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Le Journal canadien
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British Columbia

In this issue / Dans ce numéro :

Canadian Society of Hospital Pharmacists
Société canadienne des pharmaciens d'hôpitaux

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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.

CJHP Vision

The aim of the *CJHP* is to be a respected international publication serving as a major venue for dissemination of information related to patient-centred pharmacy practice in hospitals and other collaborative health care settings in Canada and throughout the world.

Mission du *JCPH*

Le JCPH est une revue spécialisée qui traite principalement des moyens que prennent les pharmaciens pour optimiser l'utilisation sûre et efficace des médicaments dans les hôpitaux et les autres milieux de soins de santé misant sur la collaboration au Canada et ailleurs dans le monde

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The Value of Drug Stability Studies and Their Publication

Glen Brown

The *Canadian Journal of Hospital Pharmacy* (*CJHP*) has a long history of publishing manuscripts that describe research into the stability of extemporaneously compounded medications. Canadian institutional pharmacists are fortunate that several of their colleagues have done extensive work in this field. The research laboratories of Ron Donnelly at The Ottawa Hospital, Dr Mary Ensom at the British Columbia Children's Hospital, and Scott Walker at Sunnybrook Health Sciences Centre have provided, through their articles in *CJHP*, much useful information that allows practitioners to understand what storage conditions are acceptable for drug formulations beyond the commercially available products. For example, this issue contains an article about the stability of an extemporaneous formulation of domperidone,[1] and the Journal's Editorial Board continues to welcome such research for publication. But why?

The provision of drug therapy in a formulation that will allow the active therapeutic moiety to reach the targeted site of action is a basic necessity of treatment. However, for certain patient populations encountered in Canadian institutions, this foundational aspect of pharmacokinetics cannot be achieved with commercially available products. A common occurrence is the clinical scenario in which oral administration is desired, but the patient is unable to tolerate commercially available solid oral dosage formulations. This situation frequently arises with patients who are either very young or very old. For the very young, the required drug dosage may be so small, or the ability to swallow so unreliable, that commercially available dosage formulations are unrealistic or unsafe.[2] Among elderly patients, the incidence of dysphagia is reportedly as high as 7%–13%,[3] making utilization of available oral dosage formulations unfeasible or unsafe. Similarly, Canadian hospital pharmacists often encounter patients with oral, neck, or gastric cancer, which may make commercial solid dosage formulations impossible to use.[4] For all of these populations, the hospital pharmacist may need to extemporaneously prepare alternative formulations that will allow the patient to receive the full benefit of the therapy. Another common scenario arises where topical therapy for a skin condition is warranted, because systemic drug administration is not desired owing to potential drug or disease interactions. In this situation, the pharmacist will want to explore the potential for preparing a topical product using a dosage formulation originally intended for oral administration.[5]

In all of the above scenarios, it is important to consider the efficacy and safety of the extemporaneously prepared product, and stability data supporting the specific formulation are desired.[6,7] Infostab, a nonprofit organization based in France, has established a database listing published stability reports for extemporaneously prepared parenteral and enteral formulations, which may assist practitioners in preparing a needed product (www.stabilis.org). Stability studies published in *CJHP* appear in this database.

The *CJHP* continues to serve as a forum for publication of new information on the stability of extemporaneous products. These articles will assist Canadian pharmacists in complying with the compounding recommendations of the National Association of Pharmacy Regulatory Authorities.[8-10]

Stability studies submitted to *CJHP* for consideration must be based on appropriate methods, which will allow readers to have confidence in extrapolating the findings to their own practice. *CJHP*'s "Information for Authors" includes information on the necessary description of materials, storage conditions, analytical techniques, and reproducibility.[11] Additional guidelines on stability studies of parenteral products[12] and anticancer drugs[13] are also available. Authors submitting manuscripts to *CJHP* are asked to comply with these compatibility guidelines[12,13] for the specific drug formulation and intended route of administration described within their research. We also welcome inquiries from readers who are willing to serve as peer reviewers for research articles on the stability of extemporaneous formulations. The expertise of reviewers allows the Journal to maintain a high standard of quality for publications on this topic.

Canadian practitioners continue to benefit from the new knowledge discovered through research into the stability of extemporaneously prepared products, and *CJHP* will continue to serve as a vehicle of dissemination for such new information.

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ON THE FRONT COVER

Garibaldi Lake, British Columbia

Robin Ensom took this photo (using a Panasonic DMC-TZ3 camera) while hiking with his wife, Mary, in Garabaldi Provincial Park, British Columbia, in 2009. The hike was part of a July 1st weekend getaway that also included a couple of nights in Whistler and some horseback riding in the BC interior. Both Robin, a former president of the Canadian Society of Hospital Pharmacists (CSHP), and Mary, a former editor of the *Canadian Journal of Hospital Pharmacy*, have been deeply involved in pharmacy practice and education throughout their careers. Their respective contributions have been recognized through the CSHP Distinguished Service Award, granted to Robin in 2009 and to Mary in 2018.

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.

La valeur des études de stabilité des médicaments et de leur publication

par Glen Brown

Le *Journal canadien de la pharmacie hospitalière* (JCPH) publie depuis longtemps des manuscrits d'études sur la stabilité de préparations extemporanées de médicaments. Les pharmaciens d'établissements du Canada sont chanceux que plusieurs de leurs collègues aient beaucoup travaillé dans ce domaine. Les laboratoires de recherche de Ron Donnelly à l'Hôpital d'Ottawa, de Dre Mary Ensom au British Columbia Children's Hospital et de Scott Walker au Sunnybrook Health Sciences Centre ont fourni grâce à leurs articles dans le JCPH une grande quantité d'information utile qui aide les praticiens à comprendre quelles conditions d'entreposage sont acceptables pour les préparations de médicaments au-delà des produits disponibles sur le marché. Par exemple, le présent numéro contient un article sur la stabilité d'une préparation extemporanée de dompéridone [1], un type d'études que le comité de rédaction est toujours heureux de publier au sein des pages du Journal. Mais pourquoi?

La fourniture d'une pharmacothérapie selon une formule qui permettra au principe actif d'atteindre le site d'action visé est essentielle au traitement. Or, pour certaines populations de patients des établissements canadiens, cet élément fondamental de la pharmacocinétique ne peut être réalisé à l'aide des produits disponibles sur le marché. Un exemple courant est le scénario clinique dans lequel l'administration par voie orale est souhaitée, mais où le patient est incapable de tolérer le médicament oral disponible sur le marché sous sa forme solide. La situation survient souvent chez les patients très jeunes ou très âgés. Chez les premiers, la posologie demandée peut être trop petite ou la capacité du patient d'avaler est à ce point peu fiable que les formes galéniques sur le marché sont dangereuses ou représentent une option irréaliste[2]. Chez les patients âgés, les cas de dysphagie sont jugés importants, allant de 7 % à 13 %[3], ce qui rend l'emploi des formes pharmaceutiques orales disponibles impossible ou dangereux. De même, les pharmaciens d'hôpitaux canadiens voient souvent des patients atteints de cancers de la bouche, du cou ou de l'estomac qui peuvent rendre impossible la prise des formes pharmaceutiques solides offertes sur le marché[4]. Pour toutes ces populations, le pharmacien hospitalier pourrait avoir à réaliser des préparations extemporanées de remplacement qui permettront aux patients d'obtenir tous les avantages du traitement. Un autre scénario courant est celui où une maladie de la peau nécessite un traitement topique, car l'administration d'un médicament par voie générale n'est pas souhaitable en raison de possibles interactions avec d'autres médicaments ou maladies. Dans ce cas, le pharmacien pourrait chercher s'il est possible de préparer un produit topique à l'aide d'une forme pharmaceutique d'abord destinée à une administration par voie orale[5].

Dans l'ensemble des scénarios ci-dessus, il est important de prendre en compte l'efficacité et l'innocuité des préparations extemporanées, tout comme il est souhaitable de s'appuyer sur des données prouvant la stabilité des préparations en question[6,7]. Infostab, un organisme français à but non lucratif, a mis sur pied une base de données présentant les rapports de stabilité publiés pour les préparations extemporanées à administration parentérale et entérale qui pourrait aider les praticiens à préparer un produit nécessaire (www.stabilis.org). Les études de stabilité publiées dans le JCPH apparaissent dans cette base de données.

Le JCPH demeure un forum pour la publication de nouvelles informations sur la stabilité de produits extemporanés. Ces articles aideront les pharmaciens canadiens à se conformer aux recommandations sur la préparation de médicaments de l'Association nationale des organismes de réglementation de la pharmacie[8-10].

Les études de stabilité soumises au JCPH doivent se fonder sur des méthodes appropriées; ainsi, les lecteurs auront suffisamment confiance aux résultats pour en tirer des conclusions qui leur serviront dans leur propre pratique. La section Renseignements pour les auteurs (*Information for Authors*) du JCPH précise les descriptions exigées en ce qui concerne le matériel, les conditions d'entreposage, les méthodes

d'analyse et la reproductibilité[11]. Des lignes directrices supplémentaires sur les études de stabilité des produits parentéraux[12] et des antinéoplasiques[13] sont aussi disponibles. Les auteurs qui soumettent des manuscrits au JCPH doivent se conformer à ces lignes directrices sur la compatibilité[12,13] pour ce qui est des préparations médicamenteuses et des voies d'administration précisées dans leurs recherches. Nous accueillons aussi les demandes de renseignements des lecteurs qui souhaiteraient devenir réviseurs d'articles de recherche sur la stabilité de préparations extemporanées. L'expertise de réviseurs permet au Journal de conserver un niveau élevé de qualité pour les publications sur ce sujet.

Les praticiens canadiens continuent de profiter des nouvelles connaissances découvertes grâce aux recherches sur la stabilité des préparations extemporanées et le JCPH continuera à servir de moteur de diffusion pour ces nouvelles informations.

[Traduction par l'éditeur]

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Stability of Extemporaneously Compounded Domperidone 5 mg/mL Suspension in Oral Mix in Plastic and Glass Bottles and Plastic Syringes

Karen Lingertat-Walsh, Shirley Law, and Scott E Walker

ABSTRACT

Background: Domperidone liquid for oral administration is not commercially available in Canada, but is needed for patients who cannot swallow intact tablets.

Objective: To evaluate the stability of domperidone 5 mg/mL suspensions prepared in Oral Mix vehicle and stored, for up to 91 days, in amber polyvinylchloride (PVC) bottles, amber glass bottles, or amber polyethylene terephthalate (PET) bottles at 4°C or 25°C or in polypropylene oral syringes at 25°C.

Methods: Three separate 300-mL batches of domperidone suspension 5 mg/mL were prepared with Oral Mix vehicle. Fifty-millilitre aliquots of the suspension were stored in 100-mL bottles (amber PVC, amber glass, or amber PET). Half of the bottles of each type were stored at 25°C and half at 4°C. On study days 0, 1, 2, 4, 7, 10, 14, 21, 28, 35, 42, 49, 63, 77, and 91, domperidone concentration was determined, with a validated reverse-phase, stability-indicating liquid chromatographic method, in samples drawn from each type of container stored at each temperature. In addition, 1.5-mL aliquots of a fourth 100-mL batch of suspension were stored in 3-mL oral syringes at 25°C and were tested on the same study days.

Results: The concentration of domperidone in all study samples remained above 93% of initial concentration after storage for 91 days. The percent remaining on day 91, based on fastest degradation rate (as represented by the lower limit of the 95% confidence interval [CI]), was at least 92.3% for suspensions stored at 4°C in PVC, glass, and PET bottles. With storage at 25°C, suspensions in PVC and glass bottles retained more than 90% of initial concentration, whereas suspensions in PET bottles and plastic syringes retained 88.9% and 88.0% of initial concentration, respectively.

Conclusions: Because suspensions of domperidone in PET bottles and oral syringes retained less than 90% of their initial concentration on day 91 (based on the 95% CI), it is suggested that such suspensions be stored at 4°C or 25°C in any bottle type or syringe with an assigned beyond-use date not exceeding 75 days.

Keywords: domperidone, stability, suspension

RÉSUMÉ

Contexte : La dompéridone sous forme liquide pour administration orale n'est pas disponible sur le marché au Canada, mais elle est nécessaire pour les patients incapables d'avaler des comprimés entiers.

Objectif : Évaluer la stabilité de suspensions de dompéridone de 5 mg/mL préparées dans l'excipient Oral Mix et conservées jusqu'à 91 jours dans des flacons de polychlorure de vinyle (PVC) ambré, de verre ambré ou de polyéthylène téréphtalate (PET) ambré à 4 °C ou à 25 °C ou dans des seringues orales de polypropylène à 25 °C.

Méthodes : Trois différents lots de 300 mL de suspension de dompéridone de 5 mg/mL ont été préparés à l'aide de l'excipient Oral Mix. Des aliquotes de 50 mL de la suspension ont été entreposées dans des flacons de 100 mL de PVC ambré, de verre ambré ou de PET ambré. La moitié des flacons de chaque type était conservée à 25 °C et l'autre moitié était conservée à 4 °C. Aux jours 0, 1, 2, 4, 7, 10, 14, 21, 28, 35, 42, 49, 63, 77 et 91 de l'étude, les concentrations de dompéridone ont été évaluées sur des échantillons tirés de chaque type de flacons conservés aux deux températures à l'aide d'une épreuve validée mesurant la stabilité par chromatographie liquide en phase inverse. De plus, des aliquotes de 1,5 mL provenant d'un quatrième lot de suspension ont été entreposées dans des seringues orales de 3 mL à 25 °C et ont été analysées aux mêmes jours.

Résultats : Les concentrations de dompéridone dans l'ensemble des échantillons de l'étude conservaient plus de 93 % de la concentration initiale après un entreposage de 91 jours. Le pourcentage restant au jour 91, selon le taux de dégradation le plus rapide (correspondant à la limite inférieure de l'intervalle de confiance (IC) de 95 %), atteignait au moins 92,3 % pour les suspensions entreposées à 4 °C dans les flacons de PVC, de verre et de PET. Lorsqu'elles étaient entreposées à 25 °C, les suspensions contenues dans les flacons de PVC ou de verre conservaient plus de 90 % de la concentration initiale alors que les suspensions contenues dans les flacons de PET ou les seringues de plastique conservaient respectivement 88,9 % et 88,0 % de la concentration initiale.

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Conclusions : Comme les suspensions entreposées dans les flacons de PET et les seringues orales conservaient moins de 90 % de leur concentration initiale au jour 91 (selon l'IC de 95 %), on suggère d'entreposer les suspensions de dompéridone à 4 °C ou à 25 °C dans n'importe lequel contenant en l'accompagnant d'une date limite d'utilisation ne dépassant pas 75 jours.

Mots clés : dompéridone, stabilité, suspension

INTRODUCTION

Domperidone suspension for oral administration is not commercially available in Canada, yet this formulation is needed for patients, especially children, who cannot swallow tablets. To date, only one study concerning the stability of domperidone suspensions has been published.[1] That study determined that 1 mg/mL and 10 mg/mL suspensions of this drug in OraBlend vehicle were stable for 91 days with storage in polyvinylchloride (PVC) bottles at 25°C and 4°C. However, there are no data for storage of domperidone suspensions in glass containers, polyethylene terephthalate (PET) containers, or oral syringes. Furthermore, our analysis of typical doses (unpublished data) suggested that a strength of 5 mg/mL, for which there are no data, would be desirable.

This study was conducted to extend the data of Ensom and others[1] by evaluating the stability of domperidone in amber PVC, amber glass, and amber PET containers and in 3-mL clear polypropylene oral syringes. Another purpose of this study was to evaluate Oral Mix, a dye-free vehicle (osmolality 1231 mOsm/kg) produced by a different manufacturer. These stability data will be useful for pharmacies wishing to compound a domperidone suspension that is easy to prepare, that has a reasonable concentration (allowing administration of convenient volumes), and that is stable for at least 30 days.

The objectives of this study were to first determine the physical suitability of dye-free Oral Mix as a vehicle for domperidone suspensions and then to determine the physical and chemical stability of 5 mg/mL domperidone suspensions in Oral Mix, with storage in amber PVC bottles, amber glass bottles, amber PET bottles, and clear polypropylene oral syringes for up to 91 days.

METHODS

Formulations Studied

Before the stability study, a separate physical study was undertaken to determine the suitability of the Oral Mix vehicle for domperidone suspensions, with regard to ease of compounding and absence of undesirable physical characteristics (e.g., unpleasant odour, caking). All samples were examined immediately after preparation for odour, taste, colour, pH (with a model PHi 510 digital pH meter, Beckman Coulter, Fullerton, California), and ease of resuspension. Samples were stored at either 25°C or 4°C and were examined periodically over 91 days for presence of clumping, ease of resuspension, and changes in odour, taste, colour, and pH. The refrigerated samples were permitted to equilibrate to room temperature before measurement of pH. In addition, all samples used in the stability study (described below) were examined immediately after preparation and on each defined study day for clumping, ease of resuspension, odour, taste, and colour.

Development and Validation of Stability-Indicating Assay

Liquid Chromatography

The liquid chromatographic system consisted of an isocratic solvent delivery pump (model P4000, Thermo Separation Products, San Jose, California), which pumped a solution of 100% potassium phosphate dibasic (Fisher Scientific, Fair Lawn, New Jersey) adjusted to pH 7 with phosphoric acid. On each study day, the strength of the mobile phase was adjusted to achieve a retention time for domperidone of 3.5 min through a 3.9 cm × 300 mm reversed-phase LC-18 column (Nova Pak, Waters Scientific, Toronto, Ontario) at 1.0 mL/min. Samples of 4 µL were introduced into the liquid chromatographic system using an auto-injector (WISP 712, Waters Scientific). The column effluent was monitored with a variable-wavelength ultraviolet–visible spectrum (UV–VIS) detector (UV 6000, Thermo Separation Products, Fremont, California) at 245 nm. The signal from the detector was integrated and recorded with a chromatography data system (ChromQuest, version 5.0, Thermo Fisher Scientific Inc, Nepean, Ontario).

Stability-Indicating Methods

Following development of the chromatographic system for domperidone, the suitability of the method for use as a stability-indicating assay was tested by analyzing samples of domperidone that had been subjected to accelerated degradation. Two 0.5 mg/mL samples of domperidone (purity > 98%; Sigma Aldrich

Canada Co, Oakville, Ontario; product D122, lot 059K4711V) were prepared. The first sample, prepared in water, was adjusted to pH 1.95 (with 1N hydrochloric acid; Fisher Scientific), placed in a 10-mL glass vial, and incubated at 95°C for 200 min. A sample was drawn from the vial every 15 min, of which a 4-µL sample was injected directly into the liquid chromatography system. The second sample, prepared in water and methanol, was adjusted to pH 11.5 (with 1N sodium hydroxide; Fisher Scientific), placed in a 10-mL glass vial, and incubated at 95°C for 227 min. A sample was drawn from the vial every 15 min, of which a 4-µL sample was injected directly into the liquid chromatography system.

The UV–VIS detector was capable of evaluating the UV–VIS spectrum of the chromatographic column effluent every 0.2 s, thus allowing evaluation of the UV-VIS purity of an eluting peak. Changes in the UV–VIS spectrum over the elution profile of the peak of interest would indicate that the peak is contaminated, that the chromatographic method does not separate domperidone from its degradation products, and that the method is therefore unsuitable. However, if (1) the UV–VIS profile does not change during the elution profile of the peak of interest, (2) the UV–VIS spectrum during the elution profile of the peak of interest is identical with that of a sample of known purity (> 98%), and (3) the drug of interest can be degraded to a measurable extent, with both conditions 1 and 2 remaining true during the evaluation of condition 3, the chromatographic system can be judged as stability-indicating.

The chromatograms obtained from each of the degraded domperidone samples were inspected for the appearance of additional peaks, and the domperidone peak was compared between samples for changes in concentration, retention time, and peak shape (by means of electronic overlay and numeric calculation of tailing). The UV spectral purity of the domperidone peak in chromatograms of the degraded samples was compared with the spectrum of the authentic, undegraded sample of domperidone obtained at time 0. These procedures met or exceeded published and accepted standards.[2-4]

Oral Mix Vehicle and Assay Interference

A sample of the Oral Mix vehicle, with and without domperidone, was assayed to ensure that the vehicle did not interfere with the chromatographic assay.

Assay Validation

Once assurance of the specificity of the analytical method had been completed, the validation phase was performed, during which accuracy and reproducibility of the standard curves were evaluated over a 5-day period, and system suitability criteria (theoretical plates, tailing and retention times) were developed to ensure consistent chromatographic performance on each study day.[5] On each validation day, 10 mg of domperidone (Sigma Aldrich Canada Co; product D122, lot 059K4711V) was accurately weighed and dissolved in methanol to prepare a 1 mg/mL stock solution. This stock solution was further diluted with water to make standards of 0.094, 0.188, 0.375, and 0.750 mg/mL. Then 4 µL of each standard, the 1 mg/mL stock solution, and a blank were chromatographed in duplicate, to create the standard curve. The range of the calibration curve encompassed the diluted test concentration of the domperidone samples. In addition, 3 quality control (QC) solutions (0.125, 0.250, and 0.500 mg/mL) were prepared on each validation day and chromatographed in duplicate. The concentrations of the QC samples were also determined from the standard curve and compared with the known concentrations.

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

Stability Study

Domperidone suspensions (5 mg/mL) were prepared, according to the procedure outlined in Appendix 1, from 10-mg tablets (Ranbaxy Pharmaceuticals Canada Inc, Mississauga, Ontario; lot 659899) in Oral Mix vehicle (Medisca Pharmaceutique Inc, Saint-Laurent, Quebec; lot K0248M; product specifications are available in the manufacturer's safety data sheet[6]). To test storage in bottles, 3 separate 300-mL batches were prepared. Each batch was divided into 50-mL aliquots for placement in the following containers: 6 amber 100-mL PVC bottles (Richards Packaging, Mississauga, Ontario), 6 amber 100-mL glass bottles (Beatson Clark, Rotherham, South Yorkshire, England; distributed by Richards Packaging), and 6 amber 100-mL PET bottles (Eastman Chemical Company, Kingsport, Tennessee; distributed by Jones Packaging, Brampton, Ontario). Each bottle was half-filled, which allowed airspace above the suspension. To test storage in syringes, a fourth 100-mL batch was prepared; from this, 1.5-mL aliquots were drawn up into 3-mL clear oral polypropylene syringes (PreciseDose dispenser system, Medisca Inc; lot 48287/A; syringe specifications include details about polydimethylsiloxane lubricant[7]). Three bottles of each type were placed in a refrigerator at 4°C, with protection from light. The remaining 3 bottles of each type were stored at 25°C with exposure to ambient fluorescent light. All of the syringes were stored at 25°C, protected from light with a brown UV-protective bag (item MP-320-28; Pharmasystems, Markham, Ontario). These conditions were designed simulate the preparation, use, and storage of suspensions likely to be encountered during clinical practice.

After initial compounding on day 0, and subsequently on days 1, 2, 4, 7, 10, 14, 21, 28, 35, 42, 49, 63, 77, and 91, the test containers (bottles and syringes) were shaken well; then, 1 mL of suspension was withdrawn by pipette from each bottle (i.e., the

3 bottles of each type stored at each temperature) and from 3 of the oral syringes stored at room temperature. These 1-mL samples were diluted to 10 mL with methanol, and each diluted sample was then mixed well before centrifugation for 10 min at 2000 rpm. Then, 4 µL of the supernatant was injected into the chromatography column. Each sample was analyzed in duplicate on the day of sampling using the validated liquid chromatographic system with UV detection at 245 nm. The area under the domperidone peak was subjected to least-squares linear regression, and the actual domperidone concentration in each sample was determined by interpolation from the standard curve and correction by the dilution factor.

