medications Documentation project.
*Fiscal year 2018 = October 1, 2017, to September 30, 2018.
Only the most common types of interventions are listed.

team comprises the patient, primary care providers (i.e., physician, physician's assistant, and nurse practitioner), registered nurse care manager, clinical staff assistant (i.e., licensed practical nurse or medical assistant), and an administrative staff member (i.e., scheduling clerk/front staff). The expanded team involves providers in clinical specialties, including a CPS, to be utilized according to each veteran's specialized medical needs (VHA model concept paper concerning patient-centred medical homes, unpublished). A total of 6373 primary care providers serve 6 272 901 veterans in the VHA. The CPPO set forth a defined ratio of one PACT CPS supporting 3600 primary care patents (based on an assumption of 1200 patients per primary care provider). Currently, 1836 pharmacists VHA-wide are functioning within the primary care practice setting.

Each PACT CPS provides CMM services in between typical visits to the PACT primary care provider, to initiate, modify, or discontinue medications, as well as to provide disease management. Multiple studies have demonstrated improved quality of care for primary care patients when VHA CPS providers are involved.[10-13] PACT CPS providers may provide transitions of care or postdischarge follow-up clinics, ensuring safe transitions between inpatient care and follow-up with the primary care team. The volume of certain types of encounters for fiscal year 2018 can be seen in Table 2. The care modality of these encounters was varied, with virtual care (e.g., telephone, clinical video telehealth) accounting for 60% of the encounters. Since 2015, there has been a 42% increase in CPS providers practising in primary care. For fiscal year 2018, the top 4 disease-related interventions involved type 2 diabetes care, anticoagulation, hypertension management, and lipid management.

Table 2. Clinical Pharmacy Specialist (CPS) Encounters Completed, According to Practice Area, Fiscal Year 2018*

Practice Area	No. of CPS Providers	No. of Encounters
Primary care/patient-aligned care team	1836	1 465 970
Mental health	426	340 106
Pain management	242	160 817
Inpatient	4805	887 106

*Fiscal year 2018 = October 1, 2017, to September 30, 2018.

For a typical panel of 1200 patients, VHA PACT primary care providers have only enough appointment slots to see each patient on average 2.5 times per year. Optimizing the utilization of primary care CPS providers to see patients for CMM in between their visits to the primary care provider visits allows the return interval to be stretched out. The "Increasing Access to Primary Care Using Pharmacist Providers: Diffusion of Excellence Gold Status Practice" project demonstrated that 27% of return appointments to a primary care provider could be averted following integration of CPS providers into the system.[14] Applying this approach across an entire VHA facility was equivalent to creating more than 850 new appointments per quarter. The increase in access VHA-wide would result in more than a quarter of a million newly opened appointments annually.

Provider satisfaction and reduction of burnout for the primary care provider will continue to be areas of focus as staff shortages reach a critical level. In a study performed within the VHA, PACT staff were surveyed with a tool that evaluated perceptions of increased access and clinician satisfaction in relation to integration of CPS providers into primary care. Using a Likert-scale rating system to indicate current perceptions of the CPS contribution to increasing provider job satisfaction (where 1 = no contribution and 5 = major contribution), physicians and nurse practitioners rated CPS involvement at 4.59 and 4.67, respectively.[15]

Mental Health

The mental health CPS provider is a core team member offering CMM expertise to veterans and within the mental health team. These comprehensive teams include psychiatrists, psychologists, nurse practitioners, and social workers, as well as a variety of other clinicians. The mental health CPS providers function as primary mental health providers, and their practice is spread across the continuum of care in general and specialty mental health clinics, behavioural health clinics embedded in primary care, residential rehabilitation facilities, specialty mental health programs, and inpatient mental health units.[16-27] The mental health CPS provider offers same-day access for veterans' needs related to medication management and has been an integral provider for timely postdischarge follow-up appointments. Additionally, the mental health CPS provider embedded in

primary care provides CMM for depression, anxiety, and post-traumatic stress disorder.[28,29] This care has been demonstrated through an electronic consult system for primary care providers, which allows them to utilize the medication expertise of the mental health CPS provider while maintaining management of the veteran in the primary care setting.[20] The mental health CPS provider regularly screens for suicide risk and performs comprehensive suicide risk evaluations for veterans. For these evaluations, the CPS provider collaborates with the psychiatrist or other designated team member in determining the patient's disposition and documents accordingly. The mental health CPS provider meets population metric goals by managing at-risk veterans within their own subset of the team's panel, but also by seeing veterans who have been discharged from hospital and have been identified as having a high risk for suicide. These veterans may require more frequent follow-ups, and the CPS provider must ensure that safety plans are completed in a timely manner.

Within the VHA, there are 426 CPS providers with a mental health scope of practice and relevant prescriptive authority, working at 119 VHA facilities, a growth of more than 134% since October 1, 2014. The mental health CPS providers are a highly trained workforce: 84% have completed a PGY-1 residency, and 61% have completed a PGY-2, with 59% specifically completing a PGY-2 in psychiatry. In addition, 67% report advanced board certification, with 53% of these individuals recognized as Board Certified Psychiatric Pharmacists (BCPPs). The VHA graduates 75 specialized PGY-2 mental health pharmacy residents annually. The number of mental health encounters for fiscal year 2018 is shown in Table 2. The modalities of these encounters included face-to-face, telephone, clinical video telehealth (home- or clinic-based), group appointments, electronic consults, and secure messaging, giving veterans opportunities to access care that meets their needs and schedules.

In the face of current psychiatrist shortages and the projected increase in this deficit (estimated to reach a 25% deficit by the year 2025), mental health CPS providers deliver timely access to care and offer a solution to psychiatrist shortages and concerns about access to mental health services.