On each study day, a standard curve was prepared using standards with concentrations as described in the section "Assay Validation" (above) and a blank. In addition, 3 QC samples were prepared, at the same concentrations as described in the section "Assay Validation". Each standard and QC sample was chromatographed in duplicate on each study day.

Statistical Analysis

For the analytical method, within-day and between-day errors were assessed by the coefficients of variation of the peak areas of both the QC samples and the standards (during both the assay validation and study periods). After determination of the coefficient of variation of the assay, a power calculation showed that duplicate injection had the ability to distinguish between concentrations that differed by at least 10% within each individual container.[8,9] On each day of the study, means and coefficients of variations were calculated for replicate analyses (i.e., each sample assayed in duplicate) of the 3 samples for each combination of container type and temperature.

Analysis of variance and multiple linear regression were used to test differences in concentration on different study days, in different containers, and at different storage temperatures. The 5% level was used as the a priori cutoff for significance.

The percent of initial concentration remaining was analyzed by linear regression, with a 95% confidence interval (CI) being constructed around the slope of the curve for percent remaining as a function of study day. The lower limit of this CI was deemed to represent the estimate of fastest degradation rate, with 95% confidence, and the intersection of this rate and 90% of the initial concentration was used to determine the recommended beyond-use date (BUD).

Concentrations were considered within acceptable limits if the measured concentration on a given study day was greater than 90% of the initial (day 0) concentration, and the concentration on that study day, estimated from the fastest degradation rate with 95% confidence, exceeded 90% of the initial (day 0) concentration.

RESULTS

Physical Study

During the preliminary physical study of domperidone suspensions in Oral Mix, ease of compounding was noted. The drug was well suspended, the suspension itself was not thick or viscous, and it was easy to pour. Some settling occurred during storage, but redispersion occurred easily with shaking. No caking or clumping occurred in any suspension stored at either 4°C or 25°C, as determined by ease of pouring and absence of residue upon visual inspection of the bottom of bottles after the suspension was poured into a graduated cylinder. All suspensions were white in colour, were of a smooth consistency, had a sweet cherry odour, and tasted bitter. The pH of the suspensions stored at both 4°C and 25°C ranged between 4.33 and 4.48 for the duration of the preliminary physical study. Similar physical properties were observed during the 91-day stability study.

Stability-Indicating Assay

During the accelerated degradation study, consistent degradation of domperidone was observed in both the acidic (pH 1.95) and basic (pH 11.5) samples (Figure 1). Under acidic conditions, 25.32% of the original concentration remained after 200 min, and 4 degradation products were observed (eluting at 1.60, 1.85, 2.00, and 5.50 min). Under basic conditions, 19.84% of the original concentration remained after 227 min, and 5 degradation products were observed (eluting at 1.60, 1.85, 2.60, 4.60, and 5.50 min). Domperidone eluted at 3.50 minutes, and the degradation products did not interfere with domperidone quantification. As a result of the chromatographic separation of the degradation products from domperidone and the similarity of the UV spectrum between an authentic domperidone standard (245 nm) and domperidone in a degraded sample, it was concluded that this analytical method was stability-indicating.

Furthermore, the Oral Mix vehicle did not interfere with the domperidone assay. During the 91-day stability study, inspection of chromatograms did not reveal any of the degradation products observed during the accelerated degradation studies (Figure 1, chromatogram B).

Assay Validation

Regression analysis of the peak area of domperidone versus the concentration of each domperidone standard demonstrated linearity over the range of concentrations tested, with coefficient of determination (r^2) of at least 0.9990 (n = 5).

Analysis of the standard curves and QC samples during the validation study indicated that domperidone concentrations were measured accurately. The standards and QC samples showed less than 3.22% deviation from expected concentration over the validation period. Within-day variation in the slope (the

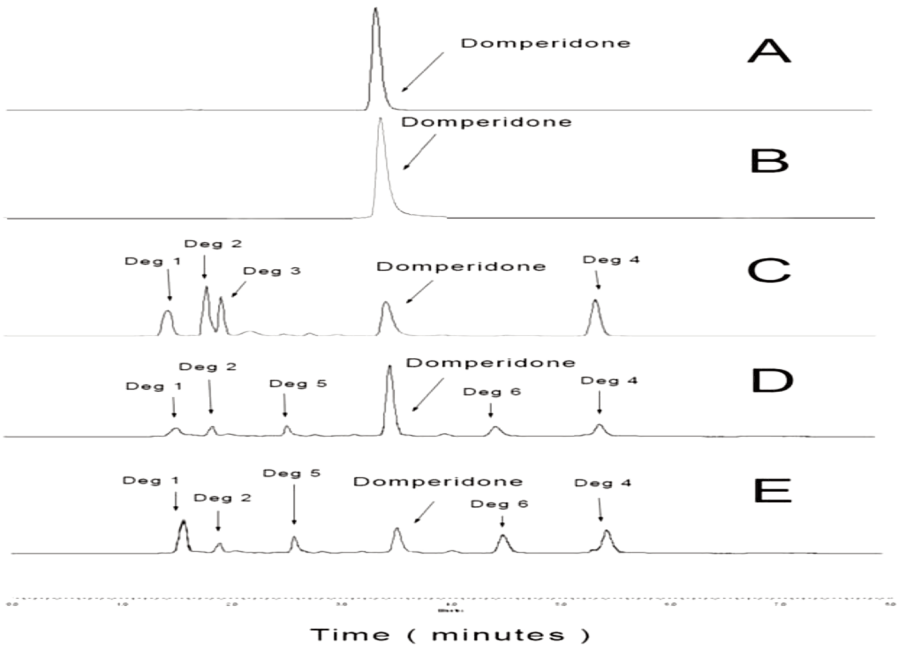

Figure 1. Representative chromatograms of domperidone: (A) 0.5 mg/mL in aqueous solution, immediately after preparation; (B) 0.5 mg/mL in aqueous solution, after storage in a polyvinylchloride bottle for 91 days at room temperature (25°C); (C) 0.5 mg/mL in aqueous solution, adjusted to a pH of 1.95 (hydrochloric acid), after incubation at 95°C for 200 min, with 25.32% of the initial concentration remaining; (D) 0.5 mg/mL in water and methanol, adjusted to a pH of 11.5 (sodium hydroxide), after incubation at 95°C for 31 min, with 73.93% of initial concentration remaining; and (E) 0.5 mg/mL in water and methanol, adjusted to a pH of 11.5 (sodium hydroxide), after incubation at 95°C for 227 min, with 19.84% of initial concentration remaining. A total of 6 degradation products are evident in chromatograms C, D, and E, eluting at 1.60 min (designated Deg 1), 1.85 min (Deg 2), 2.00 min (Deg 3), 2.60 min (Deg 5), 4.60 min (Deg 6), and 5.50 min (Deg 4). These degradation products were not evident in samples from the stability study.

reproducibility, as measured by the coefficient of variation) averaged 0.80% for the standards and 1.51% for the QC samples. Between-day analytical reproducibility, as measured by the coefficient of variation, averaged 1.24% for the standards and 2.18% for the QC samples. Accuracy, based on absolute deviation from the known concentration, averaged 1.84% for the standards and 3.22% for the QC samples.

Assay Analysis during Stability Study

Regression analysis of the peak area of domperidone versus the concentration of each domperidone standard demonstrated linearity over the range of concentrations tested, with coefficients of determination (r^2) of at least 0.9989 (n = 15).

Within-day variation in concentration, as measured by the coefficient of variation, averaged 1.79% for the standards and 2.50% for the QC samples. Between-day analytical reproducibility, as measured by the coefficient of variation, averaged 2.52% for the standards and 5.28% for the QC samples. Accuracy, based on the absolute deviation from the known concentration, averaged 2.46% for the standards and 5.04% for the QC samples. Between-day reproducibility of the study samples, based on the standard deviation of the regression, averaged 2.35%. Therefore, it can be concluded that domperidone was measured accurately and reproducibly on each day of the study, which indicates that differences of 10% or more could be confidently detected within individual containers.[8,9]

Chemical Stability and Statistics

Data for the percent of original concentration remaining on each study day are presented in Table 1. The concentration of domperidone in Oral Mix suspensions remained above 93% of the initial concentration for up to 91 days with storage in 3 types of bottles (amber PVC, amber glass, and amber PET) at 2 different temperatures (25°C and 4°C) and in oral syringes at 25°C (Table 1).

Interpretation of the study results with greatest confidence can be achieved through inspection of the amount remaining on day 91, determined with 95% confidence (see last row in

Table 1). Inspection of these data reveals that there was a greater loss of concentration at room temperature and for suspensions stored in PET bottles. More specifically, for suspensions stored in PET bottles, there was an additional loss of 1% with storage at 4°C and an additional loss of almost 3.4% with storage at room temperature, relative to PVC and glass bottles. In PVC and glass bottles, more than 93% of domperidone concentration remained (with 95% confidence) with storage at 4°C; however, storage at room temperature resulted in an additional loss of 2.5% and 0.6% in PVC and glass bottles, respectively.

Analysis of variance showed no differences in percent remaining due to temperature (p = 0.29) but did show significant differences due to study day and container type (p < 0.001 for both). Similarly, multiple linear regression showed no differences in percent remaining due to temperature (p = 0.94) but did show significant differences due to study day and container type (p < 0.001 for both).

DISCUSSION

This study has demonstrated the stability of 5 mg/mL domperidone suspensions stored in amber PVC bottles, amber glass bottles, amber PET bottles, and clear polypropylene oral syringes. Suspensions retained at least 93.2% of the initial concentration for the entire 91-day study period. Even so, after calculation of the 95% confidence limits, we recommend that the BUD not exceed 75 days for suspensions stored at 4°C or 25°C.

Table 1. Domperidone Concentration and Percent Remaining (Mean ± Coefficient of Variation)* on Each Study Day and Calculation of Time to Achieve 90% Remaining with 95% Confidence

	Storage at 4°C			Storage at 25°C			
Study Day	**PVC**	**Glass**	**PET**	**PVC**	**Glass**	**PET**	**Syringe**
Initial concentration (mg/mL)	5.33±3.06	5.25±0.99	5.20±2.96	5.29±1.47	5.25±2.91	5.43±0.52	5.15±1.49
1	99.53±1.66	99.06±0.95	100.27±3.89	99.66±2.81	98.82±2.54	100.85±1.90	101.73±1.11
2	98.73±0.30	98.38±2.77	98.31±2.18	99.90±0.39	101.75±3.90	104.56±2.46	105.76±1.13
4	95.56±1.20	97.75±2.15	96.23±1.25	97.47±3.02	97.79±3.46	102.61±1.97	101.57±3.76
7	98.12±0.83	99.31±2.40	102.22±1.81	98.61±1.87	99.88±3.14	104.47±0.72	98.90±4.86
10	98.82±1.66	97.85±0.75	99.64±1.81	96.58±2.61	102.20±1.84	101.34±0.77	98.68±4.74
14	97.81±1.98	100.86±0.96	102.53±4.01	98.67±1.73	101.64±4.01	100.30±2.39	100.06±2.48
21	98.96±2.53	95.80±2.24	99.15±7.38	95.74±2.72	97.32±2.07	94.95±5.80	99.07±3.29
28	95.69±0.98	94.99±0.65	98.85±6.16	95.65±0.86	97.99±1.03	96.70±1.40	101.00±2.73
35	101.17±2.16	102.86±4.01	107.12±3.16	102.18±3.72	104.36±0.71	105.00±0.81	103.22±3.99
42	96.82±4.29	99.42±2.37	103.90±6.00	96.64±5.42	99.33±1.49	101.93±2.38	101.01±2.34
49	94.90±2.29	95.66±1.04	98.26±1.45	94.85±1.12	96.81±2.53	98.91±2.01	95.45±2.96
63	95.90±1.80	99.05±1.29	97.64±2.02	95.96±0.54	98.03±1.54	100.04±4.40	94.45±2.21
77	96.40±2.42	96.97±2.70	98.39±1.53	93.42±1.64	98.05±1.69	96.96±0.57	95.49±3.47
91	94.95±2.21	94.46±1.09	95.73±2.53	93.20±0.98	95.68±2.27	94.05±2.06	93.74±1.68
Change in % remaining (slope)†	–0.039	–0.031	–0.025	–0.063	–0.039	–0.065	–0.086
% of initial concentration (intercept)	98.718	99.082	100.627	99.091	100.464	102.096	101.889
SD of regression (*Sy.x*)‡	1.656	2.200	3.015	1.869	2.125	2.914	2.328
CI for slope	±0.03263	±0.04335	±0.05942	±0.03684	±0.04188	±0.05743	±0.04589
Time to achieve 90% of initial concentration (T-90) (days)	254.77	321.56	397.36	159.37	256.76	154.40	116.22
Shortest T-90 using lower limit of 95% CI (days)§	139.12	134.32	118.22	100.41	123.72	81.84	75.80
Lowest % remaining on day 91 using lower limit of 95% CI	93.5	93.2	92.3	90.9	92.6	88.9	88.0

CI = confidence interval, PET = polyethylene terephthalate, PVC = polyvinylchloride, SD = standard deviation.
*Each value is based on 3 samples, assayed in duplicate. Percent remaining is relative to the amount measured on day 0 (100%).
†The slope represents the change in concentration as determined by linear regression of percent remaining on each study day.
‡The SD of the regression (*Sy.x*) is equivalent to the interday variability (error) of the analytical method, expressed as a percentage.
§Time to achieve 90% of initial concentration (T-90) is based on the degradation rate (using 95% CI) and is generally regarded as the beyond-use date, but it should never exceed the duration of the study.

The results of this study are very similar to those reported by Ensom and others.[1] Re-analysis of those earlier data[1] by a method identical with the method used in this study showed an estimated amount remaining on day 91 ranging from 81.4% to 94.5%, for suspensions with concentration of 1 mg/mL or 10 mg/mL stored in amber plastic bottles.

Ensom and others[1] reported that some samples assayed higher than 100% during the study period, which was also observed in the current study. However, variation in the analytical method due to instrumentation or volume variation with dilution, along with the technique for sampling a suspension, is very important. In the current study, assay variability averaged less than 2.5%. Although the data for some of the containers indicated that domperidone would be stable for longer than 91 days, the BUD should never be extrapolated past the last day in a stability study. Furthermore, because some suspensions (those in PET bottles and oral syringes stored at room temperature) produced a calculated BUD, with 95% confidence, that was shorter than 91 days, and because there was no significant difference among the tested temperature–container combinations, we recommend the shortest BUD estimated to ensure confidence in the dose delivered on the 75th day after preparation.

It must be appreciated that stability studies are conducted in controlled environments. In real life, compounded suspensions will be stressed during use in hospitals or the home environment. For example, suspensions will be removed from the fridge on a daily basis to retrieve doses, and suspensions intended for refrigerated storage may be inadvertently left out of the fridge for long periods and at temperatures possibly well above the 25°C study temperature tested here. Furthermore, airspace will be created and will increase over time as the suspension is used up. Therefore, a decrease in concentration over time (as was observed with domperidone in this study, especially when using the 95% CI calculation) could result in delivery of a dose up to 10% less than the intended dose. Historically, BUDs have been tied to the time when a product reaches 90% of the label claim.[10] However, we feel that this practice should be reviewed in light of the fact that stability studies are conducted in completely controlled laboratory environments. For drugs with a narrow therapeutic range, giving a dose that is 10% less than the intended dose could result in treatment failure. For this reason, we advocate the use of the 95% CI calculations, and our BUDs are based on those results, but never exceeding the duration of the study.

When a product is stored under a defined set of conditions, the observed concentration on each study day will be determined by the initial concentration, the degradation rate, the analytical variability, and the duration of storage. During a study, there will be some uncertainty associated with these observed concentrations because of error in the analytical method (accuracy and reproducibility). Therefore, daily concentrations reported in a stability study should be viewed as random estimates of the true concentration on that study day. As a result of the variability around the true concentration on any study day, the overall degradation rate from the study must be inferred from the data, and this degradation rate is best calculated using linear regression. The slope of this line is the degradation rate, and it has units of "percent per day" when the data are presented in terms of the percentage remaining.

This study had the power to detect differences in concentration of more than 3%. Neither analysis of variance nor multiple linear regression showed significant changes due to temperature; in comparisons within each container type, this translates into differences in the percent of initial concentration remaining on day 91 of less than 3%. Suspensions stored in all bottle types at room temperature or under refrigeration had differences in the average percentage remaining on day 91 of less than 2.6%, so these differences should also be regarded as nonsignificant and of no practical importance. However, at room temperature, the percent remaining in syringes relative to glass bottles differed by almost 5%. This is a statistically significant difference, and since the concentration on day 91 was determined to be less than 90% (with 95% confidence), this 5% difference is also a clinically important difference. Based on the shortest time to achieve 90% remaining (with 95% confidence), we recommend that the BUD for domperidone suspensions stored at room temperature in PET containers and oral syringes be no more than 75 days. This BUD provides assurance that suspensions stored at room temperature for less than 75 days will contain not less than 90% of the initial concentration.

Acknowledgement of analytical variability leads to the realization that the "best estimate" of the degradation rate from study data is just that: an estimate of the true degradation rate. Furthermore, there needs to be confidence that the true degradation rate is not faster than the best estimate. This is frequently ensured through use of a 95% CI.[11-13]

Assurance of the specificity of the analytical method is also important. The separation and detection of intact drug in the presence of degradation compounds must be demonstrated before the method can be considered stability-indicating. Furthermore, the accuracy and reproducibility of the assay in validation studies and during the stability study (on every assay day) provides the required confidence in the assay methodology, which is absolutely critical in any stability study.

The containers tested in this study included PVC bottles, which are no longer sold by Richards Packaging. However, we felt it was appropriate to test and report results for bottles of this type, using a previously obtained supply, because they may still be available and in use elsewhere in the world.

CONCLUSION

With storage at 4°C in various types of containers (PVC bottles, glass bottles, PET bottles, plastic syringes), more than 90% of the original concentration of domperidone remained after

91 days, with 95% confidence; however, the same did not hold true for suspensions of this drug stored at 25°C. Given that most pharmacies would prefer to store compounded domperidone suspensions at 25°C, for convenience, it is suggested that a shorter BUD of 75 days be assigned.

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Appendix 1: Compounding instructions for domperidone 5 mg/mL*

1. Count out required domperidone 10-mg tablets, and place in a mortar.
2. Soak tablets in Oral Mix vehicle until they are softened sufficiently to allow them to be crushed easily, then add an additional small amount of Oral Mix and levigate to a smooth paste.
3. Add more vehicle to the paste until a liquid is formed. Transfer contents to a graduated cylinder.
4. Use additional Oral Mix vehicle to rinse the remaining drug from the mortar and add it to the graduated cylinder.
5. Make up to the final volume with Oral Mix vehicle. Stir well.
6. Transfer desired volume of suspension to a bottle or syringe.
7. Label the container, assigning a BUD of 75 days, for storage at room temperature or under refrigeration

BUD = beyond-use date
*Based on standard formulation methodology used at The Hospital for Sick Children, Toronto, Ontario.

Ferric Gluconate Complex in Elderly Hospital Inpatients without Terminal Kidney Failure

Patrick Viet-Quoc Nguyen and Judith Latour

ABSTRACT

Background: Anemia is a common health issue for elderly patients. For patients with iron deficiency who cannot tolerate iron supplementation by the oral route, the parenteral route may be used. Options for parenteral iron supplementation include ferric gluconate complex (FGC).

Objectives: To evaluate the safety of FGC in elderly patients without terminal kidney failure and to assess its efficacy in treating iron-deficiency anemia.

Methods: An observational chart review was conducted at a tertiary care university health centre. Patients included in the study were 65 years of age or older, had received at least 1 dose of FGC between January 1, 2014, and December 31, 2015, and had a hemoglobin count of less than 130 g/L (men) or less than 120 g/L (women) at baseline. For each patient, the observation period began when the first dose of FGC was administered and ended 60 days after the last dose. The main safety outcome (occurrence of any adverse reaction) was evaluated for every patient, with the efficacy analysis being limited to patients with a diagnosis of iron-deficiency anemia.

Results: A total of 144 patients were included in the study, of whom 76 had iron-deficiency anemia. No serious, life-threatening adverse reactions were reported. The most commonly reported adverse reactions were nausea and vomiting. The mean increase in hemoglobin count was 13.5 g/L, a statistically significant change from baseline.

Conclusions: These results show that FGC is safe for use in elderly patients, with very few mild adverse reactions. Use of FGC led to increased hemoglobin count within 60 days. Of the 3 options for parenteral iron supplementation available in Canada, iron sucrose has not been studied in elderly patients, and iron dextran has a higher incidence of anaphylaxis, whereas FGC appears to be a safe alternative for patients with intolerance to oral iron.

Keywords: elderly, iron, iron-deficiency anemia, hospital pharmacy service

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RÉSUMÉ

Contexte : L'anémie est un problème de santé courant chez les patients âgés. Les patients qui présentent une carence en fer et une intolérance à la prise de suppléments de fer par la voie orale peuvent être traités par voie parentérale. Le complexe de gluconate ferrique de sodium (CGFS) représente l'une des options d'apport complémentaire en fer par voie parentérale.

Objectifs : Évaluer l'innocuité du CGFS chez le patient âgé qui n'est pas atteint d'insuffisance rénale terminale et évaluer son efficacité dans le traitement de l'anémie ferriprive.

Méthodes : Une analyse observationnelle a été menée au moyen des dossiers médicaux dans un établissement de santé universitaire de soins tertiaires. Les patients dont le dossier médical a été retenu pour l'analyse étaient âgés de 65 ans ou plus, avaient reçu au moins une dose de CGFS entre le 1er janvier 2014 et le 31 décembre 2015 et présentaient initialement un taux d'hémoglobine de moins de 130 g/L (hommes) ou de moins de 120 g/L (femmes). Pour chaque patient, la période d'observation s'étendait du moment où la première dose de CGFS avait été administrée au soixantième jour suivant la dernière dose. Le principal paramètre d'évaluation de l'innocuité (survenue de toute réaction indésirable) faisait l'objet d'une évaluation pour chaque patient. L'analyse de l'efficacité se limitait aux patients ayant reçu un diagnostic d'anémie ferriprive.

Résultats : Au total, 144 patients ont été admis à l'étude et, parmi eux, 76 présentaient une anémie ferriprive. Aucune réaction indésirable grave menaçant la vie du patient n'a été notée. Les réactions indésirables les plus souvent signalées étaient des nausées et des vomissements. L'augmentation moyenne des taux d'hémoglobine était de 13,5 g/L, un changement statistiquement significatif comparé à la valeur de départ.

Conclusions : Les résultats montrent que le CGFS est sécuritaire pour le patient âgé et qu'il ne provoque que très peu de réactions indésirables légères. L'emploi du CGFS a produit une augmentation des taux d'hémoglobine en moins de 60 jours. Parmi les 3 options d'apport complémentaire en fer pris par voie parentérale disponibles au Canada, le fer-saccharose n'a pas été étudié auprès de patients âgés et le fer-dextran est associé à une plus grande incidence de cas d'anaphylaxie; or, le CGFS semble être une solution sécuritaire pour les patients qui présentent une intolérance au fer administré par voie orale.