Pain Management

Veterans suffer more often from chronic pain conditions than those in the non-veteran population, with veterans typically experiencing higher complexity pain conditions, which in turn results in higher health care utilization rates.[30,31] VHA facilities often report difficulty in recruiting providers with expertise in pain medication management, which puts CPS providers in a position to play a critical role in improving access to pain care. Pain management programs in which CPS providers perform pain management services have demonstrated improvements in opioid prescribing, lower costs associated with opioid adverse effects, and increased patient satisfaction.[32-39] Many VHA facilities utilize CPS providers for chronic pain medication management across practice settings. Primary care providers specifically benefit from such practices through assistance with both opioid and non-opioid medication management and monitoring.

In 2013, the CPPO recognized the need to expand the CPS workforce in pain management. Lectures and coursework were developed, and more than 200 CPS providers have been trained and authorized since then to treat pain through their scope of practice. Currently, 242 CPS providers perform pain management within the VHA, representing a 600% growth from 2015. In addition, the VHA partnered with the Office of Academic Affairs to add 7 new positions for PGY-2 pain management and palliative care residencies for academic year 2019. The focus of these new PGY-2 positions is on training and skills development for chronic pain management, palliative care, and substance use disorders. The VHA currently offers 12 of the 23 PGY-2 pain management and palliative care residencies across the United States.

The VHA pain management CPS provides CMM focused on treatment appropriateness, effectiveness, safety, and adherence. Pain management CPS providers perform pain assessments, assess for both suicide risk and substance use disorders, and develop individualized treatment plans. The care offered by the CPS providers includes all facets of medication prescribing to address pain care needs, as well as initiating and monitoring opioid tapers, making needed referrals, and ensuring universal precautions. Pain management CPS providers deliver care through traditional face-to-face appointments (individually or in groups), but more than half the time, care is delivered virtually by telephone or video telehealth, chart consultation, or electronic messaging (e.g., secure e-mail). Pain CPS providers rely heavily on population management to target high-risk patients for intervention. Population management strategies driven by pain CPS providers include, but are not limited to, identifying patients for overdose education and naloxone distribution, performing CMM directed toward high-dose opioid dose reduction, performing urine drug testing, responding to prescription drug monitoring program queries, and other forms of risk mitigation for veterans and the community, including facilitating addiction treatment.

From a more global perspective, CPS providers are often designated as pain and opioid stewardship champions who work, outside of their direct patient care role, with other facility leaders (e.g., pain and mental health champions) to foster facility-wide initiatives to ensure the safety of pain care. In this role, the pharmacist stewardship champion leads efforts for both ambulatory and acute care to guide change across practice settings.

Substance Use Disorders

CPS providers collaborate with other members of the treatment team in various practice settings to deliver care for veterans with substance use disorders. CPS providers in the VHA have demonstrated improved access to treatment for alcohol use

disorder, opioid use disorder, tobacco use disorder, and other illicit substance use disorders. In addition, evidence shows that CPS-managed care improves medication-assisted treatment retention rates for opioid use disorder, tobacco abstinence, and prescribing rates for pharmacotherapy for alcohol use disorder.[40-43]

The PACT, pain, and mental health CPS providers independently address and treat alcohol use disorder and tobacco use disorder in their respective care settings, with the mental health and pain CPS providers also being commonly integrated in collaborative care models for treating opioid use disorder with medication-assisted treatment. There are distinct differences in management between opioid use disorder and other conditions, given the data waiver requirement for buprenorphine-based products. After a veteran who is seeking treatment has been seen by a qualifying practitioner and an opioid use disorder has been diagnosed, the CPS provider works with the qualifying provider and the other members of the team to initiate and manage naltrexone long-acting injectable therapy or to provide medication management in collaborative fashion with the qualifying provider during the induction, sustainment, and maintenance phases of buprenorphine treatment. The CPS provider undertakes population management strategies to identify at-risk veterans for engagement and intervention. These activities may include prompting evaluation or treatment of opioid use disorder, determining needed risk-mitigation strategies, or providing overdose education and naloxone as part of overdose prevention. Finally, the CPS provider may perform care coordination, such as risk monitoring, ensuring participation in psychosocial therapy or psychotherapy, ensuring needed referrals, and facilitating unscheduled appointments. With significant shortages of providers who are able to deliver medication-assisted treatment for opioid use disorder, CPS providers improve access to care and help the VHA to meet its goal of providing on-demand, evidence-based addiction treatment to service members.

Inpatient Clinical Pharmacy

The VHA applies CMM in the acute care setting, according to a team-based care model that allows for proactive delivery of clinical pharmacy services. The acute care inpatient setting supports clinical pharmacy contributions with a high level of autonomy, allowing for independent decision-making within the scope of practice of CPS providers.

As a member of an interprofessional team, the CPS provider performs direct patient care activities that may include prescriptive authority, consult submission and completion, and the ordering of related tests and diagnostic studies to support medication management. These advanced practice pharmacy providers may also perform the physical and objective assessments necessary to evaluate and monitor patients for initiation or modification of medication therapy to enhance patient safety and ensure appropriate therapeutic response. Their positive impact on patient care may extend to decreasing the length of stay, reducing readmission rates (e.g., for congestive heart failure, chronic obstructive pulmonary disease, or hypertension), improving antimicrobial stewardship, and facilitating timely referrals for patients who have been identified as high risk through population management and who are being discharged from the acute care setting. In fiscal year 2018, inpatient clinical pharmacists and CPS providers performed a total of 887 101 inpatient encounters (Table 2). The top 5 disease-related interventions were anticoagulation, antimicrobial stewardship, type 2 diabetes management, pain management, and hypertension management.

CPPO Innovation and CPS Practice Expansion

The CPPO routinely engages in partnership with other VHA program offices to align CPS practice with other efforts to improve veterans' access to needed care. One such project was initiated in late 2016, when the CPPO partnered with the VHA's HIV, hepatitis, and related conditions program with the goal of expanding veterans' access to treatment for hepatitis C virus (HCV) infection to prevent morbidity and mortality associated with HCV disease. This successful collaboration resulted in funding that accelerated access to HCV treatment through expansion of the CPS provider workforce. Subsequently, VHA best practices to cure HCV were demonstrated.[44] CPS providers were recognized as delivering quality care and providing timely access to HCV treatment, as measured by sustained virologic response.

In 2017, the CPPO further enhanced practice expansion by partnering with the VHA Office of Rural Health to expand access to care for rural veterans through CPS providers. Subsequently, 65 VHA facilities received funding to hire new CPS providers: 110 in primary care, 40 in mental health, and 35 in pain management. With these new positions, as of the close of fiscal year 2018, CPS providers had served 126 095 veterans for a total of 358 243 encounters. Primary care CPS providers were involved in 177 058 of these encounters, whereas mental health CPS providers recorded 54 620 encounters and pain CPS providers had 42 379 encounters. Over 50% of encounters were conducted using virtual practice delivery modalities (e.g., telephone or clinical video telehealth).

DISCUSSION

CPS providers can contribute to care in multiple ways, including (but not limited to) improving the quality of care through provision of CMM services, increasing access to care, and improving team member satisfaction. Within the VHA, the role of the CPS provider has been solidified both in policy and in function, matching the core components required for CMM. VHA policy has outlined the foundational components of CPS practice in relation to professional practice and has specifically

standardized the credentialing and scope of practice of the CPS provider. The CPPO has developed guidance focused on core implementation strategies, which highlight practice management needs allowing the CPS to function as an advanced practice provider in multiple practice arenas. The dual strategy of development of policy and provision of guidance has allowed the VHA to standardize the practice area of the PACT CPS to a greater extent than any other defined role for CPS providers within the VHA. Although challenges exist, future opportunities for expansion are limitless for the CPS providers practising in the VHA. Extending CPS practice beyond what was traditionally thought of as a disease-specific provider and allowing the provision of CMM across the breadth of many care areas gives the VHA the opportunity to increase quality of care and address provider shortages that are expected to only increase with time.

CONCLUSION

The VHA has been an advocate for the advancement and expansion of the practice of clinical pharmacy in CMM. The VHA has set standards through policy and guidance, thus providing the foundational components of CPS practice. The clinical pharmacy practice model of the VHA is one that can be replicated by other agencies, given the shift in payment model to value-based care (rather than fee-for-service).

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Have Current Systems of Pharmacovigilance Had Their Day?

THE "PRO" SIDE

The safety of a newly approved medication is based primarily on the results of preapproval clinical trials.[1,2] This can be problematic because it means that many medications are approved according to the results of 1 or 2 clinical trials. These trials typically enrol fewer than 1000 participants, who are often healthier than patients in routine clinical care.[3] In addition, although preapproval trials may accurately estimate the rate of common adverse events, rare and serious adverse events may go undetected.[4-6] Therefore, postmarketing safety studies are needed to identify potential rare adverse events associated with newly approved medications. This practice is referred to as pharmacovigilance, which the World Health Organization has defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem."[7]

In Canada, pharmacovigilance occurs predominantly through spontaneous reporting to Health Canada.[8] Adverse reactions can be reported—by patients, health care professionals, or drug manufacturers—to the *Canada Vigilance Adverse Reaction Online Database*, which is similar to the *Adverse Event Reporting System* of the US Food and Drug Administration (FDA).[9] Many adverse drug reactions have been detected through this mechanism; however, there are limitations to this approach.[10] First, reporting is voluntary and thus prone to selection bias. Second, the quality and completeness of reports are highly variable.[11] Third, because the total number of patients who received the drug (i.e., the denominator) is not reported, the relative and absolute risks cannot be accurately quantified. For example, in 2012, after dabigatran was approved, spontaneous reports of bleeding associated with this drug greatly outnumbered reports of bleeding associated with warfarin use.[11] This might suggest a higher rate of bleeding with dabigatran than with warfarin. However, a cohort study of more than 140 000 patients conducted in response to these reports showed that the rate of bleeding was about 2-fold higher with warfarin than with dabigatran.[11] Thus, the higher number of spontaneous reports associated with dabigatran resulted from reporting bias, likely because dabigatran was a new medication and warfarin was not.

An alternative to reliance on spontaneous reporting for pharmacovigilance is the use of data mining. This method uses advanced statistical methods to identify patterns and associations in large data sets. In contrast to a traditional research study, in which the researcher starts with a hypothesis and designs a study to test it, data mining involves a data-driven process in which the researcher "lets the data speak for themselves". The data sources may include health care databases (e.g., those held by ICES), prospective registries, or electronic health records.[10] Several data-mining approaches exist, including tree-based statistical scanning (described in more detail below), Gamma Poisson Shrinker, and text mining through natural language processing.[12,13]

The tree-based scan statistic has been applied in North America. TreeScan, one of the more common data-mining software programs, was developed specifically for pharmacovigilance and was first introduced in 2013.[12] The term "tree" refers to the hierarchical grouping of related diagnostic codes used with this approach.[12] For example, within the International Statistical Classification of Diseases and Related Health Problems (ICD) coding system, the code I21 (acute myocardial infarction) is considered to be a branch. The codes I21.0 (ST-elevation myocardial infarction of the anterior wall) and I21.4 (non-ST elevation myocardial infarction) are considered to be sub-branches. These codes can be further specified to the second decimal digit (e.g., I21.01 for ST-elevation myocardial infarction of the left-anterior descending artery); this terminal level is referred to as a leaf. One strength of TreeScan is that the investigator does not have to specify a priori the outcome of interest or the level of detail of the outcome. Instead, TreeScan evaluates data across all possible branches, sub-branches, and leaves to identify potential adverse events.[12]