Mots clés : patients âgés, fer, anémie ferriprive, service de pharmacie en établissement de santé

INTRODUCTION

The World Health Organization (WHO) has defined anemia as a condition in which hemoglobin count is less than 120 g/L in women and less than 130 g/L in men.[1] There is some debate about the definition of anemia in older adults; however, the WHO definition is the one most frequently used in epidemiologic studies. Anemia is a common health issue for elderly patients. Its prevalence increases with age, and it affects 7.8% of men and 8.5% of women aged 65 to 74 years, 15.7% of men and 10.3% of women aged 75 to 84 years, and 26.1% of men and 20.1% of women aged 85 years or older.[2] Anemia is associated with cognitive decline and increased risk of death in the elderly population.[3,4]

Anemia occurs in the presence of a depressed level of hemoglobin.[5-7] Among cases where a cause for the anemia can be identified, the most common causes are deficiency of iron, folate, or vitamin B_{12}; kidney failure; and chronic inflammation. However, a large proportion of cases remain unexplained. The treatment focuses on increasing iron stores through supplementation. Iron by oral administration is usually the first-line treatment, because of its low cost and less invasive mode of administration. However, its use is often limited by adverse reactions such as nausea, vomiting, constipation, abdominal pain, diarrhea, black stool, and metallic taste.[8-10] Elderly patients are vulnerable to these reactions, especially when high doses are administered.[5,11] Furthermore, iron absorption can be hindered by reduced production of stomach acid and the widespread use of proton pump inhibitors.[12,13]

Parenteral iron supplementation is an alternative mode of administration that leads to more effective and more rapid increases in hemoglobin than occur with oral iron.[5] Parenteral administration can improve iron stores without concern about absorption or gastrointestinal side effects.[6,14] It is usually recommended in situations of intolerance, contraindications, or inadequate response to oral iron.[7,15] The use of these forms of iron was previously limited by the associated risk of hypersensitivity reaction, especially with the iron dextran compound. Dextran, sucrose, and ferric gluconate complex (FGC) are the only parenteral iron salts currently available in Canada. For this study, FGC was used because of its lower risk of hypersensitivity reaction and lower cost, relative to the dextran and sucrose forms.[6,14]

In fact, FGC is indicated for treating iron-deficiency anemia in patients undergoing long-term hemodialysis who are receiving supplemental erythropoietin therapy, and the drug has to date been studied only in this context.[16] In clinical practice, FGC is also administered to elderly patients with other conditions.

The main goal of this study was to evaluate the safety of FGC in patients aged 65 years or older without terminal kidney failure. The secondary objective was to evaluate the effect of FGC on hemoglobin count. Ferritin and transferrin saturation are better than hemoglobin as markers of iron therapy response. However, these markers were deemed unsuitable for the current retrospective study, because they are not systematically measured in patients receiving parenteral iron; as such, many data would be missing, which would render any comparisons irrelevant.

METHODS

This observational chart review was carried out at the Centre hospitalier de l'Université de Montréal (CHUM), a tertiary care university health centre. To identify eligible participants, a computer-generated list of all patients 65 years of age or older who had received at least 1 dose of FGC from January 1, 2014, to December 31, 2015, was reviewed. For each patient, the observation period began when the first dose of FGC was given and ended 60 days after the last dose. FGC was administered as 125 mg diluted in 100 mL of 0.9% sodium chloride (normal saline solution) and infused intravenously over 60 min.

The following inclusion and exclusion criteria were applied. Men were included if their hemoglobin count was less than 130 g/L before receiving FGC, and women if their hemoglobin count was less than 120 g/L. Only patients with a hemoglobin count during the 60 days after the last FGC dose were included. Patients were excluded if they received an FGC dose in the ambulatory care unit without being admitted to the hospital as an inpatient. Patients with active bleeding and those receiving palliative care were also excluded. This study focused on patients without terminal kidney failure, a population that has not been considered in previous studies. Therefore, patients receiving hemodialysis and those with terminal renal failure (creatinine clearance < 10 mL/min) were excluded. Patients were also excluded if they were given any other type of parenteral iron, erythropoietin, or more than 7 days of oral iron in the 2 months before or during the study. Patients who received a blood transfusion during the study period and those whose FGC perfusion occurred over a period of more than 30 days were also excluded. For patients with multiple admissions during the study period, data were analyzed for only the first admission.

Because the study goal was to assess the safety of FGC, a diagnosis of iron-deficiency anemia was not required. FGC is prescribed for every patient receiving total parenteral nutrition (TPN) in the study hospital, with FGC and TPN being administered separately to all patients without contraindications. The FGC dose varied according to the patient's hemoglobin value. Patients receiving FGC with TPN were included in the study, as were patients with mixed-type anemia who received FGC. However, for the efficacy analysis, only patients with iron-deficiency anemia, as diagnosed by the responsible physician, were included.

The study was approved by the CHUM Research Centre Ethics Committee. Given the observational nature of the study, participants' consent was not required; in addition, identifying information was removed from the data at the beginning of the analysis.

Outcome Measures

Demographic and medical data were extracted from the medical records. Information about the cause and type of anemia was collected. The following common causes of iron-deficiency anemia[7,9] were also collected, if this information had been entered in the chart by the responsible physician: malnutrition, gastrectomy, duodenal bypass, *Helicobacter pylori* infection, tumours, intestinal cancer, inflammatory bowel disease, angiodysplasia, hemorrhoids, diverticulitis, intravascular hemolysis, menorrhagia, systemic bleeding, malabsorption syndrome, and thalassemia. The use of certain medications, such as nonsteroidal anti-inflammatory drugs, anticoagulants, and proton pump inhibitors, was also collected. The iron deficit for each patient (i.e., the total iron dose required) was calculated using the following formula: body weight × (desired hemoglobin – observed hemoglobin) × 2.4 + 500 mg.[17]

The main safety outcome (occurrence of adverse reactions) was systematically evaluated for each patient. Vital signs were assessed by nursing staff 3 times per day and during the hour following FGC infusion, and any adverse reactions were to be documented at the same time. The medical and nursing observation sheets were actively searched for known adverse reactions (i.e., anaphylaxis, nausea, vomiting, pruritus, flushing, myalgia, arthralgia, back pain, chest pain, hypotension, drowsiness, and dizziness) that occurred during FGC administration or in the subsequent 24 h. All adverse reactions described by a physician, nurse, or pharmacist were recorded for analysis. Reactions were defined as severe if they were life-threatening, caused permanent damage, or required intensive care; moderate if a specific therapy was needed to prevent further reaction; and mild if they required no therapy and resolved within 24 h. The Naranjo algorithm[18] was used to determine the likelihood of an adverse drug reaction being due to the drug, with a score of 1–4 indicating a possible adverse drug reaction, a score of 5–8 indicating a probable adverse drug reaction, and a score of 9 or higher indicating a certain adverse drug reaction.

The primary efficacy outcome was determined as an increase in hemoglobin count during the 60-day observation period. The following elements of complete blood count were also evaluated in the efficacy analysis: hematocrit, mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC). Values for ferritin, serum iron, transferrin, and total iron-binding capacity were also collected. For the purposes of this analysis, data were collected for baseline and for 3 periods after each patient's last FGC dose (1–14 days, 15–30 days, and 31–60 days). If a patient had more than one result available for a particular period, the mean value was calculated. All measurements were performed with the Sysmex XE-2100 blood analyzer, and quality control was performed daily. The acceptable standard deviation of this system was 1%.

Statistical Analysis

Continuous variables with normal distribution are reported as means with standard deviation (SD), and categorical variables are reported as proportions. The safety outcome was also described using proportions. The efficacy of FGC was evaluated in terms of the difference between the baseline and highest values for hemoglobin, hematocrit, MCV, and MCHC during the study period. The same analysis was performed for the cumulative 14-, 30-, and 60-day periods. These comparisons were tested statistically with the *t* test for paired observations. Subgroup analyses were performed for 3 variables: FGC dose (comparing total doses of 125–374 mg, 375–624 mg, and 625–1000 mg), frequency of administration (daily versus interval of 48 h or longer), and kidney function (based on a categorical variable for creatinine clearance: ≤ 60 mL/min or > 60 mL/min). For all subgroup analyses, differences in continuous variables were evaluated using analysis of variance with Bonferroni correction. The dichotomous analysis for hemoglobin increase was performed with the χ^2 test for the subgroup analyses based on kidney function and daily versus less frequent administration and by logistic regression for the subgroup analysis based on FGC dose. Missing data are inherent to retrospective, chart-based studies. By default, all missing data for categorical variables were assigned a value of 0 (meaning "not present"), and all missing data for continuous variables were deemed to be "missing", with no value assigned.

SPSS software (IBM, Armonk, New York) was used for the statistical analyses, and an α value of less than 0.05 was chosen to indicate statistical significance.

RESULTS

From January 1, 2014, to December 31, 2015, the pharmacy registry files showed an entry for dispensing of FGC for 684 patients. Of these, 144 met the eligibility criteria and were included in the current study (Figure 1). Baseline characteristics are reported in Table 1. The mean age was 77 years, and 71 (49%) of the patients were men.

Seventy-six patients had a diagnosis of iron-deficiency anemia. Twenty-nine of these patients had mixed-type anemia: 20 with kidney failure anemia, 6 with chronic inflammation anemia, and 3 with vitamin B_{12} deficiency. Thirty-six of the patients with iron-deficiency anemia had no documented risk factor. The 68 patients without a diagnosis of anemia were receiving TPN; these patients were excluded from the efficacy analysis. Table 2 describes the FGC dosage for all 144 patients.

Clinical Outcomes

A total of 402 doses of FGC were administered to the 144 patients. No serious, life-threatening adverse reactions were reported in any patient chart. Less serious adverse reactions were reported for 16 patients (11%): 9 patients with a single adverse

reaction and 7 patients with 2 adverse reactions. The most frequent side effects were nausea and vomiting, both of which affected 8 patients (6%); in addition, 3 patients (2%) experienced hypotension. Chest pain, dizziness, headache, and lower leg pain were each reported for 1 patient. All adverse reactions were scored as "possibly" related to FGC, according to the Naranjo algorithm.

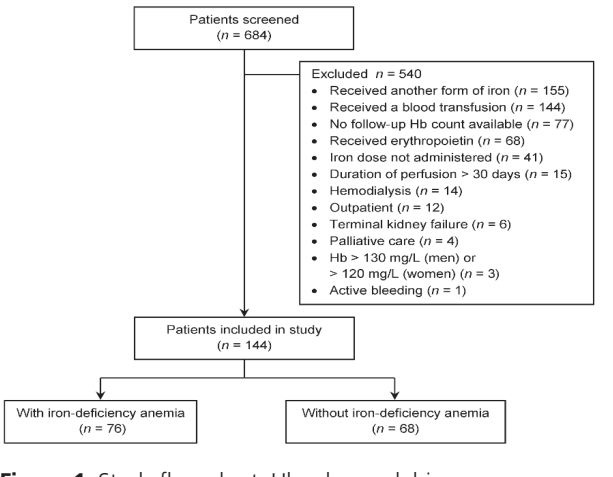

Figure 1. Study flow chart. Hb = hemoglobin.

Among the 76 patients with iron-deficiency anemia, complete blood count data were available for 60, 42, and 35 patients for days 1–14, 15–30, and 31–60, respectively (Table 3). Baseline values for ferritin, serum iron, transferrin, and total iron-binding capacity were available for 23 patients. The mean total dose of FGC administered to patients with iron-deficiency anemia was 458 mg (SD 304 mg). The calculated iron deficit was available for 70 patients (mean deficit 1161 mg, SD 301 mg), 6 of whom received an appropriate FGC dose. The highest mean hemoglobin value obtained during the observation period was 105 mg (SD 14 g/L). During their respective observation periods, 14 (18%) of the 76 patients achieved an increase of up to 10 g/L, 11 (14%) had an increase between 10.1 and 15 g/L, and 18 (24%) had an increase of 15.1 to 20 g/L. The mean increase in hemoglobin count was 13.5 g/L (95% CI 10.3–16.7 g/L). The difference in hemoglobin count relative to baseline was statistically significant for each of the subdivided observation periods and the overall period ($p < 0.01$). Similarly, hematocrit levels were significantly superior to baseline during the subsequent observation periods ($p < 0.01$). Mean hematocrit increased by 3.2%, 4.7%, and 4.2% during days 1–14, days 15–30, and days 31–60, respectively, and by 4.7% across the overall observation period.

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	No. (%) of Patients* (*n* = 144)
Age (years) (mean ± SD)	77 ± 7.8
Sex, male	71 (49)
Weight (kg) (mean ± SD)	68 ± 19
Baseline hemoglobin (g/L) (mean ± SD)	92.9 ± 12.5
Kidney function	
CrCL (mL/min) (mean ± SD)	58 ± 27
Mild–moderate kidney disease (CrCL 30–60 mL/min)	49 (34)
Severe kidney disease (CrCL 10–30 mL/min)	26 (18)
Risk factors for iron-deficiency anemia	
Systemic bleeding	24 (32)
Malnutrition	6 (8)
Intestinal cancer	5 (7)
Angiodysplasia	5 (7)
Diverticulitis	3 (4)
Hemorrhoids	2 (3)
Inflammatory bowel disease	2 (3)
Gastrectomy	2 (3)
ß-Thalassemia	1 (1)
Hypersplenism	1 (1)
Concomitant medication	
Proton pump inhibitor	109 (76)
Anticoagulant	28 (19)
NSAID	19 (13)

CrCL = creatinine clearance (calculated with Cockcroft–Gault equation),
NSAID = nonsteroidal anti-inflammatory drug, SD = standard deviation.
*Except where indicated otherwise.
†Calculated for the 76 patients with iron deficiency anemia.

Subgroup Analyses

In patients with iron-deficiency anemia, total FGC doses of 125–374 mg (*n* = 29 patients), 375–624 mg (*n* = 25), and 625–1000 mg (*n* = 22) led to increases in hemoglobin count of 10.5, 16.1, and 14.4 g/L, respectively (Table 4). The increase was similar across the 3 groups. Creatinine clearance was available for 70 patients, 26 with a value of 60 mL/min or less and 44 with a value higher than 60 mL/min. There was no statistically significant difference in hemoglobin increase between these 2 groups. Among the 76 patients who received more than 1 FGC dose, 51 received FGC every 24 h (mean total FGC administered 571 mg [SD 291 mg]), and 25 received FGC at intervals of 48 h or longer (mean total FGC administered 505 mg [SD 273 mg]). There was no significant difference in hemoglobin increase between these 2 groups.

Table 2. FGC Dosage and Number of Doses Administered

FGC Dosage	No. (%) of Patients (*n* = 144)	Mean No. of Doses Administered
125 mg once daily	53 (37)	3.4
125 mg once every 2 days	23 (16)	4.0
125 mg once every 3 days	4 (3)	3.3
125 mg once a week	42 (29)	1.8
125 mg once every 2 weeks	22 (15)	1.3

FGC = ferric gluconate complex.

DISCUSSION

In clinical practice, FGC is often administered to treat iron-deficiency anemia, mainly because of the shorter duration of therapy relative to that of oral iron, as well as more rapid onset and lower rate of gastrointestinal adverse reactions, especially constipation.[7,15] It is also a good alternative when the oral route is unavailable. However, evidence for use of FGC in patients who are not receiving hemodialysis is scarce.

An open-label randomized trial involving 113 patients compared oral iron (*n* = 25) with FGC 500 mg (*n* = 41) and FGC 1000 mg (given in 8 doses of 125 mg each; *n* = 47) during hemodialysis sessions.[16] The mean age was 55, 57.1, and 52.2 years for the 3 groups, respectively. The increase in hemoglobin with the higher dose of FGC was statistically greater than that achieved with oral iron, but there was no difference between oral iron and the lower dose of FGC. No severe adverse reactions (including anaphylaxis) were reported, but there were some mild adverse reactions, such as nausea, vomiting, and rash. Another study compared the efficacy and safety of FGC and iron sucrose

Table 3. Hematologic Results for Patients with Iron-Deficiency Anemia

Variable	Timeframe; Mean ± SD			
	Baseline (*n* = 76)	Day 1–14 (*n* = 60)	Day 15–30 (*n* = 42)	Day 31–60 (*n* = 35)
Hemoglobin (g/L)	91 ± 12	96 ± 12	103 ± 16	104 ± 15
Hematocrit	0.28 ± 0.05	0.32 ± 0.04	0.33 ± 0.05	0.32 ± 0.07
MCV (fL)	86 ± 7	89 ± 6	88 ± 6	88 ± 6
MCHC (pg)	27 ± 3	28 ± 2	28 ± 3	28 ± 2
Ferritin (µg/L)*	57.5 ± 48	–	–	–
Transferrin saturation*	0.09 ± 0.04	–	–	–

MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, SD = standard deviation.
*For these variables, baseline data were available for 23 patients.

Table 4. Change in Hemoglobin in Patients with Iron-Deficiency Anemia (Subgroup Analyses)

Subgroup	Change in Hemoglobin (g/L)* (Mean and 95% CI)
Total FGC dose administered	
125–374 mg (*n* = 29)	10.5 (6.1 to 15.0)
375–624 mg (*n* = 25)	16.1 (9.4 to 22.8)
625–1000 mg (*n* = 22)	14.4 (8.4 to 20.4)
Kidney function	
CrCl ≤ 60 mL/min (*n* = 26)	14.0 (9.8 to 18.3)
CrCl > 60 mL/min (*n* = 44)	14.1 (9.3 to 18.9)
Frequency of FGC administration	
125 mg every 24 h (*n* = 51)	14.7 (–0.5 to 29.9)
125 mg every 48 h or longer (*n* = 25)	11.0 (0.6 to 21.4)

CI = confidence interval, CrCL = creatinine clearance (calculated with Cockcroft–Gault equation), FGC = ferric gluconate complex.
*Change relative to baseline.

in 55 patients receiving hemodialysis (mean age 59 years).[19] There was no statistically significant difference between the 2 groups in terms of efficacy and safety. Various trials have assessed the safety of FGC in patients receiving hemodialysis without a test dose, in iron dextran–sensitive and iron dextran–tolerant patients, and in patients receiving a dose of 250 mg or more.[20-23] All of the patients in these studies were receiving hemodialysis, and the mean age ranged from 50 to 60 years. There was only one case of anaphylaxis with exposure of more than 5000 patients, and the other side effects were mild to moderate.[20-23] No studies investigating FGC in non-hemodialysis patients or in an elderly population were found in the literature. The current study therefore provides a first insight into the safety and efficacy of FGC in elderly patients who are not receiving hemodialysis.

This study has shown that FGC is safe for elderly patients without kidney failure and those with mild to severe kidney failure, as no severe adverse reactions and only a few mild adverse reactions were reported. These results indicate that the FGC safety profile, based on results of prior clinical trials involving younger patients receiving hemodialysis,[20-22] can be extended to elderly patients. This is not surprising, given that hemodialysis patients have many comorbidities and may be sicker than hospitalized elderly patients. Some aspects of this therapy remain to be explored; for example, adverse reactions were not assessed prospectively, and the study population was rather small for detecting serious adverse effects. For confirmation of these findings, a larger sample would be necessary, given the low incidence of serious adverse reactions, especially with low doses.[24] In addition, the possibility of anaphylaxis cannot be excluded. As reported in here, hypotension may occur after the infusion; therefore, caution and monitoring are required.

FGC use was associated with increases in hemoglobin count and hematocrit in elderly patients with anemia. Despite these increases, it is likely that patients' iron storage was not fully restored, given that the dose administered was less than the calculated iron deficit. Nonetheless, augmentation was superior to that reported in previous trials, despite the lower total infused dose. In the study by Nissenson and others,[16] a 500-mg dose of FGC led to an increase in hematocrit of 5 g/L, whereas a 1000-mg dose led to an increase of 13 g/L after 30 days. In the study by Kosch and others,[19] a total monthly FGC dose of 375 mg led to an increase in hemoglobin of 0.9 g/L after 6 months of treatment. Terminal kidney failure is associated with lower levels of erythropoietin and increased inflammation, which leads to reduced bone marrow production in reaction to anemia.[25] A weaker response to iron supplementation could be expected in these patients.

Preservation or impairment of kidney function did not seem to affect the efficacy of FGC. Daily FGC administration also seemed to be as effective as administration at intervals of 48 h or longer. This analysis is important, as the optimal administration schedule is unknown for this population. During prior clinical trials, FGC was administered during dialysis, which generally occurs 2 or 3 times a week, with a period of at least 48 h between consecutive doses. This optimal dosage regimen remains to be confirmed in a prospective study, given that a shorter interval between doses is more convenient, especially in the hospital setting.

This study had several limitations. The study design was retrospective. The study population was heterogeneous, and many different medical specialties were involved in caring for the patients. A variety of uncontrolled confounding factors may have been present, given that retrospective chart-based studies are vulnerable to missing data. The medical chart is a legal document, so documentation of severe adverse events would be expected; however, milder adverse events may have been underestimated because of lack of documentation. There was no control group for comparison of the efficacy data. Volume contraction or expansion can alter hemoglobin levels and may have confounded the results. The margin of error for hemoglobin measurements may have confounded the results. To reduce the effect of this limitation, mean values were used for the various observation periods, and data were analyzed from a large sample of 76 patients. Iron storage was not evaluated, as ferritin values were unavailable in the follow-up period. Some patients were followed as outpatients, and we cannot exclude the possibility of blood transfusion or iron or erythropoietin administration during outpatient follow-up.

Parenteral iron therapy may be considered when oral administration of iron is contraindicated. Clinicians may choose iron dextran, iron sucrose, or FGC. All of these iron formulations have demonstrated efficacy for patients with severe chronic and end-stage kidney failure, with or without hemodialysis.[26,27] However, their efficacy and safety in the elderly population remains poorly studied, and there have been no prospective, placebo-controlled trials in this age group. Nearly 30 years ago, a prospective trial of IV iron dextran was carried out in elderly patients, but it was terminated because of adverse effects.[28] A retrospective study published in 2014 evaluated the safety of iron dextran in geriatric patients, 67% of whom had severe to end-stage renal failure.[29] Iron dextran was considered safe and effective in this population. Cuenca Espiérrez and others[30] found that a single 250-mg dose of iron sucrose reduced the need for transfusion in elderly patients with hip fracture. Anaphylactic reaction remains a concern with IV administration of iron. In a comparative study, iron sucrose had the lowest incidence of anaphylactic reaction, followed by FGC, and then iron dextran.[24]

CONCLUSION

The choice of iron salt for IV infusion in elderly patients with iron-deficiency anemia remains challenging. No studies have demonstrated the efficacy of any particular iron salt for this indication. Iron sucrose may be a safe option, but its safety has

not been demonstrated within the elderly population. In addition, there have been frequent interruptions in the supply of iron sucrose in Canada in recent years. Iron dextran might be another option, but a higher incidence of anaphylaxis limits its use. FGC is a safe choice for treating iron-deficiency anemia in elderly patients, and its supply may be more reliable. This study provides the foundation for a prospective randomized clinical trial to evaluate the efficacy and safety of FGC in the elderly population.