Recently, TreeScan was used to identify potential adverse events associated with the quadrivalent human papillomavirus (HPV) and live attenuated herpes zoster vaccines.[14,15] Among 1.9 million people who received the HPV vaccine, and across 6551 potential ICD codes, TreeScan identified only 2 potential signals: cellulitis and complications of the injection.[14] Similarly, in a study of more than 1.2 million herpes zoster vaccinations, TreeScan found that local skin reactions and skin infections were the only statistically significant adverse events.[15]

Data mining has several advantages over spontaneous reporting systems. First, it leverages large sample sizes, which allows for the detection of rare adverse events.[5] Second, it does not require a priori (hypothesis-free) knowledge of a potential association between a medication and an adverse event.[12] This advantage is particularly important given that knowledge of potential adverse events is often limited when a drug first enters the market, and it therefore allows for comprehensive evaluation of all possible adverse events. Third, in the case of TreeScan, all results are adjusted for multiple-hypothesis testing, to limit the number of potential false signals.[12]

Data mining also has important limitations. First, it often uses ICD codes; therefore, associations can be measured only for diagnoses with a relevant ICD code. Second, the validity of ICD codes is variable depending on the diagnosis. Third, data mining produces statistical association signals that may not represent true adverse events (e.g., because of confounding).[12] Therefore, signals detected from data

mining should be formally evaluated with directed pharmacoepidemiologic studies (e.g., new-user active-comparator cohort study).[5]

In 2017, the FDA released the *Sentinel Initiative: Final Assessment Report*, which outlined how the agency planned to modernize the process of postmarketing drug safety surveillance, including through implementation of TreeScan and other data-mining tools.[16] In Canada, the Drug Safety and Effectiveness Network (established by the Canadian Institutes of Health Research) created CNODES, the Canadian Network for Observational Drug Effect Studies, in 2011, which is able to access data for millions of patients across the country. CNODES now plays an essential role by conducting pharmacoepidemiologic studies in response to requests from Health Canada. A natural extension of this work would be the incorporation of TreeScan or another data-mining technique to advance the current process of pharmacovigilance in Canada with the ultimate goal of preventing adverse events.

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THE "CON" SIDE

It has been suggested that the dawn of pharmacovigilance occurred in 1848, when a young English girl died after undergoing chloroform-induced anesthesia.[1] As a result of this and other anesthetic-related deaths, *The Lancet* established a commission exhorting all doctors to report any deaths associated with anesthesia. Formal systems were established in the United States in 1906, after the *Pure Food and Drug Act* was passed. Its successor, the *Federal Food, Drug, and Cosmetic Act* (1938), ruled that the safety of all drugs should be demonstrated before marketing.

The wake-up call of the thalidomide tragedy occurred in the 1950s, the first example of an effective licensed medicine having widespread, serious adverse effects. First marketed in 1956 in West Germany as a sedative and hypnotic, thalidomide was also strongly promoted to treat nausea in early pregnancy. Ultimately, it was prescribed in 46 countries, including Canada. Somewhat ironically, though, the US Food and Drug Administration (FDA) withheld approval because of a lack of evidence of safety in pregnancy, as identified by Dr Frances Kelsey (a Canadian doctor working for the FDA as a pharmacist).[2] In 1959, the first cases of congenital deformities—involving not only limbs but also internal organs—were reported. Initially, the manufacturers denied the possibility of any causal association, but the evidence became overwhelming and the drug was withdrawn: in Germany and the United Kingdom in December 1961, and in Canada in March 1962. This was not in time to prevent the estimated 10 000 cases of affected children worldwide,[3] including more than 100 in Canada.[4] Had there been in place systems of pharmacovigilance to indicate a link between medicine taken by the mother and effects on her unborn child, actions could have been taken earlier to alert doctors to the potential risks.[5] The disaster triggered the establishment, worldwide, of national systems of licensing and safety monitoring for all medicines.

In Canada, legislation regarding the control of new drugs was reinforced in late 1962,[2] and the Canadian Adverse Drug Reaction Information System was established in 1965. Now, consumers, health care professionals, and product manufacturers can report suspected adverse events to the *Canada Vigilance Adverse Reaction Online Database* (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html).

In the United Kingdom, 1963 saw the establishment of the Committee on Safety of Drugs (renamed the Committee on Safety of Medicines in 1970), and in 1964 letters were circulated to all doctors and dentists asking them to report "any untoward condition in a patient which might be the result of drug treatment". This was the precursor of the current Yellow Card Scheme, so called because in its original incarnation, reports were prepared on a yellow card. Indeed, these yellow cards are still used, although much of the reporting is now done online. Since the scheme was introduced, reporting rights have been given to other health care professionals, initially nurses and pharmacists and now any health care professional. In 2004, patient reporting was introduced, on the assumption that it would increase the number of reports and lead to earlier detection of signals. There were concerns that patient reports might be less valid, and hence create false signals from background noise, but this has not proved to be the case.[6,7]

International collaborations were also established, increasing the sample size of exposed individuals. In 1968, the World Health Organization (WHO) instituted its Programme for International Drug Monitoring.[8] Participation has grown from an initial 10 countries to about 150 countries, all of whom are eligible to submit reports of adverse reactions associated with medicinal products to the program's global database, VigiBase. In 2001 the European Agency for the Evaluation of Medicinal Products and the European Commission developed a single European database, EudraVigilance, to which all member states must submit any details of "serious" reports, as defined by the Council for International Organizations of Medical Sciences.[9]