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ORIGINAL RESEARCH

Implementation of a Pharmacist-Led Inpatient Tobacco Cessation Intervention in a Rehabilitation Hospital: A Before-and-After Pilot Study

Vivian W Li, James Lam, Pam Heise, Robert D Reid, and Kerri A Mullen

ABSTRACT

Background: Inpatient rehabilitation presents a unique opportunity for smoking interventions, given the typical lengths of stay, the relevance of smoking to the admission diagnosis of many patients, and the occurrence of nicotine withdrawal during the hospital stay.

Objective: To evaluate the feasibility of implementing a pharmacist-led version of the Ottawa Model for Smoking Cessation (OMSC) program at a rehabilitation hospital, using the indicators of reach, effectiveness, adoption, and implementation.

Methods: A before-and-after pilot study was conducted. Smoking cessation data were collected from 2 cohorts of eligible smokers identified during 4-month periods before (control) and after (intervention) implementation of the OMSC program. Control participants received usual care (i.e., no cessation intervention). Intervention participants received initial in-hospital smoking cessation support (counselling and nicotine replacement therapy), inpatient follow-up during the hospital stay, and 3 months of postdischarge follow-up calls, with all aspects led by hospital pharmacists.

Results: Among all patients admitted to participating inpatient rehabilitation units during the 2 study periods, smoking prevalence was 7.8% (127/1626). After exclusions, deaths, and withdrawals, 111 patients were retained for analysis: 55 in the control group and 56 in the intervention group. The overall mean age of participants was 64.9 (standard deviation [SD] 14.3) years, with a mean smoking history of 35.0 (SD 24.8) pack-years. There were no significant differences between groups in terms of baseline characteristics. Self-reported abstinence rates (determined 3 months after discharge) were higher after compared with before implementation of the OMSC program: for continuous abstinence, 16/56 (28.6%) versus 9/55 (16.4%), $\chi^2 = 4.462$, $p = 0.035$; for 7-day point prevalence abstinence, 21/56 (37.5%) versus 10/55 (18.2%), $\chi^2 = 6.807$, $p = 0.009$.

Conclusions: Implementation of the OMSC program at a large rehabilitation hospital was feasible and led to an increase in 3-month smoking abstinence. This study provides preliminary evidence to support inclusion of smoking interventions as part of inpatient rehabilitation care.

RÉSUMÉ

Contexte : La réadaptation des patients hospitalisés représente une occasion unique de procéder à des interventions de désaccoutumance du tabac, notamment en raison de la durée habituelle des séjours, du rapport entre le tabagisme et le diagnostic posé à l'admission, et de la survenue du syndrome de sevrage de la nicotine durant le séjour.

Objectif : Étudier la possibilité de mettre en œuvre une version dirigée par des pharmaciens du programme Modèle d'Ottawa pour l'abandon du tabac (MOAT) dans un centre de réadaptation en employant les indicateurs pour la portée, l'efficacité, l'adoption et la mise en œuvre.

Méthodes : Une étude pilote avant-après a été menée. Des données sur la désaccoutumance ont été recueillies auprès de deux cohortes de fumeurs admissibles qui ont été repérés pendant des périodes de quatre mois avant (groupe témoin) et après (groupe expérimental) la mise en œuvre du programme du MOAT. Les participants du groupe témoin ont reçu les soins habituels (c.-à-d. sans intervention de désaccoutumance). Les participants du groupe expérimental ont reçu un soutien initial à l'hôpital pour la désaccoutumance du tabac (des conseils et un traitement de remplacement de la nicotine), un suivi pendant le séjour à l'hôpital, et des appels de suivi pendant les trois mois suivant le congé, le tout sous la direction de pharmaciens d'hôpitaux.

Résultats : Parmi l'ensemble des patients admis dans les unités de réadaptation participantes au cours des deux périodes de l'étude, la prévalence du tabagisme était de 7,8 % (127/1626). Mis à part les exclusions, les décès et les abandons, 111 patients ont été retenus pour l'analyse : 55 dans le groupe témoin et 56 dans le groupe expérimental. L'âge moyen des participants était de 64,9 (écart-type de 14,3) ans et leur antécédent de tabagisme moyen était de 35,0 (écart-type de 24,8) paquets-années. Aucune différence significative n'a été relevée entre les groupes en ce qui touche aux caractéristiques de base. Les taux d'abstinence autodéclarée (déterminée 3 mois après le congé) étaient plus élevés après la mise en œuvre du programme du MOAT : pour une abstinence continue, 16/56 (28,6 %) contre 9/55 (16,4 %), $\chi^2 = 4,462$, $p = 0,035$; pour une abstinence ponctuelle de sept jours consécutifs, 21/56 (37,5 %) contre 10/55 (18,2 %), $\chi^2 = 6,807$, $p = 0,009$.

Conclusions : La mise en œuvre du programme du MOAT dans un important centre de réadaptation a été possible et a mené à une

Keywords: smoking cessation, rehabilitation hospital, Ottawa Model for Smoking Cessation, pharmacist

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amélioration de l'abstinence du tabac à trois mois. Cette étude donne des résultats préliminaires en appui à l'inclusion d'interventions de désaccoutumance du tabac aux soins de réadaptation de patients hospitalisés.

Mots clés : désaccoutumance du tabac, centre de réadaptation, Modèle d'Ottawa pour l'abandon du tabac, pharmacien

INTRODUCTION

Smoking rates have been decreasing over the past 50 years in Canada, but smoking tobacco is still the number 1 preventable cause of morbidity and mortality.[1] In April 2011, the Ontario government renewed its commitment to building a smoke-free Ontario, which included strategies to expand smoking cessation services in health care settings.[2] With the mandated implementation of smoke-free policies in hospitals, the availability of smoking cessation services for hospitalized patients is becoming increasingly important.[3]

For various reasons, inpatient rehabilitation settings provide unique opportunities for smoking intervention and prevention of relapse: most smokers temporarily abstain from tobacco before rehabilitation because of the smoke-free policies that are in effect in acute care hospitals; stroke and other medical crises caused by the health risks associated with cigarette smoking can trigger quit attempts; patients in rehabilitation programs are generally in stable health, which facilitates their participation in cessation programs; and an extended stay in a rehabilitation centre permits intensive and repeated tobacco intervention.[4,5] Moreover, the pooled results from published studies on cessation interventions in rehabilitation hospitals have demonstrated significant increases in smoking cessation rates.[5]

The Ottawa Model for Smoking Cessation (OMSC) is a well-documented cessation model that provides a systematic approach to delivering an evidence-based intervention for tobacco dependence to hospitalized patients.[6-8] The OMSC program, which has been implemented in various hospitals across Canada, has to date been led primarily by nurses or respiratory therapists.[6-8] Pharmacist-led interventions have been shown to be feasible and efficacious in community and ambulatory settings, but results in hospital settings have been mixed.[9-12] To the authors' knowledge, no studies to date have evaluated pharmacist-led smoking cessation programs in rehabilitation centres.

The primary objective of this before-and-after pilot study was to evaluate the feasibility of implementing a pharmacist-led smoking cessation program at a rehabilitation hospital using the RE-AIM framework.[13]

METHODS

Setting

This study was conducted at Providence Healthcare, a large rehabilitation hospital in Toronto, Ontario, with 7 clinical units and an annual admission rate of 2780 patients in 2015/16.[14] This hospital provides transition-of-care rehabilitation services between acute care and home for adults of all ages after stroke, orthopedic surgery, lower limb amputation, and other complex medical conditions generally associated with aging. In 2015/16, the average length of stay for inpatients was 29 days.[14] No formal smoking cessation program existed at the hospital before this study was undertaken.

Study Population

All smokers admitted to the inpatient rehabilitation units (i.e., those self-reporting any tobacco use in the past 6 months) were considered for participation. Patients were excluded if they died during the hospital stay, were receiving palliative care, were transferred to another hospital, or did not speak English. The research was conducted in accordance with the ethical standards of the Providence Healthcare Research Ethics Board (which also approved the study procedures) and the principles set forth in the Helsinki Declaration. All participants read and signed a consent form that had been approved by the Research Ethics Board (Study File no. 2014-013-1501).

Study Design

A before-and-after study was conducted to evaluate the impact of a pharmacist-led smoking cessation program in a rehabilitation setting. Pre-intervention data were collected over the 4 months before the program was launched (from April 1 to July 31, 2015). The control group consisted of all smokers identified during this period who were agreeable to an evaluation call 3 months after discharge. This control group received "usual care" as regards smoking cessation (i.e., no cessation intervention). Post-implementation data were collected for 4 months following the program launch (from August 1 to November 30, 2015). The

intervention group consisted of all smokers identified during this period who were agreeable to an evaluation call 3 months after discharge. Intervention participants received in-hospital smoking cessation support (counselling and nicotine replacement therapy [NRT]), follow-up during the hospital stay, and 3 months of post-discharge follow-up calls.

Ottawa Model for Smoking Cessation Program

The OMSC's "10 Best Practices for Hospital-Initiated Smoking Cessation Interventions"[15] were used to guide smoking cessation intervention practices within the hospital. In preparation for the program launch, a smoking cessation task force was formed to facilitate training of clinical staff, to create standardized clinical tools, to develop protocols for smoking cessation strategies, and to add all first-line smoking cessation medications to the pharmacy formulary. All front-line clinical staff received mandatory training about the OMSC program, and clinical pharmacists received additional training on tobacco-dependence interventions. A dedicated pharmacist specialist (V.W.L.), who had been trained as a Certified Tobacco Educator, was hired on a part-time basis (2 days/week) to facilitate implementation and delivery of the program.

The smoking cessation program was introduced on all participating clinical units on August 1, 2015. The unit pharmacists screened all new admissions for smoking status and documented patients' responses on the admission order form. The dedicated pharmacist specialist delivered the cessation intervention at the bedside using a standardized smoking consultation form, which was based on the 5A's framework: *Ask* (for smoking history), *Advise* (patient to quit), *Assess* (readiness to quit), *Assist* (by providing counselling and pharmacotherapies), and *Arrange* (follow-up, in person or by telephone).[16] Patients who agreed to scheduled follow-up after discharge received up to 5 live calls (on days 3, 14, 30, 60, and 90 after discharge). A standardized follow-up consult form was used to guide patient counselling with regard to quitting. Those who wished to use NRT at home purchased their own supply. Patients were provided with community resources for smoking cessation support beyond the 3-month postdischarge date.

Outcome Measures

The RE-AIM framework[13] guided evaluation of the overall public health impact of the program. Of the 5 components of this framework (reach, effectiveness, adoption, implementation, and maintenance), only the first 4 were used to evaluate this project. The fifth component will be considered in future research.

Reach was assessed by means of the following recruitment variables: prevalence of smoking among all admitted patients, proportion of smokers eligible for the study, proportion of smokers recruited to participate in the study, proportion of smokers who withdrew consent to participate during study follow-up, proportion of participants who died, and proportion of participants who were lost to follow-up.

Effectiveness was examined by comparing self-reported continuous and 7-day point prevalence abstinence rates, determined 3 months after discharge, between the control and intervention groups. Participants in both groups were contacted by telephone at 3 months after discharge and asked to respond "yes" or "no" to the following 2 questions: Have you smoked any form of tobacco in the past 3 months? Have you used any form of tobacco in the past 7 days? An intention-to-treat principle was used, whereby, for the purposes of this analysis, participants who were lost to follow-up were considered to be smoking, as per the Russell standard.[17]

Adoption was measured as the proportion of all possible hospital units that implemented the program.

Finally, the indicators of implementation were the proportion of possible smoking cessation consultations that were completed, the proportion of intervention participants who received smoking cessation pharmacotherapies, and the proportion of intervention participants who were enrolled in telephone follow-up counselling upon hospital discharge.

Statistical Analysis

Analyses were performed with IBM SPSS Statistics 24 software (IBM, Armonk, New York). Participant characteristics were summarized using *t* tests for continuous variables and χ^2 tests for categorical variables. Program efficacy was assessed by comparing unadjusted and adjusted 3-month abstinence rates between groups using binary logistic regression. The following variables were included in the adjusted models: age, sex, number of cigarettes smoked per day at baseline, length of stay in the hospital, and whether or not the primary admitting diagnosis was smoking-related (i.e., related to cancer, a chronic lung condition, cardiovascular or peripheral vascular disease, or stroke).[18]

RESULTS

Reach

During the pre-intervention data collection period, 812 patients were admitted, of whom 62 were smokers, for a smoking prevalence of 7.6%. Of these 62 pre-intervention smokers, 2 (3.2%) did not meet the inclusion criteria because of inability to communicate in English, and 2 (3.2%) declined participation (Figure 1). Therefore, 58 (93.5%) of the initial 62 smokers were recruited into the control group. Over the 3-month follow-up period, 3 (5.2%) of these control participants died. As a result, 55 (94.8%) of participants in the control group were eligible for the 3-month postdischarge evaluation.

During the post-intervention data collection period, 814 patients were admitted, of whom 65 were smokers, for a smoking

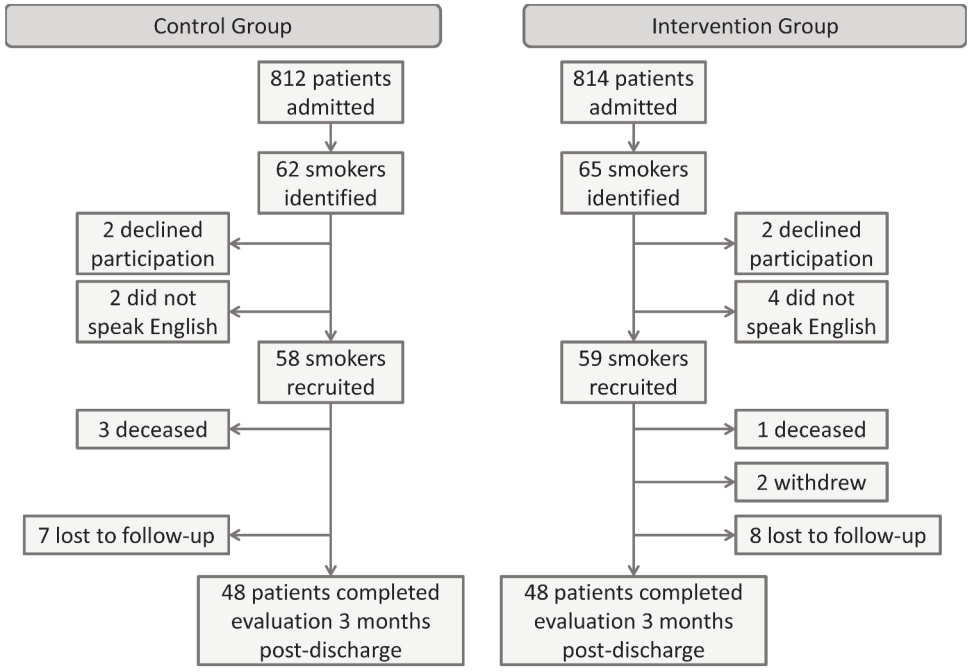

Figure 1. Study flow diagram.

prevalence of 8.0%. Of these 65 post-intervention smokers, 4 (6.2%) did not meet the inclusion criteria because of inability to communicate in English, and 2 (3.1%) declined to participate in the study. Therefore, 59 (90.8%) of the initial 65 smokers were recruited into the intervention group and received the intervention. Over the 3-month intervention follow-up period, 1 participant (1.7%) died and 2 participants (3.4%) withdrew consent for follow-up evaluation. As a result, 56 (94.9%) of participants in the intervention group were eligible for the 3-month post-discharge evaluation.

Seven (12.7%) of the 55 participants in the control group and 8 (14.3%) of the 56 participants in the intervention group could not be reached for the 3-month postdischarge evaluation. For the purposes of the intention-to-treat analysis, these participants were considered to be current smokers.[17]

Participant Characteristics

There were no significant differences between groups in terms of baseline characteristics (Table 1). Overall, the mean age of participants was 64.9 (standard deviation [SD] 14.3) years, and more than half of the smokers were male (65/111, 58.6%). Participants had long smoking histories, with a mean of 35.0 (SD 24.8) pack-years and an average 17.9 (SD 13.1) cigarettes smoked per day. Forty-eight (43.2%) of the participants were admitted for rehabilitation because of a smoking-related illness.[18] The median number of days since the person's last cigarette, as reported at the time of admission, was 7 (range 0.04–90) for the control group and 10 (range 0.04–135) for the intervention group. The median length of stay in hospital was 23 (range 6–159) days for the control group and 23 (range 7–79) days for the intervention group.

Effectiveness

Self-reported abstinence rates, determined 3 months after discharge and adjusted for baseline characteristics, were higher after than before implementation of the OMSC program (Figure 2). For continuous abstinence, the rates were 28.6% (16/56) in the intervention group and 16.4% (9/55) in the control group ($\chi^2 = 4.462$, $p = 0.035$); for 7-day point prevalence abstinence, the rates were 37.5% (21/56) in the intervention group and 18.2% (10/55) in the control group ($\chi^2 = 6.807$, $p = 0.009$). Participants who died were excluded from the analyses, and those lost to follow-up were counted as smokers.[17]

Adoption

Six (86%) of the 7 hospital units adopted the smoking cessation program, The sole exception was the palliative care unit, because palliative care was one of the exclusion criteria. Routine identification of patients who smoked and referral to the smoking cessation program were incorporated into usual hospital practice.

Implementation

The standardized smoking cessation consultation forms were completed for 90.8% (59/65) of smokers identified in the 4 months after OMSC implementation. All participating patients

Table 1. Baseline Characteristics of Study Participants

Characteristic	Overall (*n* = 111)	Control (*n* = 55)	Intervention (*n* = 56)	Test Statistic	*p* Value
Mean age (years) ± SD	64.9 ± 14.3	64.5 ± 14.1	65.3 ± 14.5	t = –0.30 df = 109	0.77
Mean no. of cigarettes/day ± SD	17.9 ± 13.1	18.8 ± 13.3	17.0 ± 13.0	t = 0.72 df = 106	0.48
Sex, no. (%) male	65 (58.6)	34 (61.8)	31 (55.4)	χ^2 = 0.48 df = 1	0.49
No. (%) with smoking-related admission diagnosis*	48 (43.2)	28 (50.9)	20 (35.7)	χ^2 = 2.61 df = 1	0.11
Median time since last cigarette and range (days)	8 (0.04–135)	7 (0.04–90)	10 (0.04–135)	F = 1.02	0.32
Median hospital length of stay and range (days)	23 (6–159)	23 (6–159)	23 (7–79)	F = 1.75	0.19

SD = standard deviation.
*The following admission diagnoses were classified as smoking-related: neoplasm or cancer-related, cardiovascular disease (including acute coronary syndrome and heart failure), stroke, respiratory condition (including chronic obstructive pulmonary disorders and bronchitis), and limb amputation for peripheral vascular disease.

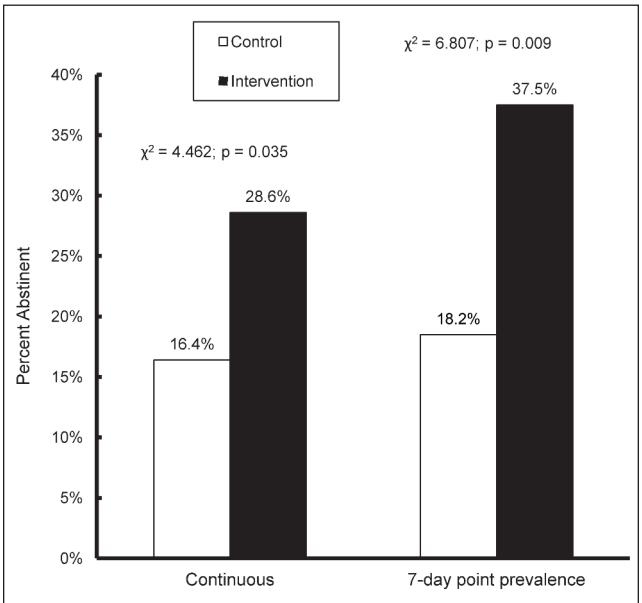

Figure 2. Smoking abstinence rates (continuous and 7-day point prevalence), as reported by participants 3 months after discharge from the rehabilitation hospital.

received a structured, brief counselling session during completion of the consultation. Each consultation lasted 30 to 40 min, and inpatient follow-up ranged from 20 to 30 min. Overall, NRT was prescribed to 71.2% (42/59) of the intervention group during the hospital stay; other smoking cessation medications were available but not utilized. In addition, NRT was used after discharge by 28.6% (16/56) of patients in the intervention group. Among participants in the intervention group, the majority (40/56, 71.4%) were ready to quit at the time of dischange and received the scheduled telephone follow-up. Those who declined scheduled follow-up calls either felt they had already quit while in hospital (and thus did not require follow-up calls) or did not wish to quit. Each follow-up telephone call took 10 to 20 min.

DISCUSSION

This study demonstrated the feasibility of implementing a pharmacist-led smoking cessation intervention in a rehabilitation hospital. Following implementation of the OMSC program, pharmacists provided smoking cessation interventions to more than 90% of admitted smokers, which led to high uptake of both in-hospital NRT and follow-up support after discharge. Over the short term (i.e., at 3 months after discharge), participants in the intervention group showed higher rates of smoking abstinence than those in the control group.

A meta-analysis of results from 9 OMSC hospital sites in Ontario, most of which used a nurse-led intervention, showed that in-hospital NRT use ranged from 6% to 58%; in contrast, the pharmacist-led intervention in the current study resulted in 71.2% of patients using NRT during their hospital stay for the purposes of nicotine withdrawal management and smoking cessation.[6] It is possible that the longer lengths of stay among patients in a rehabilitation hospital (relative to acute care hospitals) led to greater use of NRT to manage the discomfort of nicotine withdrawal. It is also possible that pharmacists are more likely than other health care professionals to recommend NRT to patients who smoke, because of their knowledge about and comfort in using and managing the relevant medication. The proportion of patients who used NRT at home (after discharge) dropped to 28.6%. It is possible that patients had less need for NRT at home following prolonged abstinence during the hospital stay. The cost of NRT may have also contributed to low utilization of NRT after discharge. Future research should investigate whether providing free NRT to patients after hospitalization has positive effects on the cessation rate.

Two-thirds of the participants enrolled in postdischarge follow-up, a rate much higher than reported in evaluations of the OMSC program in general hospitals (8% to 32%).[6,7] Participants in the current study received live calls from the pharmacist

specialist, a person whom they had met during their initial consultations. More commonly, follow-up offered by hospitals using the OMSC intervention begins with automated telephone calls that are monitored by nurse counsellors, who are different from the nurses with whom patients originally spoke while in hospital. Only patients who indicate during the automated calls that they are struggling with cessation receive a call-back from a nurse counsellor. It is possible that patients prefer follow-up from a health professional whom they have met in person. The 12.2% absolute improvement in 3-month continuous postdischarge cessation rate was similar to that observed in previous evaluations of other inpatient smoking cessation programs adapted from the OMSC program, in which 6-month absolute improvements in cessation rates ranged from 11% to 15%.[6,7,14]

To the authors' knowledge, this is the first investigation of a pharmacist-led smoking cessation program in a rehabilitation hospital. The results obtained here were positive, in contrast to the negative results obtained in a previous study of pharmacist-led smoking cessation at tertiary care hospitals.[11] It is possible that pharmacists in rehabilitation settings have more opportunities to engage smokers and optimize the use of NRT. Because the majority of admissions to the rehabilitation hospital came from smoke-free acute care hospitals, the pharmacist-led interventions in this study focused on managing nicotine withdrawal symptoms and maintaining continued abstinence during hospitalization. Differences in cessation management in rehabilitation hospitals may also have affected the study results. Two key facilitators of program implementation in the current study were (1) the presence of an existing hospital protocol, whereby a full-time unit pharmacist was available to screen smoking status of new admissions on each unit, and (2) the use of a dedicated specialist pharmacist (2 days/week) to provide the tobacco-dependence interventions. Expansions in scope of practice for pharmacists in Ontario have encouraged the profession to shift toward providing smoking cessation interventions as part of clinical practices.[19] This study demonstrated the feasibility of having pharmacists lead a smoking cessation initiative in an inpatient rehabilitation setting.