Currently, although there are differences between national schemes in terms of eligibility to report and what to report, all of the above approaches, however systematically introduced, whether voluntary or mandatory, depend on a system known as spontaneous reporting. This has been much criticized for under-reporting, even in countries where reporting is mandatory, such as Sweden, France, and Italy. Indeed a systematic review of 37 studies conducted in 12 countries suggested a median under-reporting rate of 94% (range 6%–100%).[10] In Canada, although more than 90% of pharmacists and 63% of physicians were aware of how to report an adverse reaction, this proportion was reduced to just 55% for health professionals overall.[11]

Despite a certain level of under-reporting, this is not the time to abandon a well-established system that has prevented another disaster on the scale of thalidomide. Because of the level of detail requested at the point of reporting, generation of an adverse event signal need not necessarily result in withdrawal of a useful drug, but there will be warnings about use. For example, a warning might refer to contraindications, such as the recent restriction of domperidone to people over 12 years of age,[12] because of a lack of evidence of benefit in younger children, or the recommendation that gabapentin not be prescribed to patients with respiratory risk factors.[13] Some warnings may relate to drug-drug interactions, such as the interaction between fluconazole and citalopram causing serious cardiovascular events, or food-drug interactions, such as the interaction between grapefruit juice and a range of common medicines.[14] Sometimes a medicine will be withdrawn completely; examples have included both prescribed medicines (e.g., rosiglitazone, because of cardiovascular effects[15]) and non-prescribed over-the-counter or herbal medicines (e.g., *Aristolochia* in Chinese medicines, because of renal failure).[16]

As premarketing safety assessments become more rigorous and well informed, we can hope that drug withdrawals will become less common. However, premarketing exposure to a drug is limited to perhaps hundreds of people, and it remains likely that rare and potentially fatal events may only be identified once thousands of people are using the drug. Any system can always be improved, but that is no reason to discard it. Efforts are needed to increase professional and public engagement with current spontaneous reporting systems. Approaches could include better education, individualized feedback, multiple reporting routes, and local initiatives. New approaches linked to big data may also provide complementary information but should not replace current systems.

In Canada, the *Protecting Canadians from Unsafe Drugs Act*, also known as Vanessa's Law,[17] will strengthen Canada's ability to collect information and make decisions about potential health risks from treatments. It is now mandatory for hospitals to report serious adverse events related to drugs and devices within 30 days after first documentation of the event (reporting by manufacturers was already mandatory). Multiple reporting routes are available. As experts in medicines, pharmacists must ensure adherence with the new law, so that patients can continue to take medicines as needed, in the knowledge that effective surveillance systems are in place.

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Competing interests: Christine Bond has received grants from the University of Aberdeen to evaluate patients' reporting to the Yellow Card system. She was also a member of a group that undertook an independent review of access to the Yellow Card system in 2004 (cited as reference 16 in the current article).

ON THE FRONT COVER

Sherbrooke Lake, Yoho National Park, British Columbia

This image of a serene, glistening lake, with Cathedral Mountain in the background, was captured by June Chen while she was en route to Mount Niles in August 2017. June is a clinical pharmacist with the University of Alberta Hospital in Edmonton. She practises on the cardiac intensive care and cardiovascular surgery units. During the summer months, she enjoys hiking in the mountains, and all-year-round, she likes to dance contemporary jazz.

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.

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Les sensations : Tout est une question de perspective

par Zack Dumont

En tant que fonction physiologique, la vue n'a certainemenpas la vie facile. Habituellement, nous critiquons sa façon de s'imposer aux autres sens : nous fermons les yeux pour bien entendre, ressentir, goûter et sentir. Inversement, les autres sens semblent servir à la renforcer.

Au cours des derniers mois, la direction de la Société canadienne des pharmaciens d'hôpitaux (SCPH) a recueilli de l'information de diverses manières pour faire progresser la vision de notre Société (voir le récent commentaire présidentiel « Oser la différence »; *Journal canadien de pharmacie hospitalière* 2019;72[6]:469). Nous avons fureté partout et suivi des pistes prometteuses pour dénicher de belles occasions potentielles et nous préparer à affronter les menaces. Nous nous sommes délectés, nous avons absorbé les congrès de l'SCPH (savouré les calembours au sujet des excès alimentaires, qui ont égayé la conférence), dévoré le contenu du Journal et profité de tous les produits et services de la Société. Nous avons écouté, mené un sondage auprès des membres, organisé un sommet de planification stratégique inclusive et maintenant, nous menons une série de discussions ouvertes qui commencent à la Conférence sur la pratique professionnelle. Ces activités nous ont permis d'entendre les membres s'exprimer au sujet des problèmes qu'ils rencontrent dans le domaine de la pharmacie. Et pour finir, je demande la permission d'étendre l'analogie pour la bonne cause : l'utilisation du « toucher » pour symboliser les soins; nous sommes restés bien conscients des personnes pour qui nous entreprenons tout cela : les patients.

À mesure qu'elle s'approche du lancement du plan stratégique, la SCPH subit un certain nombre de changements. Nous évaluons tous les processus pour être certains de faire les choses pour les bonnes raisons et non pas « parce qu'elles ont toujours été faites ainsi ». Des solutions technologiques actuelles et conviviales visant à mieux interconnecter les membres (p. ex. les réseaux des spécialités en pharmacie) et les parties prenantes (p. ex. un nouveau site Web) sont à l'étude. Des options mieux centrées sur les membres remplacent les anciens services. De plus, nos comités ont fait l'objet d'un examen et d'un réalignement pour que les bénévoles consacrent leur temps et leurs efforts à la stratégie, tandis que le bureau prend les rênes des opérations. Bien que l'aiguillon du changement puisse piquer, ces actions visent à « combler les sens » le moment venu.