This pilot study had several limitations. The sample was small because of the low prevalence of smoking among patients admitted to the study institution and the limited recruitment period. However, we did collect important recruitment and effectiveness data that will support planning for a larger trial. There was no biochemical verification of smoking abstinence at follow-up, so these data relied completely on self-reporting.[6] Smoking cessation was evaluated only once, 3 months after discharge; therefore, we cannot draw inferences about the long-term effects of the cessation program. However, as part of this pilot program, patients were informed about community resources to support smoking cessation beyond 3 months, and these may contribute to long-term smoking cessation outcomes. In addition to determining long-term outcomes, future studies should examine the impact of hospital-based smoking cessation interventions on in-hospital smoking cessation and on health and health care outcomes, including recovery, healing, procedure complications, and length of stay. Evaluation of the sustainability of the cessation program was not assessed in the current study.

CONCLUSION

Implementation of a pharmacist-led OMSC program at the study rehabilitation hospital was feasible and led to an increase in 3-month smoking abstinence rates. This study provides preliminary evidence to support the inclusion of smoking interventions as part of inpatient rehabilitation care, both to ensure patient comfort and safety and to improve patient outcomes.

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Interventions visant l'application des connaissances en pratique pharmaceutique

par Apolline Adé, Denis Lebel et Jean-François Bussières

RÉSUMÉ

Contexte : La littérature scientifique portant sur l'application des connaissances (AC) est vaste et complexe et les publications sur les interventions dans le domaine de la santé concernent surtout les médecins et les infirmières. Pour autant que les auteurs sachent, il n'existe pas de revue documentaire s'intéressant à l'AC et à ses retombées en pharmacie.

Objectif : Décrire le profil des interventions visant l'AC en pratique pharmaceutique.

Source des données : La plateforme Knowledge Translation+ (KT+) a été utilisée pour en extraire des articles publiés entre janvier 2010 et décembre 2016 à l'aide du terme « pharmacist ».

Sélection des études et extraction des données : Les principales variables retenues pour établir le profil des interventions visant l'AC en pratique pharmaceutique étaient le protocole de recherche de l'étude, le lieu de l'intervention, les rôles du pharmacien, les types de connaissances transférées et les retombées. Le codage de la nature des interventions pharmaceutiques reposait sur la classification du site Impact Pharmacie.

Synthèse des données : Au total, 114 articles ont été sélectionnés : revues systématiques (n = 25, 22 %), études contrôlées à répartition aléatoire (n = 45, 40 %) études rétrospectives (n = 21, 18 %), études prospectives (n = 13, 11 %), études pré-post intervention (n = 10, 9 %). Les études se déroulaient surtout en établissement de santé (74 %). La majorité des interventions ciblaient des étapes de soins pharmaceutiques et la réalisation de séances d'éducation thérapeutique et de conseils prodigués aux patients. Il existait un manque de rigueur méthodologique lors de la conception des interventions et quant à leur description.

Conclusion : Le pharmacien est le principal producteur de connaissances et oriente les interventions visant leur application vers les patients ou les professionnels de santé. Celles-ci concernaient principalement la démarche de soins pharmaceutiques et le travail en interdisciplinarité. La mise en place d'une formation initiale et continue, la gestion de l'information et la désignation d'un pharmacien responsable de l'AC au sein de chaque département de pharmacie pourraient encourager le développement de cette mise en application des connaissances. Ce concept peut être utile pour soutenir la création d'un modèle de pratique pharmaceutique cohérent.

Mots clés : intervention, pharmacien, pharmacie, application des connaissances, transfert des connaissances

ABSTRACT

Background: The scientific literature on knowledge translation (KT) is vast and complex, and most publications concerning health care interventions involve physicians and nurses. To the authors' knowledge, there have been no literature reviews on KT and its impact on pharmacy practice.

Objective: To determine the profile of interventions relating to KT in pharmacy practice.

Data Sources: The term "pharmacist" was used to search the web platform Knowledge Translation+ (KT+) to identify pertinent articles published between January 2010 and December 2016.

Study Selection and Data Extraction: The main variables analyzed to determine the profile of KT interventions in pharmacy practice were the study's research protocol, the geographic location of the intervention, pharmacist roles, the types of knowledge transferred, and impacts of the interventions. The nature of pharmacy interventions was coded according to the classification on the Impact Pharmacie website.

Data Synthesis: A total of 114 articles were selected: systematic reviews (n = 25, 22%), randomized controlled trials (n = 45, 40%), retrospective studies (n = 21, 18%), prospective studies (n = 13, 11%), and pre-post intervention studies (n = 10, 9%). Most of the studies (74%) were conducted in a health care institution. The majority of interventions targeted pharmaceutical care steps, therapeutic educational sessions, and patient education. There was a lack of methodological rigour during the development of interventions and in their description.

Conclusion: Pharmacists are key generators of knowledge, and their interventions related to KT are directed toward patients or other health care professionals. These interventions have mainly addressed the pharmaceutical care process and interdisciplinary work. The implementation of initial and continuing education, the management of information, and the designation of a pharmacist responsible for KT in each pharmacy department might promote the development of such KT. This concept might in turn support the design of a coherent pharmacy practice model.

Keywords: intervention, pharmacist, pharmacy, knowledge translation, knowledge transfer

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INTRODUCTION

L'application des connaissances (AC) est un processus visant à favoriser l'utilisation des données de la recherche dans la pratique des professionnels de la santé pour améliorer la qualité et la sécurité des soins offerts aux patients. Il s'agit d'un processus dynamique, bidirectionnel et itératif, d'échange et de transfert de preuves, d'information et de données entre les producteurs et les utilisateurs des connaissances[1]. Les interventions représentent un élément-clé du processus d'AC, car elles permettent la mise en application concrète des connaissances[2]. Dans la littérature scientifique, le terme « intervention » est utilisé de façon interchangeable avec le terme « stratégie de mise en œuvre ». D'après Curran et collab., la stratégie de mise en œuvre constitue une méthode efficace pour améliorer l'adoption, la mise en œuvre et la durabilité d'un programme clinique ou de pratiques cliniques[3]. Il existe différents types d'interventions (p. ex. simples c. multiples, actives c. passives) mais il n'existe pas de classification unique de celles-ci. En effet, la plateforme WhatisKT recense vingt-trois taxonomies et huit listes classifiant les interventions[4]. Une des classifications les plus utilisées est celle du groupe EPOC, coordonné depuis 1997 par l'équipe de Grimshaw Shepherd et collab. qui recense des études évaluant l'efficacité d'interventions professionnelles destinées à promouvoir les changements de pratique et l'AC[5].

Jusqu'à maintenant, les chercheurs n'ont pas réussi à déterminer la stratégie ou la combinaison de stratégies la plus efficace. On admet que chaque contexte requiert une stratégie sur mesure. Ainsi, il faut notamment tenir compte des organisations, des acteurs impliqués et des caractéristiques des connaissances à transférer avant de développer une stratégie pour maximiser les chances de succès[6]. La revue systématique de Grimshaw et collab. publiée en 2004 montre que les réunions éducatives et les interventions de rappels semblent être les interventions les plus efficaces alors que l'appui de leaders d'opinion, la distribution de matériel éducationnel et les audits avec rétroaction semblent avoir une efficacité plus limitée[7]. Les interventions multiples ne sont pas forcément plus efficaces que les interventions simples[7,8]. Dans une revue systématique, LaRocca et collab. ont démontré que les stratégies multiples avaient entrainé des changements du niveau des connaissances des participants mais pas des pratiques[9]. Ils ont également montré que les stratégies passives (p. ex. utilisation de supports imprimés) sont souvent moins efficaces. À partir d'une analyse de 33 revues de littérature publiées, Prior et collab. ont conclu que les interventions les plus efficaces étaient diversifiées et comportaient notamment des sessions éducatives et des rappels[10].

Le pharmacien est plus que jamais au cœur du circuit du médicament, comme soignant de première ligne tant en officine qu'en pharmacie hospitalière, et il possède une vue d'ensemble de toute la pharmacothérapie du patient tout en détenant une solide expertise en matière de médicament. Ainsi le processus d'AC présente de nombreux intérêts pour le pharmacien, dont le rôle n'est plus seulement de dispenser des médicaments mais aussi de gérer les échanges de connaissances au sens général du terme entre les patients et les professionnels de santé et de favoriser leur mise en pratique.

La littérature scientifique portant sur l'AC est vaste et complexe et les publications sur les interventions dans le domaine de la santé concernent surtout les médecins et les infirmières[11]. À notre connaissance, il n'existe pas de revue documentaire s'intéressant à l'AC et à ses retombées en pharmacie.

MÉTHODES

Il s'agit d'une revue de la littérature dont l'objectif principal est de décrire le profil des interventions pharmaceutiques ayant pour objet l'AC. Entreprendre une recherche bibliographique sur l'AC n'est pas simple. D'abord, la terminologie associée au processus est très diverse et variable (différents termes peuvent désigner le même concept) et il existe de nombreuses définitions pour chaque terme. Ensuite, la littérature sur l'AC est complexe, car il s'agit d'une discipline nouvelle liée à de nombreuses autres disciplines (p. ex. sociologie, anthropologie, philosophie), le volume d'articles publiés est très large, la recherche d'articles est chronophage et enfin, il n'est pas évident de déterminer quelle est la meilleure ressource à utiliser.

Afin de décider des articles portant sur les interventions pharmaceutiques en AC, nous avons utilisé la plateforme Knowledge Translation+ (KT+). KT+ est une banque de données du Health Information Research Unit de McMaster University au Canada[12]. Ce projet d'AC est soutenu par les Instituts canadiens de recherche en santé (IRSC). Cette plateforme recense les articles et documents relatifs au domaine de l'AC et à celui de l'amélioration de la qualité des soins. Une équipe de recherche évalue des articles originaux et des revues de systématiques sur le sujet provenant de 122 journaux y compris la bibliothèque Cochrane. Toutefois, aucun des journaux retenus ne porte spécifiquement sur les pratiques pharmaceutiques[13,14]. La banque de données permet deux types de consultation, soit des articles satisfaisant aux critères d'inclusion du projet, *quality-filtered KT articles*, et des articles sélectionnés et recensés par l'équipe mais qui n'ont pas été évalués *non-quality filtered KT articles*. Les articles sélectionnés dans ces deux catégories doivent présenter un contenu pertinent par rapport aux interventions d'AC. Toutefois, seuls les *quality-filtered KT articles* sont classés selon la pertinence clinique de leur contenu et la rigueur de la méthodologie. Le classement est réalisé par trois membres d'un panel international de professionnels de santé s'intéressant à l'AC. La base de données est continuellement mise à jour.

Une stratégie de recherche à partir du terme « *pharmacist* » a été menée dans la plateforme KT+ sur une période de sept ans, soit de janvier 2010 à décembre 2016. Le terme « *pharmacist* » a été préféré au terme « *pharmacy* », car ce dernier n'est pas assez précis pour rechercher des articles ayant pour thème principal le rôle du pharmacien. Le terme « *pharmacist* » présentait l'avantage de cibler des articles portant sur les interventions du pharmacien.

De plus, nous avons choisi d'effectuer la recherche sur une période postérieure à la publication de la définition de l'AC par les IRSC (2008) afin de mesurer la fréquence de la mention de ce processus dans les études.

La recherche dans cette plateforme a été privilégiée à une recherche plus traditionnelle dans les banques de données Pubmed ou Google Scholar, car les recherches d'études originales sur des interventions d'AC sont difficiles à découvrir, faute de termes ciblés dans le vocabulaire et compte tenu de leur codification non spécifique à la pharmacie.

À partir des articles retenus, nous avons établi le profil des interventions pharmaceutiques ayant pour objet l'AC en extrayant les variables suivantes : pays, protocole de recherche, lieu de l'intervention, les interventions (c.-à-d. producteurs / courtiers de connaissances, utilisateurs de connaissances), les pathologies concernées par les interventions, les interventions elles-mêmes (c.-à-d. catégories d'interventions, rôles du pharmacien, types de connaissances transférées), les répercussions (c.-à-d. objectifs primaires évalués, impact des interventions, soit positif, neutre, négatif). Les rôles du pharmacien et les pathologies ont été codifiés après une analyse des données recueillies. La nature des interventions pharmaceutiques a été codifiée selon la classification proposée sur le site Impact Pharmacie[15]. En effet, la classification EPOC, habituellement utilisée pour décrire les interventions professionnelles dans le domaine de la santé, n'est pas adaptée pour décrire les interventions pharmaceutiques. Le site Impact Pharmacie recense les preuves relatives aux rôles et aux répercussions de l'activité du pharmacien et classe les interventions pharmaceutiques en neuf catégories.

À partir des données recueillies, nous avons établi un profil des interventions pharmaceutiques et déterminé des pistes de réflexion entourant l'AC en pharmacie.

Seules des statistiques descriptives ont été réalisées.

RÉSULTATS

Au total, 114 articles portant sur des interventions pharmaceutiques ayant pour objet l'AC ont été retenus (pour la liste complète des articles, voir l'annexe 1, publiée au https://www.cjhp-online.ca/index.php/cjhp/issue/view/155/showToc). Ils représentent 17 % (114/666) des articles de la plateforme KT+ recensés lorsque la recherche s'effectue avec le terme « *pharmacist* ». La figure 1 représente un diagramme de flux des articles sélectionnés pour l'analyse. Le critère d'inclusion principal était le thème des articles, c'est-à-dire qu'ils devaient évoquer des interventions pharmaceutiques visant l'AC.

Des 114 articles retenus, on trouve 25 revues systématiques (22 %), 45 études contrôlées à répartition aléatoire (39 %), 21 études rétrospectives (18 %), 13 études prospectives (11 %), 10 études pré- post intervention (9 %). Plus des deux-tiers (n = 79, 69 %) des études originales recensées sont incluses dans au moins une revue systématique.

Parmi les articles inclus, 29 sont qualifiés de *quality-filtered KT articles*, dont 21 revues systématiques et huit articles originaux, et 85 articles sont qualifiés de *non-quality filtered KT* articles, dont quatre revues systématiques et 81 articles originaux. Nous n'avons pas tenu compte de la distinction entre *quality-filtered KT articles* et *non-quality filtered KT articles* au cours de notre analyse, car tous les articles répondaient au critère principal d'inclusion.

Études originales

Des 114 études retenues, 89 sont des études originales. Soixante-treize pour cent (n = 65) des études proviennent des États-Unis, 7 % (n = 6) du Canada, 6 % (n = 5) du Royaume Uni, 3 % (n = 3) des Pays-Bas et 11 % (n = 10) d'autres pays. L'expression « *knowledge translation* », traduite par « application des connaissances », n'a toutefois été trouvée que dans une seule étude[16].

Le tableau 1 présente un profil des interventions pharmaceutiques mettant en valeur l'AC.

Les études se déroulent surtout en établissement de santé (74 %), y compris les centres hospitaliers universitaires, les centres de soins de longue durée, les cliniques privées, les établissements pour anciens combattants.

Dans ces études, le pharmacien est producteur ou courtier des connaissances dans 94 % des études tandis que ce rôle est confié à d'autres professionnels de santé dans 6 % des cas. Le producteur de connaissances crée les connaissances (p. ex. en tant que chercheur) et les synthétise sous forme de message clair adapté au public visé. Par la suite, il planifie et met en œuvre des approches afin de pousser (disséminer) les connaissances vers ce public, encore appelé utilisateurs de connaissances[2]. Le courtier de connaissances est un intermédiaire qui facilite la collaboration entre les producteurs et les utilisateurs des connaissances, il trouve des données scientifiques qui serviront à la prise de décisions, interprète et adapte les résultats de recherche en fonction du contexte local et cerne les nouveaux problèmes que la recherche peut contribuer à résoudre[17]. Son rôle est de créer des interactions entre les producteurs et les utilisateurs de connaissances. L'intervention pharmaceutique amène le pharmacien à collaborer avec les médecins (18 %), les infirmières (12 %) ou les deux (11 %). Les patients représentent les principaux utilisateurs des connaissances (74 %), suivis des professionnels de la santé (26 %). L'utilisateur des connaissances est une personne capable d'utiliser les connaissances issues de la recherche pour prendre des décisions éclairées au sujet de politiques, de programmes ou de pratiques en matière de santé. Le niveau de participation de l'utilisateur des connaissances au processus de recherche peut varier en intensité et en complexité, selon la nature de la recherche et les besoins de l'utilisateur de l'information[18]. Le pharmacien est également considéré comme un des utilisateurs des connaissances dans 19 % des études.

Les interventions pharmaceutiques ciblent surtout des patients atteints de certaines pathologies (p. ex. diabète [19 %] ou encore hypertension [15 %]) tandis que 20 % des interventions ne ciblent aucune affection en particulier.

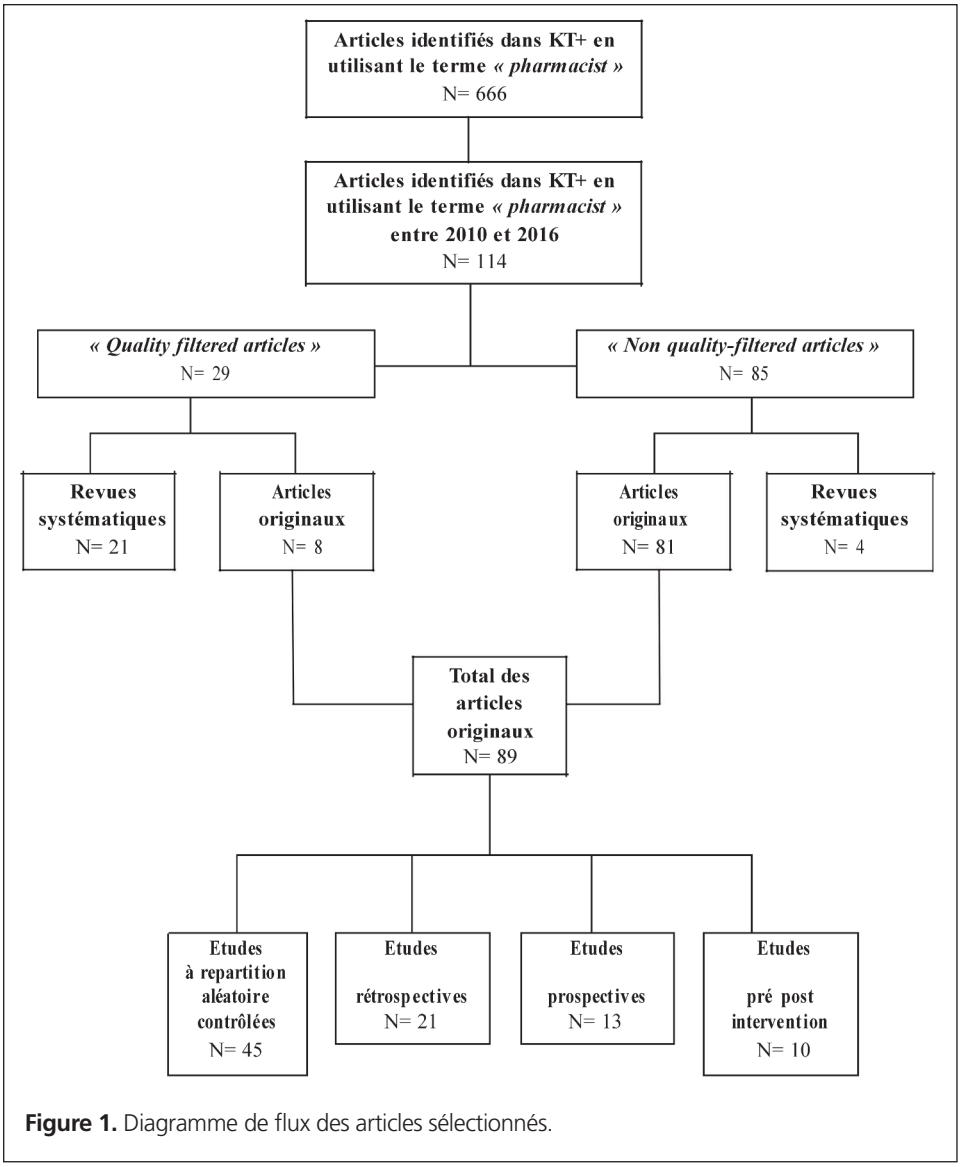

Figure 1. Diagramme de flux des articles sélectionnés.

La majorité des interventions concerne des étapes de soins pharmaceutiques et des séances d'éducation thérapeutique ou de conseils aux patients (64 %). L'éducation thérapeutique participe à l'amélioration de la santé du patient, de sa qualité de vie et de celle de ses proches[19]. Dans un premier temps, le professionnel de la santé réalise un « diagnostic éducatif » visant à déterminer les besoins et les attentes du patient, à formuler avec lui les compétences à acquérir et les priorités d'apprentissage. Dans un second temps, des séances d'éducation thérapeutique individuelles ou collectives sont mises en place pour permettre au patient d'atteindre ses objectifs. On parle également de gestion de la thérapie médicamenteuse (GTM ou *medication therapy management*)[20-22]. Celle-ci comporte la revue et l'ajustement de la thérapie médicamenteuse pour l'ensemble des médicaments lors de services (c.-à-d. dispensation de médicaments) ou de soins (c.-à-d. au chevet des patients) en fonction des besoins des patients, des cibles fixées par les médecins et autres cliniciens, de l'évolution clinique et des résultats observés sur la santé. Dans le cadre de cette démarche, le pharmacien prévient ou résout les problèmes potentiels et réels liés à la pharmacothérapie. Parmi les études originales, on trouve des interventions de GTM pour le diabète, l'hypertension, le VIH, la prise en charge de pathologies chroniques diverses lorsque les patients présentent plusieurs comorbidités, comme une dyslipidémie, le diabète, l'hypertension, les troubles de la coagulation, l'ostéoporose, la dépression, le delirium, l'insuffisance rénale chronique et l'utilisation d'érythropoïétine ou encore en pédiatrie. Le pharmacien assure le suivi et l'interprétation des résultats biologiques, comme la mesure de la pression artérielle, le rapport international normalisé ou la glycémie. Cette surveillance se fait parfois à distance, comme le télémonitorage. La GTM est réalisée en collaboration avec les autres professionnels de la santé (p. ex. médecins, infirmières).