À ce propos, notre vision ne peut rester fixée uniquement sur le court terme. Nous positionnons la Société en vue d'une croissance importante au cours des années à venir, de manière à bénéficier d'une communauté avec laquelle il est possible d'aborder les problèmes de la pharmacie hospitalière à très long terme. Cela dit, quelle est votre vision? Non seulement de votre Société, mais également de votre profession de pharmaciens? Dans quelle mesure êtes-vous sûrs qu'elle est partagée par votre voisin œuvrant dans l'autre hôpital ou qu'elle s'est imposée dans la région ou la province voisine? Dans quelle mesure êtes-vous certains de prendre en compte tous les points de vue? La vision claire de la pharmacie hospitalière canadienne dépend de l'intégration d'autant de points de vue que possible. Des cliniques de première ligne aux hôpitaux – les grands et les petits; les femmes, les hommes et les autres; les personnes nées au Canada et les nouveaux arrivants; les jeunes professionnels et les plus expérimentés. Plus la contribution sera diversifiée et inclusive, plus la vision sera incontestable. C'est maintenant le moment où jamais d'entendre nos parties prenantes au complet. Nous devons écouter l'avis de tous nos membres actuels et en accueillir davantage. Nous devons favoriser un environnement sécuritaire qui encourage les membres à s'exprimer. Et nous devrions disposer de la meilleure unité de traitement prête à recevoir ces messages et à les transformer en quelque chose de plus grand. L'un de nos nouveaux comités – Vision de la pratique pharmaceutique – a été constitué pour être le catalyseur de ce processus. Restez à l'affût des occasions favorables qui contribuent à façonner notre profession.

Préparez-vous à vous concentrer sur l'essentiel au cours de ces prochaines années, et nous nous efforcerons ensemble de réaliser cette vision de la Société et de l'ensemble de la pharmacie hospitalière. Tant que nous utilisons *tous* nos sens pour rester ouverts à une perspective collective, la vue – la vision – peut être « sens-ationnelle ».

[Traduction par l'éditeur]

Zack Dumont, BSP, ACPR, M. S. (Pharm.), est président élu et liaison interne de la Société canadienne des pharmaciens d'hôpitaux.

Sensations: They're All about Perspective

Zack Dumont

As a physiological function, sight sure gets a bad rap. Although it is usually criticized for taking away from the other senses, we close our eyes to truly hear, feel, taste, and smell. Conversely, when it comes to sight, the other senses seemingly serve to enhance.

In recent months, the Canadian Society of Hospital Pharmacists (CSHP) leadership has been exercising many forms of information gathering to enhance the vision for our Society (see Tania Mysak's recent presidential commentary, "Daring To Be Different", *Can J Hosp Pharm*. 2019;72[6]:470). We've been sniffing around—following hot leads to determine potential opportunities and prepare for threats. We've been tasting—taking in CSHP conferences (puns regarding the conference-related dietary excess are welcome), devouring the Journal's content, and experiencing all Society products and services. We've been listening—a member survey, an inclusive strategic planning summit, and now a series of Town Halls, starting at the Professional Practice Conference, have allowed us to hear from members regarding pharmacy issues. And lastly, I'll request permission to stretch the analogy for a worthy cause, using "touch" as a symbol of caring: we've remained cognizant of who this is all for, the patient.

While the new strategic plan nears launch, CSHP has been undergoing a number of changes. We're evaluating every process to ensure we're doing things for the right reasons and not simply "because they've always been done that way". Contemporary user-friendly technology solutions are being designed to better connect members with one another (e.g., Pharmacy Specialty Networks) and stakeholders (e.g., a new website). Old services are being replaced with better member-centred options. Further, our committees have undergone a review and realignment to ensure volunteers' time and effort is spent on strategy, while the office takes the reins on the operations. While change can sting, these actions ultimately aim to "please the senses" in time.

On that note, our line of sight cannot remain fixed solely on the short term. We're positioning the Society for significant growth within the next several years, so that you have a community with whom you can tackle hospital pharmacy issues far into the future. Speaking of which, what is your vision, not just for your Society, but for your pharmacy profession? How confident are you that it is shared by your neighbour at the other hospital, in the next region, or the province one over? How certain are you that your vision considers all points of view? A strong vision for Canadian hospital pharmacy depends on incorporating as many perspectives as possible. From primary care clinics to hospitals large and small; women, men, and others; Canadian-born and newly arrived; young professionals and experienced—the more inclusive and diverse the contribution, the more incontrovertible the vision. If there's ever been a time when we need to hear from the entirety of our stakeholders, the time is now. We want to hear from all our current members and bring more aboard. We must foster a safe environment that encourages members to speak up. And we should have the best processing unit ready to receive those messages and turn them into something greater. One of our new committees—Pharmacy Practice Vision—is being inaugurated to catalyze this process. Stay tuned for opportunities to help shape our profession.

Prepare for razor-sharp focus over these next few years, and together we'll strive toward that vision for the Society and for all of hospital pharmacy. If we're using *all* senses to remain open to a collective perspective, then sight—vision—can be sensational.

Zack Dumont, BSP, ACPR, MS(Pharm), is President Elect and Internal Liaison for the Canadian Society of Hospital Pharmacists.

Antiviral Therapy during the Coronavirus Disease (COVID-19) Pandemic: Is It Appropriate to Treat Patients in the Absence of Significant Evidence?

THE "PRO" SIDE

The strengths of formal research to evaluate investigational therapies are well known. In an ideal world, when a new question or problem is recognized, rigorous testing in well-designed clinical trials would be performed. However, the coronavirus disease (COVID-19) pandemic has given new meaning to the word "unprecedented". Here, we argue that it is ethically appropriate to offer investigational agents outside of a clinical trial during an emergency, such as the current COVID-19 pandemic, and that the precedent to do so has been set in other outbreaks, such as the Ebola epidemics in Africa. The World Health Organization (WHO) has developed an ethical framework for the use of investigational agents, called MEURI, which stands for "monitored emergency use of unregistered and investigational interventions".[1] According to MEURI, the criteria for using investigational agents outside of clinical trials are the following: no proven effective therapy exists; it is not possible to initiate clinical trials immediately; data providing preliminary support for the investigational agents' safety and efficacy exist (i.e., in vitro or animal studies and support from clinical experts); relevant country authorities and ethics committees have approved such use; adequate resources are in place to minimize risk; the patient's informed consent has been obtained; and the use is monitored, with the results being documented and shared with the scientific community in a timely fashion. The WHO has stated that no proven therapy exists for the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and we argue that the other criteria for MEURI are met as well.

Argument 1: Research Bureaucracy Is Inefficient and Prohibitive—Lessons from Ebola

In March 2014, an outbreak of Ebola was declared in Guinea, but it was not until 5 months later, in August 2014, that the WHO declared a public health emergency of international concern. A research group developed a protocol for clinical investigation of brincidofovir, a process that took 3 months, and another 6 weeks was consumed by additional bureaucratic delay. The narrative account, published in *Nature* in 2015, described the pace at which the trial was started as "unprecedented" (in its rapidity), in contrast to the norm of 18 months,[2] yet during that time the epidemic hit its peak,[3] and affected patients had no access to potentially life-saving investigational agents through clinical trials. The author's advice for the future was the following: "Government leaders must give the WHO the money and support it needs to ensure that the world is 'research ready' for the next outbreak. A properly funded and empowered WHO could oversee the design and implementation of an on-call global task force of clinical-trial staff."

Perhaps this would be a viable strategy for a limited outbreak of a predicted pathogen; however, COVID-19 demonstrates that in a truly global outbreak, such a strategy would be grossly insufficient. We applaud the research response to COVID-19 thus far. At the time of writing, on May 14, 2020, an incredible 1486 protocols had been registered at www.clinicaltrials.gov, and many clinical trials have been initiated by the WHO and other investigators within extremely short timeframes. At the same time, however, there were more than 4.2 million confirmed cases worldwide, or about 2826 cases per clinical protocol. Of course, not all cases would be appropriate for drug therapy, but it is inconceivable that research protocols could be mobilized to enrol even a fraction of those who are eligible.

Argument 2: Variation in Research Infrastructure and Capacity May Introduce Inequities

Equity and fairness are foundational ethical principles in the management of outbreak resources.[4,5] Even if rapidly mobilized, clinical research is generally associated with urban universities. Residents of smaller centres therefore have less opportunity to access investigational therapy through clinical trials, which represents a substantial inequity in the availability of potentially life-saving therapy. In addition, clinical trials often exclude those with a lower likelihood of response or deemed to be at higher risk, such as pregnant or elderly patients.[6-8] The WHO's MEURI emphasizes the ethical principle of patient autonomy or the right of patients to make their own risk/benefit assessments in accordance with their own personal values, goals, and health conditions. Excluding patients because of geography or demographic characteristics that would not exclude them from on-label drug prescriptions overrides this principle of patient autonomy.

On March 24, 2020, the British Columbia Centre for Disease Control issued a statement indicating a preference for clinical trials, with the additional proviso that where such trials are not available, compassionate use of therapies is appropriate, provided patients are advised of the risks and benefits and safety data are collected.[9] These directions align with the WHO's guidance on MEURI and with the explanation of Gostin and Berkman, in the second of the WHO discussion papers addressing ethical issues in pandemic influenza planning.[10] In that document, the authors recognize the provision of investigational agents as ethically appropriate, provided that they are "proportionate in terms of benefits and burdens" and that resources for population-based research are inadequate.

Canada's health care system may not be designed to allow equitable access to new therapies through clinical trials in the context

of widespread COVID-19 infection, but it is able to support access to investigational therapies in a safe and monitored environment per the conditions of MEURI.

Argument 3: Absence of Evidence Is Not Evidence of Absence (of Positive or Negative Effects)

A common logical fallacy suggests that an untested therapy has no effect. This is a non sequitur. If the therapy is untested, the only reasonable conclusion is that its efficacy is unknown. However, the situation is rarely as simple as a complete absence of study data. Clinicians are often faced with the dilemma of poor evidence or data from one condition that they are attempting to extrapolate to another. In the absence of strong evidence, therapies are routinely prescribed that are considered unproven. Indeed, some therapies informed by low-quality evidence are commonly recommended, including aminoglycosides or ceftriaxone in enterococcal endocarditis,[11] combination antibiotics for persistent methicillin-resistant *Staphylococcus aureus* bacteremia,[12] and almost every off-label indication for any therapy.[13] Investigational agents for COVID-19 may not have proven efficacy, but equally they are not proven to be inefficacious. For all of the agents currently proposed for the treatment of COVID-19, biological plausibility for activity has been demonstrated and human safety data are available, therefore meeting the WHO MEURI criteria for a scientific rationale and support of clinical experts in the field.

Conclusion

The modern world has no experience with a pandemic of this proportion. The medical and scientific community has much to learn about this virus and the associated disease. Formal acquisition of knowledge through clinical trials is highly desirable, but it accumulates at a far slower pace than the pandemic has progressed to date. The ideal for evaluation of therapy in clinical trials must be balanced against efficiency, equity, autonomy, and beneficence. We do not advocate for indiscriminate use, but we do advocate for access to reasonably safe and possibly effective therapy under clinician oversight and with informed patient consent, as suggested by guidance documents of the WHO.