Tableau 1 (partie 1 de 2). Profil des interventions pharmaceutiques mettant en valeur l'application des connaissances

Devis d'étude	Type d'étude; nombre d'études				Nombre total (%) (*n* = 89)
	Étude contrôlée à répartition aléatoire (*n* = 45)	Étude prospective (*n* = 13)	Étude rétrospective (*n* = 21)	Étude pré-post-intervention (*n* = 10)	
Lieux de l'intervention					
Établissement de soins	31	12	16	7	66 (74)
Réseau de soins communautaire	14	1	5	3	23 (26)
Producteurs ou courtiers de connaissances					
Pharmacien	43	12	21	8	84 (94)
Médecin	12	4	1	3	20 (22)
Médecin + pharmacien	10	3	1	2	16 (18)
Infirmière	8	3	0	3	14 (16)
Pharmacien + infirmière	8	0	0	3	11 (12)
Médecin + pharmacien + infirmière	6	2	0	2	10 (11)
Utilisateurs des connaissances					
Patient	40	6	17	3	66 (74)
Pharmacien	7	3	3	4	17 (19)
Médecin	3	4	1	8	16 (18)
Infirmière	5	0	0	4	9 (10)
Pathologies et secteurs concernés par l'intervention					
Diabète	8	0	8	1	17 (19)
Hypertension	9	2	2	0	13 (15)
Gériatrie	6	2	0	1	9 (10)
Pédiatrie	1	3	0	4	8 (9)
Maladies cardiovasculaires	6	0	2	0	8 (9)
Anticoagulation	3	0	2	0	5 (6)
Antibiothérapie et immunisation	1	0	0	2	3 (3)
Insuffisance rénale chronique	1	1	1	0	3 (3)
VIH	0	0	2	0	2 (2)
Dépression	1	0	0	0	1 (1)
Delirium	1	0	0	0	1 (1)
Ostéoporose	1	0	0	0	1 (1)
Aucune affection ciblée avec précision	7	5	4	2	18 (20)
Catégories d'interventions					
Travailler en interdisciplinarité	45	13	17	10	85 (96)
Transfert de connaissances vers le patient et les autres intervenants	45	13	17	10	85 (96)
Établir une relation de confiance avec le patient et les autres intervenants	34	13	11	10	68 (76)
Évaluer les besoins du patient et de l'équipe traitante	34	11	16	7	68 (76)
Évaluer la pharmacothérapie et les mesures non pharmacologiques	34	6	19	3	62 (70)
Assurer le suivi des patients	34	5	17	2	58 (65)
Demeurer compétent	4	6	0	6	16 (18)
Effectuer un bilan comparatif des ordonnances	2	3	1	1	7 (8)
Gérer et préparer les médicaments	3	1	0	0	4 (4)

suite à la page 192

Tableau 1 (partie 2 de 2). Profil des interventions pharmaceutiques mettant en valeur l'application des connaissances

Devis d'étude	Type d'étude; nombre d'études				Nombre total (%) (*n* = 89)
	Étude contrôlée à répartition aléatoire (*n* = 45)	Étude prospective (*n* = 13)	Étude rétrospective (*n* = 21)	Étude pré-post-intervention (*n* = 10)	
Évaluation des objectifs primaires					
État clinique du patient ou observance	33	3	16	1	53 (60)
Prescription médicamenteuse	10	6	5	5	26 (29)
Ressources (hospitalisation, coûts)	15	4	5	1	25 (28)
Niveau de connaissances des professionnels santé	1	3	0	4	8 (9)
Conformité à des lignes directrices	3	0	0	0	3 (3)
Effet des interventions					
Positif	29	9	18	10	66 (74)
Neutre	10	2	2	0	14 (16)
Négatif	6	2	1	0	9 (10)

Onze pour cent des études ciblent plus particulièrement cette collaboration pluridisciplinaire et l'optimisation de la collaboration entre professionnels de santé.

Les interventions du pharmacien portent sur la réduction des erreurs de prescription ou les effets indésirables par la réalisation de bilans comparatifs des médicaments (13 %), l'utilisation de logiciels de prescription, la vérification de l'ordonnance de sortie par le pharmacien, l'utilisation des critères STOPP/START en gériatrie, la formation des prescripteurs ou encore l'affectation d'un pharmacien dans le service pour vérifier les prescriptions.

D'autres interventions pharmaceutiques consistent à former les professionnels de la santé (11 %) sur l'utilisation des antibiotiques, l'administration de médicaments, la culture de la sécurité à l'hôpital, les pratiques d'analgésie, la vérification des signes vitaux du patient. De plus, les interventions pharmaceutiques visent à estimer l'adhésion aux lignes directrices sur l'asthme, l'antibiothérapie, la vaccination contre la grippe des professionnels de santé et l'effet d'incitations financières sur l'adhésion aux lignes directrices.

En utilisant les catégories d'interventions proposées par la plate-forme Impact Pharmacie, les interventions recensées impliquent le plus souvent plus d'une catégorie, de sorte que la somme des catégories dépasse largement 100 %. Toutes les interventions rapportées dans les études sont multiples, c.-à-d. qu'elles font appel à plusieurs types d'interventions.

Dans les études recensées, l'objectif primaire évalué porte sur l'état clinique des patients ou l'observance (60 %), la prescription médicamenteuse (29 %), les ressources (28 %), le niveau de connaissances des professionnels de la santé (9 %) ou encore l'adhésion à des lignes directrices (3 %). Les types de ressources évaluées concernent principalement la durée de l'hospitalisation et le coût des médicaments et des ressources professionnelles. L'impact des interventions pharmaceutiques se révèle positif (74 %), neutre (16 %) ou négatif (10 %). Le résultat qualifié de neutre signifie que l'intervention du pharmacien n'a généré aucun changement.

Revues systématiques

Des 114 études retenues, 25 sont des revues systématiques dont cinq méta-analyses. Elles proviennent des États-Unis (*n* = 7, 28 %), du Royaume Uni (*n* = 4, 16 %), d'Irlande (*n* = 2, 8 %), de Norvège (*n* = 1, 4 %), de Thaïlande (*n* = 1, 4 %), de France (*n* = 1, 4 %), d'Espagne (*n* = 1, 4 %) et du Canada (*n* = 1, 4 %). Sept études proviennent du groupe Cochrane réunissant des chercheurs de différents pays (28 %). Ces revues systématiques comportent un nombre variable d'études originales (c.-à-d. jusqu'à 20 études [36 %], entre 21 et 50 études [28 %], plus de 50 études [36 %]) et décrivent des interventions qui se déroulent surtout en établissement de santé (80 %).

Dans ces revues systématiques, le pharmacien est producteur ou courtier de connaissances dans 100 % des études. L'intervention pharmaceutique amène le pharmacien à collaborer notamment avec les médecins (28 %) et les infirmières (28 %). Les patients représentent les principaux utilisateurs des connaissances (72 %), suivis des médecins (40 %) et des infirmières (40 %). Le pharmacien est également considéré comme un des utilisateurs des connaissances dans 28 % des études.

Les interventions pharmaceutiques ciblent des populations et des affections particulières (p. ex. gériatrie [28 %], pathologies chroniques [12 %], anticoagulation [8 %], pédiatrie [8 %], insuffisance rénale chronique [8 %], hypertension [8 %], risque cardiovasculaire [4 %]) tandis que 24 % des interventions ne ciblent aucune population ou affection particulière.

Les revues systématiques visent à évaluer le rôle du pharmacien dans l'amélioration de l'état clinique du patient à travers la GTM, la diminution des erreurs de prescription ou la survenue d'effets indésirables ou encore la formation des professionnels de la santé, par exemple pour les inciter à se faire vacciner contre la grippe.

Dans les revues systématiques, l'objectif primaire évalué porte principalement sur l'état clinique du patient ou l'adhésion (38 %)

et la prescription médicamenteuse (38 %). L'impact des interventions pharmaceutiques se révèle positif (44 %) ou neutre (56 %).

DISCUSSION

Que retenir de cette revue de la littérature scientifique?

À partir de la plateforme KT+, nous avons été en mesure de recenser 114 études décrivant des interventions pharmaceutiques publiées en sept ans de 2010 à 2016. Il s'agit d'une revue de littérature originale utilisant l'AC comme filtre spécifique de l'évaluation des répercussions de l'intervention des pharmaciens. Ce nombre d'études est relativement important étant donné qu'il représente 17 % des articles de la plateforme KT+ recensés lorsqu'on effectue une recherche avec le terme « *pharmacist* ». Compte tenu de la méthode proposée par cette équipe de recherche, il s'agit d'études comportant une méthodologie valable et des protocoles de recherche permettant d'évaluer les retombées de l'intervention pharmaceutique. À titre comparatif, la plate-forme Impact Pharmacie recense 892 études pour la même période d'étude. Ceci tient au fait que les critères d'inclusion de cette plateforme sont plus larges que ceux de KT+ (p. ex. articles descriptifs, articles avec des retombées avec ou sans groupe contrôle).

La revue de la littérature révèle qu'une majorité des études originales prises en compte ont été réalisées en établissement de santé, où le pharmacien est à la fois producteur, courtier et utilisateur des connaissances. Il est souvent plus facile de mettre en pratique le concept d'AC en établissement de santé qu'en milieu communautaire, compte tenu de la présence d'équipes interdisciplinaires, d'activités d'enseignement et de recherche. Une partie du temps est consacrée aux échanges entre professionnels tandis que le pharmacien communautaire exerce souvent seul, aidé du personnel technique, et ses contacts avec les autres professionnels sont épisodiques et téléphoniques. Ainsi, il est plus difficile de réaliser des activités similaires en milieu communautaire où tous les intervenants exercent dans des lieux différents.

Les interventions pharmaceutiques en AC portent sur des pathologies chroniques (p. ex. diabète, hypertension, maladies cardiovasculaires, insuffisance rénale, ostéoporose, VIH, dépression) ou ciblent des patients exposées à la polypharmacie, comme la gériatrie.

Il existe deux principaux types d'interventions pharmaceutiques visant l'AC, le premier est orienté vers le patient et le second, vers les autres professionnels de santé. Ainsi, la majorité des interventions pharmaceutiques étudiées concernent les étapes dans la démarche de soins pharmaceutiques (c.-à-d. établir une relation de confiance [76 %], effectuer un bilan comparatif des ordonnances [8 %], évaluer les besoins du patient [76 %], évaluer la pharmacothérapie et les mesures non pharmacologiques [70 %], gérer et préparer les médicaments [5 %], assurer le suivi des patients [65 %]). La minorité des interventions portent sur le maintien de la compétence (18 %). Pour le second type, la majorité des interventions pharmaceutiques ciblent le travail en interdisciplinarité et le transfert des connaissances aux autres intervenants. Ce transfert contribue notamment à limiter les erreurs médicamenteuses et à optimiser le circuit du médicament.

La revue de la littérature montre que les études retenues comportent des objectifs primaires permettant d'évaluer des interventions pharmaceutiques dont l'impact est soit positif dans 74 % des cas, soit neutre dans 16 % des cas, soit négatif dans 10 % des cas. Ces proportions sont relativement similaires à celles observées dans la plate-forme Impact Pharmacie depuis 1990 (60 %, 29 %, 1 %)[23] ou à celles de l'étude de Tanguay et collab.[24]. Ainsi, dans environ deux-tiers des études, les auteurs sont en mesure de démontrer des répercussions favorables de l'intervention de pharmaciens.

Que doit-on faire en recherche sur les pratiques pharmaceutiques?

La recherche en pratique pharmaceutique doit encore relever de nombreux défis et cette revue documentaire met en évidence certains enjeux méthodologiques (p. ex. répartition aléatoire dans un contexte de soins, maintien de l'insu). En 2009, Charrois et collab. ont revu les enjeux en recherche appliquée[25]. Parmi les difficultés notées dans les revues systématiques publiées, la pauvreté de la description de l'intervention est évidente (intervenant, formation de base, rôle, nature de l'intervention, outils utilisés, etc.). Il existe différents outils de planification d'une intervention, surtout si elle fait l'objet d'une évaluation structurée et d'une publication ultérieure (p. ex. *Template for Intervention Description and Replication (TIDieR) Checklist and Guide*)[26]. Un autre groupe de recherche brésilien a proposé un outil appliqué aux interventions pharmaceutiques (*Descriptive Elements of Pharmacist Intervention Characterization Tool* – DEPICT)[27].

Grimshaw et collab. soulignent que l'absence de standardisation dans les études portant sur l'AC peut compliquer le choix du type d'intervention à développer à cause du manque de données systématiques portant sur les interventions, l'absence de cadre de planification rigoureux, la réalisation et la communication des résultats des interventions[28]. De plus, souvent les résultats des études ne peuvent pas être utilisés dans leur intégralité, car les interventions sont peu ou mal décrites, s'appuient rarement sur une base théorique, et il n'existe pas de guide pratique permettant de les appliquer dans un nouveau contexte.

Ainsi, la recherche en AC se heurte entre autres à la difficulté de mettre en place une standardisation de la description des interventions dans le but de faciliter l'établissement des déterminants (obstacles et facteurs favorisant le succès de l'intervention) ainsi que la comparaison de ceux-ci entre différentes études, de comprendre comment l'intervention est construite et sur quel mécanisme elle repose pour pouvoir ensuite la reproduire dans un autre contexte.

De même, le rapport de l'Institut national de santé mentale sur les progrès en science de l'AC paru en 2004 appelle à des avancées dans la définition, la description et l'évaluation des

interventions[29]. Le groupe WIDER (Workgroup for Intervention Development and Evaluation Research) a également fait paraitre des recommandations destinées aux chercheurs voulant publier dans des journaux scientifiques afin qu'ils optimisent la description des interventions liées aux changements de comportement[30]. Walter et collab. proposent une taxonomie des interventions[31]. Enfin, Proctor et collab. ont proposé des recommandations pour harmoniser les descriptions des stratégies de mise en œuvre (composantes, méthodes de réalisation), pour faciliter leur mise en place et leur évaluation en AC[32]. Ils recommandent de nommer l'intervention, de lui attribuer une définition et de la décrire en détail. Cette dernière étape repose sur sept dimensions, soit l'acteur (celui qui délivre l'intervention), l'action (description de l'intervention), les cibles de l'action (public visé, connaissances transférées), la temporalité (moment de l'intervention elle-même), la dose (fréquence de l'intervention), l'objectif primaire (impact), la justification (théorie, modèle, preuve empirique, cadre conceptuel sur lequel repose l'intervention).

Que faire en pratique au sein du département de pharmacie?

Notre revue documentaire et notre réflexion mettent en évidence les éléments suivants : il faut encourager l'intégration des concepts de l'AC et des théories du changement comportemental dans le cursus de pharmacie, désigner un pharmacien responsable de l'AC au sein de chaque département de pharmacie, encourager ce pharmacien à participer à des communautés de pratique et intégrer l'AC dans le plan de communication du département et dans les activités d'évaluation des pratiques pharmaceutiques. Nous pensons qu'un modèle en quatre étapes d'AC (c.-à-d. analyse du contexte, synthèse des connaissances, partage des connaissances, évaluation de l'intervention) répond aux besoins de la pratique pharmaceutique. Les IRSC proposent une liste de vérification en neuf étapes pour guider les professionnels de la santé désireux de mettre en place des interventions en AC[33]. L'utilisation de cet outil au sein du département de pharmacie pourrait améliorer la formation des pharmaciens, résidents et étudiants en pharmacie ainsi que des assistants techniques. Par ailleurs, il faudrait créer des projets transversaux visant à optimiser la qualité des soins prodigués aux patients et l'accès à l'innovation entre le département de pharmacie et les services de l'hôpital. Cet outil pourrait aussi servir de base à l'élaboration d'un plan de communication du département de pharmacie. Ce plan devrait englober des modes de communication efficaces et multiples pour rejoindre les différents publics et des objectifs spécifiques (p. ex. augmentation de la conformité de *X* % pour l'utilisation d'un médicament *Y* dans telle situation). De plus, la réalisation d'interventions d'AC impose la mise en place d'une gestion de l'information. Une bonne gestion des informations requiert une sélection des sources d'informations selon des critères objectifs (c.-à-d. rigueur et justesse du contenu scientifique, actualisation des données, auteurs) puis une régulation de la consultation de ces informations (c.-à-d. allocation d'un temps prédéterminé) et une prise de décision sur la possibilité et l'intérêt de la mise en pratique des informations retenues.

Cette revue documentaire comporte des limites. Notre stratégie de recherche ne cible que la plateforme KT+. Une recherche dans Pubmed, Embase, Google Scholar et parmi les revues non indexées permettrait sans doute de recenser un nombre plus élevé d'études originales. Toutefois, comme il existe des dizaines de termes relatifs à l'AC, l'adoption d'une définition claire et opérationnelle serait nécessaire pour compléter la sélection et la prise en compte des études. À titre de revue documentaire exploratoire sur la thématique de l'AC, cette revue de la littérature constitue un point de départ intéressant pour encourager davantage la recherche sur le sujet.

CONCLUSION

Cette revue de la littérature scientifique décrit le profil des interventions visant l'AC en pratique pharmaceutique. Le pharmacien est le principal producteur de connaissances et oriente ses interventions vers les patients ou les professionnels de santé.

Le transfert des connaissances contribue notamment à limiter les erreurs médicamenteuses et à optimiser le circuit du médicament. La majorité des interventions concerne la démarche de soins pharmaceutiques et cible le travail en interdisciplinarité. L'impact de ces interventions est positif dans la majorité des études. Cependant, le manque de rigueur méthodologique lors de leur conception et la disparité de leur description limite l'exploitation des résultats et la reproductibilité des interventions dans d'autres contextes. La standardisation de la description des interventions pourrait permettre de faire progresser la recherche sur la science de l'AC.

Les pharmaciens devraient prendre conscience qu'ils sont les acteurs de l'AC dans leur activité professionnelle quotidienne afin de devenir proactifs en la matière. À l'avenir, trois mesures pourraient contribuer à soutenir le développement de l'AC en pharmacie : la mise en place d'une formation initiale et continue, la gestion de l'information et la désignation d'un pharmacien responsable de l'AC au sein de chaque département de pharmacie. Une formation continue constituée d'activités d'autoapprentissage et de conférences offertes par nos associations provinciales ou nationales pourrait permettre de rejoindre un large public. Ces initiatives devraient servir à encourager la recherche et à promouvoir la mise en place de stratégies par les pharmaciens. Le concept d'AC peut être utile pour soutenir la création d'un modèle de pratique pharmaceutique cohérent.

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REVIEW

Interaction between Monoamine Oxidase B Inhibitors and Selective Serotonin Reuptake Inhibitors

Abdullah Aboukarr and Mirella Giudice

ABSTRACT

Background: Monoamine oxidase B (MAO-B) inhibitors are used to treat the motor symptoms of Parkinson disease. Depression is commonly associated with Parkinson disease, and selective serotonin reuptake inhibitors (SSRIs) are often used for its management. Tertiary sources warn that the combination of MAO-B inhibitors and SSRIs can result in increased serotonergic effects, leading to serotonin syndrome.

Objective: To explore the mechanism, clinical significance, and management of this potential drug interaction through a review of the supporting evidence.

Data Sources: PubMed, MEDLINE (1946 forward), Embase (1947 forward), PsycINFO (1806 forward), and International Pharmaceutical Abstracts (1970 forward) were searched on February 4, 2017.

Study Selection and Data Extraction: Studies and case reports describing aspects of the potential interaction between MAO-B inhibitors and SSRIs in patients with Parkinson disease and published in English were identified by both title and abstract.

Data Synthesis: The search identified 8 studies evaluating the potential interaction between SSRIs and the MAO-B inhibitors selegiline and rasagiline. The largest, a retrospective cohort study of 1504 patients with Parkinson disease, found no cases of serotonin syndrome with coadministration of rasagiline and an SSRI. A survey of 63 investigators in the Parkinson Study Group identified 11 potential cases of serotonin syndrome among 4568 patients treated with the combination of selegiline and antidepressants (including SSRIs). In addition, 17 case reports describing the onset of serotonin syndrome with coadministration of an SSRI and either selegiline or rasagiline were identified. Following discontinuation or dose reduction of one or both of the agents, the symptoms of serotonin syndrome gradually resolved in most cases, with none being fatal.

Conclusions: According to the literature, serotonin syndrome occurs rarely, and the combination of SSRI and MAO-B inhibitor is well tolerated. Therefore, SSRIs and MAO-B inhibitors can be coadministered, provided that their recommended doses are not exceeded and the SSRI dose is kept at the lower end of the therapeutic range. Among the SSRIs, citalopram and sertraline may be preferred.

Keywords: Parkinson disease, serotonin syndrome, selegiline, rasagiline, selective serotonin reuptake inhibitor, drug interactions

RÉSUMÉ

Contexte : Les inhibiteurs de la monoamine oxydase B (MAO-B) sont employés dans le traitement des symptômes moteurs de la maladie de Parkinson, maladie à laquelle la dépression est souvent associée et fréquemment traitée à l'aide d'inhibiteurs sélectifs de la recapture de la sérotonine (ISRS). Des sources tertiaires mettent en garde contre la combinaison d'inhibiteurs de la MAO-B et d'ISRS car elle peut mener à une augmentation des effets sérotoninergiques, dégénérant en un syndrome sérotoninergique.

Objectif : Chercher à connaître le mécanisme, la signification clinique et la prise en charge de cette potentielle interaction médicamenteuse en procédant à une revue des preuves à l'appui.

Sources des données : Les bases de données PubMed, MEDLINE (depuis 1946), Embase (depuis 1947), PscyINFO (depuis 1806), et International Pharmaceutical Abstracts (depuis 1970) ont été interrogées le 4 février 2017.

Sélection des études et extraction des données : Des études et des observations cliniques, publiées en anglais, portant sur des aspects de la potentielle interaction entre les inhibiteurs de la MAO-B et les ISRS chez les patients atteints de la maladie de Parkinson ont été repérées par une recherche ciblant les titres et les résumés.

Synthèse des données : La recherche a permis de trouver 8 études analysant la potentielle interaction entre les ISRS et deux inhibiteurs de la MAO-B : la sélégiline et la rasagiline. La plus importante d'entre elles, une étude de cohorte rétrospective sur 1504 patients atteints de la maladie de Parkinson, n'a relevé aucun cas de syndrome sérotoninergique en présence d'une prise concomitante de rasagiline et d'un ISRS. Une enquête auprès de 63 chercheurs dans le Parkinson Study Group a permis de relever 11 potentiels cas de syndrome sérotoninergique chez 4568 patients traités avec une combinaison de sélégiline et d'antidépresseurs (notamment des ISRS). De plus, 17 observations cliniques qui décrivaient un début de syndrome sérotoninergique en présence d'une prise concomitante d'un ISRS et de sélégiline ou de rasagiline ont été recensées. Suivant la réduction de la posologie ou l'interruption d'un ou des deux médicaments, les symptômes du syndrome sérotoninergique se sont graduellement résolus dans la plupart des cas, et il n'y a eu aucune mortalité.

Conclusions : Selon la documentation, le syndrome sérotoninergique est rare et la combinaison d'ISRS et d'inhibiteurs de la MAO-B est bien

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tolérée. Ainsi, les deux types d'inhibiteurs peuvent être administrés conjointement pourvu que l'on ne dépasse pas la posologie recommandée et que la dose d'ISRS demeure dans le bas de l'intervalle thérapeutique. Parmi les ISRS, il peut être préférable d'employer le citalopram ou la sertraline.

Mots clés : maladie de Parkinson, syndrome sérotoninergique, sélégiline, rasagiline, inhibiteur sélectif de la recapture de la sérotonine, interaction médicamenteuse

INTRODUCTION

The monoamine oxidase B (MAO-B) inhibitors selegiline and rasagiline are among the agents used to treat the motor symptoms of Parkinson disease.[1] Depression is commonly associated with Parkinson disease, with up to 50% of patients being affected.[1,2] The treatment of depression in patients with Parkinson disease should be individualized, with particular emphasis on concomitant therapy.[1,3] Although selective serotonin reuptake inhibitors (SSRIs) are often used to manage the symptoms of depression associated with Parkinson disease,[2] these drugs have the potential to worsen the motor symptoms of the disease (tremor, restless legs, and periodic limb movement).[3-5] Furthermore, a potential interaction between SSRIs and MAO-B inhibitors can lead to serotonin syndrome.[6-8] This review explores the mechanism of, supporting evidence for, clinical significance of, and management of potential serotonin syndrome with concomitant use of MAO-B inhibitors and SSRIs.

DIAGNOSTIC CRITERIA FOR SEROTONIN SYNDROME

Serotonin syndrome is a measure of central nervous system (CNS) hyperexcitability in relation to an excess of serotonin. This hyperexcitability can manifest in multiple ways, and ultimately there is no true "gold standard" for the diagnosis of serotonin syndrome. Published diagnostic criteria have attempted to identify symptoms or symptom combinations that best capture the nature of CNS hyperexcitability related to an excess of serotonin.[9]

Serotonin syndrome can manifest as symptoms that range from mild to life-threatening. Initially, the patient may present with akathisia and tremor, followed by mental status changes and inducible clonus. The clonus can become sustained, and may then evolve to muscular rigidity or hypertonicity. Hyperthermia is a symptom that manifests later; it can be life-threatening.[10] Most cases of serotonin syndrome present within 24 h of a dose increase or initiation of a new serotonergic agent.[11]

Sternbach[12] first suggested diagnostic criteria for serotonin syndrome in 1991. The Sternbach criteria require at least 3 of the following clinical features, coincident with adding or increasing the dose of a serotonergic agent: mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever.[12] Despite their widespread use, the Sternbach criteria have some limitations. They can be nonspecific, because of heavy reliance on mental status changes. Furthermore, the inclusion of incoordination (ataxia), a cerebellar feature, is controversial, because serotonin toxicity is not known to affect the cerebellum. Any patient who is agitated or confused may also appear ataxic or uncoordinated. Lastly, the Sternbach criteria were developed on the basis of a series of published cases; therefore, any clinical features not identified as features of serotonin syndrome by the authors of the original cases may have been missed.[9,13]

In 2003, Dunkley and others[13] undertook to improve the Sternbach criteria, and developed the Hunter serotonin toxicity criteria (HSTC). According to these criteria, a diagnosis of serotonin syndrome requires the presence of a serotonergic agent and one of the following conditions:

- clonus
- inducible clonus AND agitation or diaphoresis
- ocular clonus AND agitation or diaphoresis
- tremor AND hyperreflexia
- hypertonicity AND temperature > 38°C AND ocular clonus or inducible clonus

The HSTC are currently the most accurate criteria for diagnosing serotonin syndrome, being both more sensitive and more specific than the Sternbach criteria.[12-14] Nonetheless, the HSTC have their shortcomings. They are based solely on cases of SSRI overdose, making them potentially nongeneralizable to cases of serotonin syndrome involving therapeutic doses. In addition, a subset of cases used to derive the criteria were also used for validation, leading to a potential overestimate of validity.[9] Lastly, clonus or hyperreflexia may not be elicited in patients with severe serotonin syndrome who have peripheral neuropathy or muscle rigidity, which can cloud the clinical diagnosis of serotonin syndrome.[9,10]

MECHANISM OF DRUG INTERACTION

MAO exists as 2 isoforms, MAO-A and MAO-B. Inhibition of MAO-A reduces the metabolism of both serotonin and noradrenaline, whereas inhibition of MAO-B does not affect the metabolism of these neurotransmitters, unless sufficient doses (as described below) are used.[15] Inhibition of MAO-B, the major

isoform in the human brain, prevents the breakdown of extracellular levels of dopamine in the striatum. The resulting increase in dopaminergic activity in the striatum may explain the mechanism by which MAO-B inhibitors exert their beneficial effects in Parkinson disease.[16,17] Inhibition of MAO can also be reversible or irreversible; irreversible inhibitors can lead to longer-lasting toxic reactions caused by MAO inhibition, including serotonin syndrome.[15] Selegiline and rasagiline, both irreversible MAO-B inhibitors, are selective for MAO-B at therapeutic doses of 10 mg daily and 1 mg daily, respectively, for patients with Parkinson disease. At higher doses, they lose selectivity and inhibit both MAO-B and MAO-A.[15] Higher doses of MAO-B inhibitors alone have resulted in serotonin syndrome.[17,18]

Serotonin syndrome results from increased serotonergic activity in the CNS. The SSRIs increase serotonin activity by blocking the reuptake of serotonin from synapses.[5] Serotonin receptors are classified into 7 families, which are designated 5-HT_1 to 5-HT_7, with specific families having multiple subtypes. The development of serotonin syndrome has not been attributed to one specific receptor; however, evidence suggests that agonism of the 5-HT_{2A} subtype may play a considerable role. The 5-HT_{1A} subtype may also be implicated in the development of serotonin syndrome through a pharmacodynamic interaction in which increased synaptic concentrations of serotonin can saturate all receptor subtypes.[10]

MAO-A inhibitors can augment the serotonergic effects of SSRIs by preventing the breakdown of serotonin.[6,19] Consequently, serotonin syndrome has been reported with concomitant use of SSRIs and nonselective MAO inhibitors (e.g., phenelzine, tranylcypromine), as well as with selective

Table 1. Recommendations for Management of the Interaction between MAO-B Inhibitors and SSRIs from Tertiary Sources

Reference	Recommendation
Selegiline product monograph[16]	Concomitant use of selegiline and fluoxetine should be avoided. Administration should be separated by a washout period of at least 5 weeks after discontinuing fluoxetine and starting an MAO inhibitor, and at least 2 weeks after discontinuing an MAO inhibitor and starting fluoxetine.
Rasagiline product monograph[17]	Concomitant use of rasagiline and SSRIs should be avoided. Administration should be separated by a washout period of at least 2 weeks after discontinuing rasagiline and starting an SSRI, and at least 2 weeks after discontinuing most SSRIs (5 weeks after discontinuing fluoxetine) and starting rasagiline.
Selegiline product label[27]	Concomitant use of selegiline and SSRIs should be avoided. Administration should be separated by a washout period of at least 2 weeks after discontinuing selegiline and starting an SSRI, and at least 5 weeks after discontinuing fluoxetine and starting selegiline.
Rasagiline product label[28]	Concomitant use of rasagiline and SSRIs is not recommended. Administration should be separated by a washout period of at least 2 weeks after discontinuing rasagiline and starting an SSRI, and at least 5 weeks after discontinuing fluoxetine and starting rasagiline.
Lexi-Interactions database: SSRIs and MAO inhibitors[6] Supporting literature for the interaction includes Suchowersky,[29] Suchowersky and DeVries,[30] and Panisset et al.[31]	Concomitant use is contraindicated. Administration should be separated by a washout period of at least 1–2 weeks, and 5 weeks for fluoxetine, depending on the half-life of the agent being discontinued.
Interaction Checking (MicroMedex database): SSRIs and MAO inhibitors[7] Supporting literature for the interaction includes Suchowersky[29] and Suchowersky and DeVries[30]	Concomitant use is contraindicated. Selegiline: Administration should be separated by a washout period of at least 2 weeks after discontinuing selegiline and starting an SSRI, and at least 2 weeks after discontinuing most SSRIs (5 weeks after discontinuing fluoxetine, and 1 week after discontinuing sertraline) and starting selegiline. Rasagiline: Administration should be separated by a washout period of at least 2 weeks after discontinuing rasagiline and starting an SSRI, and at least 2 weeks after discontinuing most SSRIs (5 weeks after discontinuing fluoxetine) and starting rasagiline.
Medscape Drug Interaction Checker: SSRIs and MAO inhibitors[8]	Selegiline: Concomitant use of selegiline and SSRIs is contraindicated. Rasagiline: Concomitant use of rasagiline and SSRIs should be avoided. Administration should be separated by a washout period of at least 14 days (≥ 5 weeks after discontinuing fluoxetine).
Stockley's Drug Interactions[20]: MAO-B inhibitors + SSRIs or SNRIs Supporting literature for the interaction includes Laine et al.,[32] Suchowersky,[29] Suchowersky and DeVries,[30] Ritter and Alexander,[33] Kurlan and Dimitsopulos,[34] Jermain et al.,[35] Montastruc et al.,[36] Waters[37] and Toyama and Iacono[38]	This reference refers to the manufacturers' recommendations regarding management of the drug interaction.
UpToDate: Management of nonmotor symptoms in Parkinson disease[4]	MAO-B inhibitors should be prescribed only at recommended doses. Caution is advised when combining MAO-B inhibitors and SSRIs because of the risk of serotonin syndrome.
Physician Guide: Non-motor Symptoms of Parkinson's Disease[2]	The interaction between MAO-B inhibitors and SSRIs is theoretical and may not be clinically relevant. Selegiline has been combined with SSRIs for many years with only infrequent reports of serotonin syndrome; data on rasagiline are limited. However, patients must be warned of this theoretical interaction as it commonly flagged by pharmacy management software.

MAO-B = monoamine oxidase B, SNRI = serotonin and norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

MAO-A inhibitors (e.g., moclobemide).[6,20] According to references reporting these interactions, patients have experienced symptoms such as agitation, confusion, myoclonus, rigidity, nausea, and insomnia; some cases were fatal.[6,20] MAO-B inhibitors have also been implicated in the development of serotonin syndrome, as discussed below (see "Summary of Evidence").

RECOMMENDATIONS FROM TERTIARY REFERENCES

The product monographs for escitalopram, paroxetine, fluoxetine, sertraline, citalopram, and fluvoxamine all recommend avoiding their concurrent use with selective and nonselective MAO inhibitors and separating administration of these drugs by a washout period ranging from 2 to 5 weeks.[21-26] The product monograph for sertraline reports serious, sometimes fatal reactions with concomitant use of selegiline.[24] Various drug interaction references and the product monographs and labels for selegiline and rasagiline (Table 1) reiterate these recommendations.[2,4,6-8,16,17,20,27,28]

Based on the Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder,[39] SSRIs vary in their overall potential for drug–drug interactions: citalopram and escitalopram have minimal or low potential; sertraline has moderate potential; and fluoxetine, fluvoxamine, and paroxetine have high potential. Selegiline is also classified as having a higher potential for drug–drug interactions relative to other antidepressants; rasagiline is not classified.[39] Selegiline is metabolized primarily via the cytochrome P450 isozymes CYP2B6, CYP2C9, CYP3A4, and CYP2A6, whereas rasagiline is metabolized via CYP1A2.[40,41]

SUMMARY OF EVIDENCE

A search of PubMed, MEDLINE (1946 forward), Embase (1947 forward), PsycINFO (1806 forward), and International Pharmaceutical Abstracts (1970 forward) was conducted on

Table 2 (part 1 of 2). Studies Examining the Interaction between Selegiline or Rasagiline and SSRIs

Study	Design	Population	Interventions and Duration of Therapy	Outcomes
Hilli et al. (2009)[42]	Open, sequential-setting study	12 healthy male volunteers	Rasagiline 1 mg/day + escitalopram 10 mg/day OR Rasagiline 1 mg/day Duration: 7 days	• Combination was generally well tolerated, with 91% of adverse events classified as mild or moderate. One patient had severe headache and another had severe tiredness. • No cases of serotonin syndrome. • Slight but significant decrease in heart rate with concomitant escitalopram and rasagiline (mean 56 beats/min) versus rasagiline alone (mean 58 beats/min; $p = 0.0047$) and baseline (mean 60 beats/min; $p = 0.0097$).
Laine et al. (1997)[32]	Part 1: Randomized, double-blind, parallel study Part 2: Open-label, crossover study	18 healthy male volunteers; mean age 24 years (citalopram) and 25 years (placebo)	*Part 1* Group A: citalopram 20 mg/day for 14 days, with selegiline 10 mg/day added for days 11–14 Group B: Placebo for 14 days, with selegiline 10 mg/day added for days 11–14 *Part 2* After a 5-week washout period, patients from group A were crossed over to selegiline 10 mg/day for 4 days	• Combination therapy was well tolerated. The most frequent adverse events were headache, dry mouth, sweating, nausea, and sleep disturbances. Reported adverse events were similar in both groups, both before and after initiating selegiline. • No cases of serotonin syndrome. • Lack of clinically relevant interaction.
Panisset et al. (2014)[31]	Multicentre, retrospective cohort study	1504 patients with PD; mean age 67.0 years; 58.8% male	Group 1: rasagiline + antidepressant (74.5% SSRIs*; 10.0% were using > 1 antidepressant) Duration: 50.5–53.5 weeks Group 2: antidepressant only (77.0% SSRIs*; 16.6% were using > 1 antidepressant) Duration: 51.7–80.9 weeks Group 3: rasagiline	• No cases of serotonin syndrome in any group.

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Table 2 (part 2 of 2). Studies Examining the Interaction between Selegiline or Rasagiline and SSRIs

Study	Design	Population	Interventions and Duration of Therapy	Outcomes
Richard et al. (1997)[43]	Survey of investigators from Parkinson Study Group	4568 patients with PD	Selegiline + antidepressant (including SSRIs); doses not stated	• 11 patients (0.24%) experienced symptoms possibly related to serotonin syndrome; 2 patients (0.04%) experienced symptoms judged to be serious. • See Table 3 for details about SSRI cases for which detailed information was available.
Ritter and Alexander (1997)[33]	Retrospective chart review	28 male patients with PD; mean age 68 years	Selegiline + antidepressant (7/40† SSRIs)	• One possible case of serotonin syndrome involving selegiline 10 mg/day and fluoxetine 20 mg/day.
Rihmer et al. (2000)[44]	Observational study	8 patients with PD; mean age 74.1 years, 75% male	Selegiline 5–10 mg/day + citalopram 20 mg/day Duration: 8 weeks	• No cases of serotonin syndrome. • No other adverse events.
Waters (1994)[37]	Retrospective chart review	23 patients with PD; mean age 64.6 years, 56.5% male	Selegiline 5–10 mg/day + fluoxetine 5-40 mg/day Duration: 1 month – ongoing	• No cases of serotonin syndrome. • One patient experienced worsened parkinsonian tremor, both with fluoxetine alone and with the combination of fluoxetine and selegiline.‡
Toyama and Iacono (1994)[38]	Case series	16 patients with PD	Selegiline 5–10 mg/day + SSRI (sertraline 25–100 mg/day or paroxetine 10–40 mg/day) with or without trazodone 25–150 mg/day Duration: 2–30 weeks (mean 10 weeks)	• No cases of serotonin syndrome. • No other adverse events.

PD = Parkinson disease, SSRI = selective serotonin reuptake inhibitor.
*Mean SSRI doses in antidepressant + rasagaline group and antidepressant-only group, respectively: citalopram 23.7 and 26.0 mg, escitalopram 13.8 and 14.2 mg, fluoxetine 24.1 and 27.2 mg, paroxetine 22.3 and 22.9 mg, and sertraline 78.0 and 85.0 mg.
†There were a total of 40 selegiline–antidepressant combinations, because some patients were treated with more than 1 trial of different antidepressants.
‡Tremor improved after discontinuation of fluoxetine.

February 4, 2017, using the MeSH (Medical Subject Heading) term "drug interaction" and combined keywords "selegiline and SSRI," "rasagiline and SSRI", "fluoxetine and selegiline", "fluvoxamine and selegiline", "sertraline and selegiline", "paroxetine and selegiline", citalopram and selegiline", "escitalopram and selegiline", "fluoxetine and rasagiline", "fluvoxamine and rasagiline", "sertraline and rasagiline", "paroxetine and rasagiline", citalopram and rasagiline", and "escitalopram and rasagiline". Studies and case reports were identified by both title and abstract. Duplicate citations, identified by author, journal, and date of publication, were excluded. Only studies and case reports published in English were considered.

Studies

Eight relevant studies were identified (3 retrospective studies, 1 observational study, 1 open sequential-setting study, 1 case series, 1 survey study, and 1 randomized controlled trial) that evaluated the potential for an interaction between SSRIs and the MAO-B inhibitors selegiline and rasagiline (Table 2).[31-33,37,38,42-44] Most of the studies had a small sample size, and most evaluated selegiline; this finding was unsurprising, given that selegiline was approved by the US Food and Drug Administration (FDA) in 1989 and has therefore been available much longer than rasagiline, which was approved by the FDA in 2006.[45]

Two studies involved healthy patients, so their results may not be applicable to patients with Parkinson disease.[32,42] In one of these studies,[42] which involved rasagiline and escitalopram, the area under the curve (AUC) for rasagiline increased by 42% ($p < 0.0001$) and oral clearance decreased by 35% ($p < 0.001$) after 7 days of combination therapy, relative to rasagiline treatment alone. The elimination half-life, peak plasma concentration (C_{max}), and time from drug intake to peak concentration (t_{max}) of rasagiline were not significantly affected by escitalopram.[42] In the other study,[32] which involved selegiline and citalopram, the AUC of selegiline decreased by 29% with concomitant citalopram, relative to selegiline alone; C_{max} and t_{max} were not significantly affected. Citalopram pharmacokinetics were unaffected, and the authors reported a lack of clinically relevant pharmacokinetic interaction.[32]

The largest study, involving rasagiline,[31] was a multicentre, retrospective cohort study, in which the authors systematically evaluated the incidence of serotonin syndrome among patients

taking rasagiline plus an antidepressant. Study centres were selected from individual neurology practices with medical records for 50 or more patients with Parkinson disease who had received rasagiline, 50 or more patients with Parkinson disease who had received an antidepressant, and 50 or more patients with Parkinson disease who had received the combination of rasagiline and an antidepressant. Serotonin syndrome was defined using the HSTC, which to date are the most sensitive and specific criteria for diagnosing serotonin syndrome.[31] Out of 1507 patients initially considered, all with Parkinson disease, 471 were taking rasagiline in combination with an antidepressant (351 or 74.5% using SSRIs), 511 were taking rasagiline without an antidepressant (3 of whom did not meet the eligibility criteria and were later excluded from analysis), and 525 were taking antidepressants (404 or 77.0% using SSRIs) without rasagiline. The mean SSRI doses in the antidepressant + rasagiline group and the antidepressant-only group were, respectively, citalopram 23.7 and 26.0 mg, escitalopram 13.8 and 14.2 mg, fluoxetine 24.1 and 27.2 mg, paroxetine 22.3 and 22.9 mg, and sertraline 78.0 and 85.0 mg, which fall mainly at the lower end of the therapeutic ranges of these drugs. Of the 1419 patients (94.3%) with known outcomes, none experienced serotonin syndrome. The authors stated that the lack of serotonin syndrome cases suggests a rarer-than-expected incidence of the syndrome, which was below the study's detection threshold.[31] They further stated that future studies should increase the sample size to assess the true incidence of serotonin syndrome with concomitant use of rasagiline and antidepressants.[31] This study had both strengths and limitations. One major strength was the independent, systematic review of each case according to the HSTC, which ensured that cases of serotonin syndrome that might not have been properly recognized during a medical encounter were reassessed against robust criteria for this syndrome. Conversely, a major limitation was the retrospective study design, which meant that roughly 20% of medical records were unavailable for ascertainment of serotonin syndrome. Furthermore, there was limited access to the medical records of deceased patients, because of the requirement for informed consent at several study centres, which potentially prevented the capture of further cases of serotonin syndrome. A final limitation was the potential dismissal of symptoms of serotonin syndrome as features of the underlying disease. As such, practitioners might not have documented unusual findings as symptoms of serotonin syndrome, giving rise to false negatives.[31]

A survey of 63 investigators in the Parkinson Study Group utilized a standardized questionnaire to identify patients treated with the combination of selegiline and antidepressants.[43] Forty-seven investigators responded, which allowed identification of a total of 4568 patients who were taking this combination. Of these patients, 11 (0.24%) experienced symptoms "possibly consistent" with serotonin syndrome, with 2 patients having symptoms that were considered serious. Details were provided for only 5 patients, and one of these cases was already published (in 2 reports).[29,30] All 5 patients had used an SSRI (see "PSG cases" in Table 3 for further details).[29,30,43] Because details were unavailable for the remaining 6 patients, it is unknown whether they were taking an SSRI or another antidepressant.[43] In addition to their survey of the Parkinson Study Group investigators, the authors obtained a summary of all possible cases of drug interactions with concomitant use of selegiline and an antidepressant that had been submitted to the FDA between 1989 and 1996. Fifty-seven cases were identified, of which 27 involved an SSRI. From these 27 cases, only 2 were stated as having possibly fulfilled the Sternbach criteria for serotonin syndrome (see "FDA cases" in Table 3 for further details).[43] Lastly, the authors conducted a MEDLINE search and reviewed bibliographies for published cases of adverse events associated with concomitant use of selegiline and an antidepressant. Six cases were identified, 5 of which (including one of the cases identified by the Parkinson Study Group survey) involved an SSRI (see "published cases" in Table 3 for further details).[43]

Apart from these 11 potential cases of serotonin syndrome (4 cases from the survey [excluding the published case], 2 cases submitted to the FDA, and 5 cases from the MEDLINE search [including the case identified in the survey]), a retrospective chart review of 28 patients with Parkinson disease identified 1 possible case of serotonin syndrome.[33] The patient in question experienced increased nervousness, anxiety, tremor, and confusion less than 1 week after starting fluoxetine 20 mg/day (in addition to selegiline 10 mg/day). Although the authors stated that the reaction was consistent with serotonin syndrome, it was not possible to establish a firm diagnosis. Soon after stopping fluoxetine, the patient's symptoms improved, but they had not completely resolved 3 weeks later.[33]

Overall, the combination of SSRI and MAO-B inhibitor was well tolerated in these studies, with 12 possible cases of serotonin syndrome (1 additional case from the retrospective chart review). One additional patient experienced worsening of a parkinsonian tremor, which was attributed to fluoxetine.[37] The evaluated doses of selegiline and rasagiline were both within the recommended range for Parkinson disease, and the doses of SSRIs were generally at the lower end of the therapeutic range for depression. From these studies, it appears that selegiline or rasagiline can be used with an SSRI, provided that the recommended doses of both agents are not exceeded and, ideally, the SSRI dose is kept at the lower end of the therapeutic range. However, further studies using larger sample sizes would be welcome to determine the true incidence of this drug interaction.