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THE "CON" SIDE

The Issue of Using Unproven Treatments

The emergence and rapid transmission of the coronavirus disease (COVID-19), with its relatively high risk of death among patients with comorbidities and severe disease, are compelling the medical community to make decisions before the underlying science has been fully developed. Because there are no licensed vaccines or drug treatments for COVID-19, clinicians have been forced to consider investigational and unproven treatment alternatives in the absence of solid scientific data. When clinicians are confronted with severely ill patients who are at risk of dying, it seems obvious that they should immediately attempt to treat patients with "something", even if the medications available are unproven. However, such action is associated with major pitfalls,

which include placing patients at substantial risk of harm (from adverse events) that outweighs the benefits, wasting precious resources in times of urgency, compromising the conduct of clinical trials, and offering false hope to patients and their family members. When a clinician faces a dilemma in which limited data are available to support treatment, what should they do? We believe that the appropriate scientific and ethical approach is for experimental and unproven medications—including treatments considered for "emergency use" and "compassionate use"—to be made accessible to patients only through clinical trials.

The Concept of Evidence-Based Medicine

The World Health Organization (WHO), in its interim guidance on clinical management of severe acute respiratory infection in patients with suspected COVID-19, states that "Use of investigational anti-COVID-19 therapeutics should be done under ethically approved, randomized, controlled trials."[1]

Evidence-based medicine, which requires that treatments be based on established scientific evidence, is the current paradigm for the practice of medicine.[2] Before a drug can be licensed for commercial use in humans, it must undergo a rigorous scientific development process involving clinical trials. The main purpose of this methodological approach is to determine, to the best of the researchers' ability, the safety and efficacy of the drug for its intended indications; the data generated in this way form the basis of evidence-based practice. This process, however, does not ensure the safety or efficacy of the medication when used for non-intended indications, and patients may be placed at risk for adverse events in those circumstances. For example, during the outbreak of severe acute respiratory syndrome in 2003, ribavirin (an antiviral agent) was used experimentally, despite a lack of clinical trial data, but was later found to be ineffective and harmful to patients, causing hemolytic anemia, liver dysfunction, and poor outcomes.[3] This misuse of ribavirin highlights the importance of properly conducted, robust clinical studies to assess the effects and safety of drug therapy.

The Perils of Emotionally Based Medicine

On March 19, 2020, US President Donald Trump, in his White House briefing, stated that hydroxychloroquine "showed tremendous promise" and "could be a game-changer."[4] This statement has caused numerous clinicians and patients to consider using hydroxychloroquine even though data regarding its safety and efficacy are limited.

In fact, the evidence for hydroxychloroquine as a treatment for COVID-19 is still evolving. At the time of writing (mid-May 2020), this drug has been shown to exhibit in vitro antiviral activity against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[5] and preliminary clinical reports have shown both positive and negative results.[6-8] Clinicians are trained to "do no harm", so they feel an ethical obligation to offer treatment; however, simply acting on this feeling and starting hydroxychloroquine for all patients with COVID-19 would represent a great leap of faith. Hydroxychloroquine and a similar drug, chloroquine, failed in clinical trials, despite having in vitro activity against several viruses, including the Ebola, influenza, HIV, dengue, and Chikungunya viruses. Even worse, chloroquine has been shown to cause harm in an animal model for Chikungunya.[9] Interventions may not offer any more value than best estimated chance. In COVID-19 studies, the dosing regimen for hydroxychloroquine varies considerably, and the occurrence of serious cardiac arrhythmias has been described.[8] In addition, patients treated with unproven therapy may be given false hope, which adds a psychological component to the complexities when determining benefits of treatment.[10] Furthermore, any data collected from such patients would not be reliable when making informed health care decisions for evidence-based practice changes.[11] Thus, unproven interventions require thorough study and should not be offered outside of clinical trials.

The Effects on the Community

In a disaster response, the widespread use of unproven interventions—for both "emergency use" and "compassionate use"—with inadequate collection of data concerning patient outcomes must be avoided.[12] The use of unproven treatments on humans without proper oversight can lead to devastating consequences. Unscrutinized prescribing and dispensing of medications can distort access to therapy for patients who would otherwise benefit from these treatments.[13] In the case of hydroxychloroquine, which is usually prescribed for the management of lupus and arthritis (among other diseases), indiscriminate use for prevention or treatment of COVID-19 may lead to drug shortages, reducing access to the drug by patients who have those other conditions.[4] Such shortages can increase anxiety and uncertainty for all patients. In addition, the availability of investigational and unproven treatments outside of clinical trials would interfere with the ability to conduct research and thus would subsequently reinforce knowledge deficits.[10] Enrolment of patients into clinical trials may be affected, because some patients would already have access to these medications. There would also be a reduced requirement and urgency for researchers to develop new interventions for management, because the perceived need would be negated.[10] Furthermore, use of unproven treatments at one site would perpetuate usage at another, as clinicians would seek to emulate the practices of their peers. Ethically, research should be part of the public health response during an epidemic, based on the moral duties of caregivers, as stated by the WHO Working Group on Ethics and COVID-19.[14]

The Overall Approach

We believe that evidence-informed clinical studies should be the foundation of any treatment used for COVID-19. To deviate from this approach and "jump the gun" on the science would place patients at risk of adverse events, poor outcomes, psychological stresses, reduced medication access, uncertainty and wastage of valuable resources, and would cause confusion for clinicians.

In summary, we feel that the statement from the British Columbia Centre for Disease Control (as quoted in a joint statement of the College of Physicians and Surgeons of British Columbia, the College of Pharmacists of British Columbia, and the British Columbia College of Nurse Professionals[15]) effectively summarizes our opinions:

> It is important to understand that there are potential harms to the patient, risks to our understanding of what is truly a beneficial treatment or not, and depleting access to therapies known to be helpful or essential in other disease states. For these reasons, the use of unproven therapies for COVID 19 is not recommended outside clinical trials.

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