Case Reports

Although the largest study found no evidence of a clinically relevant interaction between MAO-B inhibitors and SSRIs,[31] and only 12 possible cases of serotonin syndrome were identified in other studies, 6 further case reports have described the onset of

Table 3 (part 1 of 3). Case Reports of Possible Serotonin Syndrome Induced by Concomitant Use of Selegiline or Rasagiline with SSRI

Study and Patient	MAO-B Inhibitor*	SSRI*	Onset of Symptoms	Clinical Presentation	Outcome	Hunter Criteria[13]	Sternbach Criteria[12]†
Richard et al. (1997)[43]							
72-year-old man (PSG case 1)	Selegiline 10 mg/day	Sertraline 50 mg/day	2 weeks after adding SSRI	Worsened PD symptoms, nausea, lightheadedness, increased orthostatic hypotension, agitation, confusion	Sertraline discontinued. All symptoms improved at 2-month follow-up, except worsened PD symptoms.	Could not be assessed on basis of "worsened PD symptoms"; agitation alone does not fulfill criteria.	Could not be assessed on basis of "worsened PD symptoms"; agitation and confusion (mental status changes) do not fulfill criteria.
67-year-old man (PSG case 2)	Selegiline 10 mg/day	Fluoxetine 20 mg/day	4 months after adding SSRI	Worsened PD symptoms, nausea, restlessness, insomnia	Selegiline reduced to 5 mg/day. All symptoms improved at 3-month follow-up, except worsened PD symptoms.	Could not be assessed on basis of '"worsened PD symptoms".	Could not be assessed on basis of '"worsened PD symptoms".
73-year-old woman (PSG case 3)	Selegiline 10 mg/day	Fluoxetine 20 mg/day	A few weeks after adding SSRI	Urinary incontinence (transient), orthostatic hypotension, syncopal episodes, gait problems, insomnia, restlessness, anxiety, agitation, anorexia	Selegiline dose reduced, leading to improvement in orthostatic hypotension and syncope. Selegiline discontinued, leading to complete resolution of these symptoms. Fluoxetine discontinued, leading to resolution of gait problems, insomnia, restlessness, anxiety, agitation, and anorexia.	No; agitation alone does not fulfill criteria.	No; agitation alone does not fulfill criteria, and could not be assessed on basis of "gait problems".
57-year-old woman (PSG case 4)	Selegiline 10 mg/day	Fluoxetine 20 mg/day	A few weeks after adding SSRI	Worsening headaches, diaphoresis, increased nausea, elevated blood pressure (190/100 mm Hg)	Fluoxetine discontinued. Symptoms resolved.	No; diaphoresis alone does not fulfill criteria.	No; diaphoresis alone does not fulfill criteria.
Suchowersky (1990)[29,30]							
56-year-old woman (PSG case 5, published case 1)	Selegiline 5 mg/day	Fluoxetine 20 mg/day	Several days after adding SSRI	Shivering, vasoconstriction of hands, blue and mottled fingers, elevated blood pressure (200/120 mm Hg), diaphoresis	Selegiline and fluoxetine discontinued. Symptoms resolved within a few days. Patient later restarted fluoxetine with no AEs.	No; diaphoresis alone does not fulfill criteria.	No; shivering and diaphoresis alone do not fulfill criteria.
46-year-old woman (published case 2)	Selegiline, dose not stated	Fluoxetine 20 mg/day	The next month after adding selegiline	Increased hyperactivity, over-communication, elation, creativity	Selegiline and fluoxetine discontinued. Symptoms slowly resolved over 2 months.	No	No
Jermain et al. (1992)[35] 66-year-old woman (published case 3)	Selegiline 10 mg/day	Fluoxetine 20 mg/day	1 month after adding SSRI	Ataxia	Selegiline discontinued. Ataxia improved over 6 weeks. Fluoxetine reduced to 10 mg/day, with further improvement over 4 weeks. Fluoxetine discontinued, with complete resolution after 1 month.	No	No

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Table 3 (part 2 of 3). Case Reports of Possible Serotonin Syndrome Induced by Concomitant Use of Selegiline or Rasagiline with SSRI

Study and Patient	MAO-B Inhibitor*	SSRI*	Onset of Symptoms	Clinical Presentation	Outcome	Hunter Criteria[13]	Sternbach Criteria[12]†
Garcia-Monco et al. (1995)[46] 72-year-old woman (published case 4)	Selegiline 10 mg/day	Fluoxetine, dose not stated	Days after adding fluoxetine	Diaphoresis, distal tremor, confusion, moderate increase in blood pressure	Fluoxetine discontinued. Symptoms resolved and did not recur upon initiation of amitriptyline.	No; combination of diaphoresis and tremor does not fulfill criteria.	Yes; combination of diaphoresis, tremor, and confusion (mental status changes) fulfills criteria. Onset of symptoms coincident with adding fluoxetine.
Montastruc et al. (1993)[36] 44-year-old woman (published case 5)	Selegiline 10 mg/day	Fluoxetine 20 mg/day	1 month after adding SSRI	"Probable" generalized tonic–clonic seizure, elevated blood pressure (250/130 mm Hg), headache, flushes, palpitations	Selegiline and fluoxetine discontinued. Blood pressure and urine catecholamines normalized within 2 days.	No; tonic–clonic seizure may have resulted from hyperthermia.	No
Richard et al. (1997)[43] 77-year-old woman (FDA case 1)	Selegiline, dose not stated	Fluoxetine, dose not stated	After 8 days of concomitant therapy	"Serotonergic reaction"	Not stated	Could not be assessed, based on lack of description of symptoms of "serotonergic reaction".	Could not be assessed, based on lack of description of symptoms of "serotonergic reaction".
82-year-old man (FDA case 2)	Selegiline, dose not stated	Paroxetine, dose not stated	2 days after adding SSRI	Extreme confusion, gross tremor of all extremities, agitation, rigidity	Paroxetine discontinued. Symptoms resolved.	Could not be assessed, as rigidity may have masked any clonus. Combination of tremor, agitation, and/or rigidity does not fulfill criteria.	Yes; combination of agitation, tremor, and confusion (mental status changes) fulfills criteria. Onset of symptoms coincident with adding paroxetine.
Suphanklang et al. (2015)[47] 77-year-old man	Rasagiline, dose not stated	Escitalopram, dose not stated	2 days after adding rasagiline	High-grade fever, confusion, agitation, hallucinations, behavioural changes	Rasagiline and escitalopram discontinued. Worsening renal function, leading to acute kidney injury.	Could not be assessed because only abstract was available for case information; agitation alone does not fulfill criteria.	Yes; combination of fever, confusion (mental status changes), and agitation fulfills criteria. Onset of symptoms coincident with adding rasagiline.
Duval et al. (2013)[48] 75-year-old woman	Rasagiline 1 mg/day	Sertraline 100 mg/day	1 week after sertraline dose increase from 50 to 100 mg/day	Agitation, delusion, altered consciousness, diaphoresis with hyperthermia (38.5°C), unstable blood pressure, generalized myoclonic tremor with rigidity, hyperreflexia	Rasagiline and sertraline discontinued. Symptoms resolved within 3 days.	Yes; combination of tremor and hyperreflexia fulfilla criteria.	Yes; combination of agitation, diaphoresis, myoclonic tremor, and hyperreflexia fulfills criteria. Onset of symptoms coincident with adding sertraline.
Sanyal et al. (2010)[49] 73-year-old woman	Selegiline 5 mg/day	Escitalopram 10 mg/day	1 week after adding SSRI	Agitation, restlessness, shivering, sweating, diarrhea, hyperthermia (102°F), tremor, ataxia, hyperreflexia, mydriasis, tachycardia, hypotension, confusion, anxiety. ICU admission was required	Selegiline and escitalopram discontinued, cyproheptadine started. Symptoms improved and vital signs stable next day.	Yes; combination of tremor and hyperreflexia fulfills criteria.	Yes; combination of agitation, shivering, sweating (diaphoresis), diarrhea, tremor, hyperreflexia, and confusion (mental status changes) fulfills criteria. Onset of symptoms coincident with adding escitalopram.

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Table 3 (part 3 of 3). Case Reports of Possible Serotonin Syndrome Induced by Concomitant Use of Selegiline or Rasagiline with SSRI

Study and Patient	MAO-B Inhibitor*	SSRI*	Onset of Symptoms	Clinical Presentation	Outcome	Hunter Criteria[13]	Sternbach Criteria[12]†
Hébant et al. (2016)[50] 72-year-old man	Rasagiline, 1 mg/day	Paroxetine, 20 mg/day	3 weeks after adding SSRI	Fever, profuse sweating, confusion, hyperventilation, tremor affecting all 4 limbs, which was different from patient's usual PD tremor	Rasagiline and paroxetine discontinued. Symptoms resolved within a few days.	No; tremor alone does not fulfill criteria.	Yes; fever, sweating, confusion (mental status changes), and tremor fulfill criteria. Onset of symptoms coincident with adding paroxetine.
Noyes et al. (1995)[51] 72-year-old man	Selegiline, dose not stated	Fluoxetine, dose not stated	After 9 weeks of concomitant therapy	Lethargy, malaise, progressive myoclonic jerking, grand mal seizure	Fluoxetine discontinued after grand mal seizure. Seven days later, patient had acute delirium, convulsive movements, akathisia, and unresponsiveness. Selegiline discontinued. Symptoms resolved within 1 week.	No; myoclonus is a symptom of serotonin syndrome,[10,13] but does not fulfill criteria.	No; myoclonus is a symptom of serotonin syndrome,[10,13] but does not fulfill criteria.
Kurlan and Dimitsopulos (1992)[34] 41-year-old man	Selegiline, dose not stated	Fluoxetine, dose not stated	Within 3 months of concomitant therapy	Manic episode	Selegiline discontinued. Two months later, patient experienced another manic episode while not on selegiline.	No	No

AE = adverse event, FDA = Food and Drug Administration (US), ICU = intensive care unit, MAO-B = monoamine oxidase B, PD = Parkinson disease, PSG = Parkinson Study Group, SSRI = selective serotonin reuptake inhibitor.
*At stated doses until development of symptoms.
†Onset of symptoms deemed coincident if reaction developed within 4 weeks, the upper limit of the clinical reports used to develop the Sternbach criteria.[12]

possible serotonin syndrome with coadministration of an SSRI and either selegiline or rasagiline.[34,47-51] Table 3 describes these cases, in addition to the 11 cases identified by the Parkinson Study Group (including the survey, literature search, and review of FDA-reported cases).[29,30,34-36,43,46-51] For one published case identified by the Parkinson Study Group, we noted discrepancies between their description[43] and the reports of the original authors.[29,30] As such, the authors' original description[29,30] has been included in Table 3.

The onset of serotonin syndrome varied from days to weeks following a dose increase (1 case only) or initiation of the new serotonergic agent (most reports). This finding is inconsistent with the statement by Mason and others[11] that most cases of serotonin syndrome manifest within 24 h after a dose change or initiation of a serotonergic agent; however, the observations of those authors were based on only 41 patients. Although most of these patients had underlying diseases, none had Parkinson disease.[11] In addition, selegiline was not implicated in any of the cases, rasagiline had not yet been approved,[45] and a substantial proportion of the patients (26%) experienced serotonin syndrome after more than 24 h, with the longest period of symptom onset being 36 days.[11] Therefore, serotonin syndrome cannot be ruled out on the basis of timeframe alone, and a specific timeframe is not a requirement to fulfill the HSTC.[13]

The most commonly implicated MAO-B inhibitor and SSRI were selegiline and fluoxetine, respectively, likely because of their lengthier market approval and the relatively longer half-life of fluoxetine. This longer half-life is important because changes in plasma concentration will not be fully observed for several weeks. Similarly, when fluoxetine is discontinued, plasma concentrations drop slowly, and the drug remains in the body for several weeks.[23] In these case reports, the doses of the MAO-B inhibitor were within the recommended range for Parkinson disease, and the doses of the SSRI were at the lower end of the therapeutic range for depression.[16,17,21-24]

Following discontinuation or dose reduction of one or both serotonergic agents, symptoms of serotonin syndrome gradually resolved in most cases; no cases were fatal. In 2 cases, the patients also experienced worsened symptoms of Parkinson disease. In the first case, worsening of tremor persisted despite sertraline discontinuation.[43] In the second case, worsening of tremor also persisted, but no mention was made of whether the SSRI was discontinued; notably, however, the dose of selegiline had been reduced.[43] It is interesting to note the similarities between the motor symptoms of Parkinson disease, specifically resting tremor and rigidity, and the motor symptoms of serotonin syndrome.[1,2] Both of these cases were published before development of the HSTC, which include both tremor and hypertonicity as clinical features of serotonin syndrome.[13] Therefore, a mild form of serotonin syndrome might have been considered, had the HSTC been available at the time of the event in these 2 cases.

In the case presented by Montastruc and others,[36] the patient experienced a tonic–clonic seizure. Seizures are more severe complications of serotonin syndrome, often associated with hyperthermia.[10,14] The authors did not report the patient's temperature. For this reason, it was not possible to confirm the cause of the seizure as serotonin syndrome.

Cyproheptadine has been proposed as an off-label treatment for serotonin syndrome. It is a histamine-1 receptor antagonist with additional nonspecific binding at the 5-HT_{1A} and 5-HT_{2A} receptors. It is recommended as an antidote for serotonin syndrome,[10] despite a lack of evidence for its efficacy. The suggested dosage is 12 mg initially, followed by 2 mg every 2 h, or 4–8 mg every 6 h until symptoms are controlled. Because of its anticholinergic activity, it causes sedation.[10,14,52] In only one of the identified cases was cyproheptadine reported as having been used to manage serotonin syndrome.[49] The dosing in this case differed somewhat from the previously proposed dosing: it was prescribed as 4 mg orally every 2–4 h, with up to 30 mg per day. The patient's vital signs stabilized, and her symptoms had improved by the next day.[49]

Four cases of serotonin syndrome[47-50] were reported after publication of the HSTC in 2003, and we determined that 2 of them met these criteria.[48,49] Fulfillment of the HSTC in these 2 cases is noteworthy because it may indicate that the HSTC are emerging as a new standard for diagnosis. It may also suggest that the HSTC can be applied to cases of serotonin syndrome occurring in patients who receive therapeutic doses, despite the criteria being based solely on cases of SSRI overdose. Of these 2 cases, Duval and others[48] used the HSTC for their diagnosis of serotonin syndrome, whereas Sanyal and others[49] used the Sternbach criteria. Conversely, we determined that all 4 of the cases published after 2003 met the Sternbach criteria,[47-50] which would suggest that these criteria are still being used to diagnose serotonin syndrome. Of the 2 cases that we deemed as not meeting the HSTC criteria, the case reported by Suphanklang and others[47] would not be classified as serotonin syndrome, on the basis of information available in the abstract; the full article could not be obtained for examination. In the other case, Hébant and others[50] diagnosed serotonin syndrome with the Sternbach criteria and made no mention of the HSTC.

Three further case reports (describing 2 individual patients) did not explicitly mention serotonin syndrome, but described the occurrence of mania with concomitant use of selegiline and fluoxetine. In the first case (described in 2 separate articles),[29,30] the authors thought the prolonged mania resulted from concomitant use of fluoxetine and selegiline, because both medications are known to induce mania when used alone. In the other case, the patient experienced a second manic episode 2 months after discontinuing selegiline. At that point, the authors did not further clarify the patient's psychiatric diagnosis.[34] Mania alone does not fit the Sternbach criteria[12] or the HSTC.[13]

CLINICAL MANAGEMENT

The benefits of MAO-B inhibitor and SSRI in combination in the treatment of depression related to Parkinson disease generally outweigh the risks; therefore, either selegiline or

rasagiline can be used cautiously with an SSRI, if their recommended doses are not exceeded (i.e., total daily doses of up to 10 mg and 1 mg for selegiline and rasagiline, respectively) and doses of SSRI are kept at the lower end of the therapeutic range. When adding an SSRI to either selegiline or rasagiline, the SSRI should be initiated at the lowest possible dose and titrated slowly. The use of other serotonergic agents should be avoided; drugs that can decrease the metabolism of either MAO-B inhibitors or SSRIs should also be avoided. Among the SSRIs, citalopram and sertraline may be preferred because of their demonstrated efficacy and tolerability as antidepressants in Parkinson disease.[2,4,5] Sertraline is the SSRI that appears to have the least potential for inducing parkinsonism,[4] whereas citalopram has an overall low potential for drug interactions.[39] Proper patient monitoring is imperative. According to case reports, the onset of the interaction is variable, ranging from a few days to weeks after initiation of the new agent. Therefore, clinicians must remain vigilant for this interaction at all times. As a cautionary measure, the patient and/or caregiver should be advised of the signs and symptoms of serotonin syndrome, despite the low risk.

CONCLUSION

To date, the only report to estimate the incidence of serotonin syndrome with the coadministration of an MAO-B inhibitor and antidepressants (including SSRIs) is the Parkinson Study Group survey.[43] In that survey, the authors found an incidence of 0.24%, although these were not cases of serotonin syndrome retroactively assessed using the Sternbach criteria, and the survey report predated the development of the HSTC. Furthermore, the large retrospective study that used a preset definition of serotonin syndrome based on the HSTC did not identify any cases of serotonin syndrome.[31] The clinical data supporting this potential interaction are therefore based on case reports alone. Given that the benefits of this combination in treating depression related to Parkinson disease generally outweigh the risks, either selegiline or rasagiline can be used cautiously with an SSRI, provided that their recommended doses are not exceeded and the doses of SSRIs are kept at the lower end of the therapeutic range.

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CASE REPORT

Brevundimonas vesicularis Causing Bilateral Pneumosepsis in an Immunocompetent Adult: A Case Report and Literature Review

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INTRODUCTION

Brevundimonas vesicularis is an aerobic, nonfermenting gram-negative bacillus that produces oxidase and catalase.[1] Previously known as *Pseudomonas vesicularis*, this organism was reclassified under the genus *Brevundimonas* on the basis of differentiating genotypic and phenotypic characteristics.[1] It is commonly found in soil and water, is considered ubiquitous in the environment, and is a rare cause of infection in humans.[1-4] Most case reports have described infection with *Brevundimonas* spp. in immunocompromised patients, although there are isolated reports of infection in immunocompetent patients.[2-5] To the authors' knowledge, there are no published case reports to date describing *B. vesicularis* pneumonia in immunocompromised or immunocompetent patients.

CASE REPORT

A previously healthy adult patient (age early 40s) presented to the emergency department with a 4-day history of fever, cough, and shortness of breath.* On admission, the rectal temperature was 39.8°C, heart rate 133 beats/min, blood pressure 137/84 mm Hg, oxygen saturation 91% on room air, and respiratory rate 26 breaths/min. The patient had originally resided in India, but denied any travel outside Canada during the previous year. The patient's HIV status was negative, there was no evidence of immunoglobulin deficiency, and there were no known sick contacts or recent interactions with the health care system.

Chest radiography on admission showed bilateral pulmonary infiltrates, larger on the right side than the left. The initial leukocyte count was 2.4 × 10^9/L (normal range 4–11 × 10^9/L) , with a neutrophil count of 1.7 × 10^9/L (normal range 2–8 × 10^9/L) and eosinophils undetectable. Serum sodium was 121 mmol/L (normal range 135–145 mmol/L), potassium 3.1 mmol/L (normal range 3.5–5 mmol/L), C-reactive protein 209 mg/L (normal range < 7.5 mg/L), γ-glutamyl transpeptidase 466 U/L (normal range < 31 U/L), and lactate dehydrogenase 531 U/L (normal range < 220 U/L); all other laboratory results were within normal limits. Examination showed bilateral coarse crackles in both lung fields, but all other physical findings were unremarkable.

The patient was stabilized, and blood and urine samples were sent for culture and sensitivity testing; the patient was unable to expectorate sputum sample adequate for testing. Supplemental oxygen and antibiotic therapy, with IV administration of ceftriaxone and azithromycin, were initiated for a provisional diagnosis of community-acquired pneumonia. Despite appropriate empiric treatment, there were no signs of clinical improvement. After 3 days, the patient's respiratory system decompensated, with progressive hypoxemia and hypotension necessitating additional supplemental oxygen, vasopressor support, intubation, and mechanical ventilation.

At this time, culture results for blood and urine samples obtained at the time of presentation became available; all were negative. However, because of the patient's declining clinical status, azithromycin and ceftriaxone were discontinued, and IV therapy with piperacillin–tazobactam was started.

An endotracheal aspirate sent for culture and sensitivity testing at the time of intubation was found to be mucopurulent, and eventually grew *Brevundimonas vesicularis*. The results of additional testing (multiplex viral polymerase chain reaction assay, and antigen testing for *Legionella pneumophilia* and *Mycoplasma pneumoniae*) were negative. Subsequent quantitative culture of samples obtained during bronchoscopy yielded negative results. Acid-fast staining for *Mycobacterium tuberculosis* and immunofluorescent staining for *Pneumocystis jirovecii*

*Despite repeated attempts, the authors were unable to reach the patient to request consent for publication of this report. Therefore, personal details not pertinent to understanding of the case have been omitted to protect confidentiality.

(Fungi-Fluor kit for fungal detection, Polysciences, Inc, Warrington, Pennsylvania) were also negative. All additional culture results were negative.

Bronchoscopy performed 36 h after intubation showed inflamed airways, but the findings were otherwise unremarkable. Mucopurulent respiratory secretions were noted; no hemorrhage, obstruction, or tumours were visualized. Samples taken during bronchial washing showed no malignant cells and no fungal elements. Contrast-enhanced computed tomography of the chest showed widespread centrilobular pulmonary nodularity with ill-defined margins and ground-glass density. Confluent airspace consolidation was identified in the subpleural lower lobes and in the right middle lobe. Trace pleural effusions were noted.

The patient gradually began to improve, with extubation after 5 days of mechanical ventilation. A 14-day course of piperacillin–tazobactam was given, and the patient was eventually discharged home with no sequelae.

Microbiology Results

Gram staining of the endotracheal aspirate obtained on the day of intubation showed 2+ polymorphonuclear cells, 2+ monomorphonuclear cells, 1+ squamous epithelial cells, 1+ organisms suggestive of respiratory flora, and 1+ yeast (quantitation per local laboratory protocol). After 48 h of incubation on sheep's blood agar and chocolate agar, there was heavy growth of grey colonies that were nonhemolytic and did not form satellites. Gram staining showed these organisms to be small gram-negative bacilli. The results of oxidase and porphyrin fluorescence tests were negative. The organism was identified by the API 20 NE identification system (bioMérieux) as *B. vesicularis* (profile 1440200, 98.3% probability).[6] Furthermore, the isolate tested positive for esculin hydrolysis, D-glucose assimilation, and D-maltose assimilation, results that strongly corroborated the identification and reliably differentiated the organism from *B. diminuta*.[7]

Susceptibility testing was performed with the Kirby–Bauer disk diffusion method, using an inoculum of 0.5 McFarland standard on Mueller–Hinton agar and interpreted according to the performance standards of the Clinical and Laboratory Standards Institute (M100 document, 17th edition, Table 2B-1, "Zone diameter interpretive standards and equivalent minimal inhibitory concentration [MIC] breakpoints for *Pseudomonas aeruginosa* and non-*Enterobacteriaceae*").[8] The organism was reported as susceptible to the following antibiotics (zone diameters in parentheses): meropenem (42 mm), piperacillin (45 mm), gentamicin (50 mm), tobramycin (45 mm), and trimethoprim–sulfamethoxazole (52 mm); the organism was reported as resistant to the following antibiotics: ceftazidime (0 mm) and ciprofloxacin (0 mm).

DISCUSSION

To the authors' knowledge, this is the first reported case describing *B. vesicularis* as a causative pathogen for pneumonia.

From the literature search, we identified a total of 78 cases, from 21 case reports and 3 case series (where a case series was defined as $n \geq 4$), describing *B. vesicularis* as a causative pathogen.[2-5,9-28] There was high variability among the cases as to the site and severity of infection, the age and immune status of the patient, and the geographic location. However, most cases occurred in immunocompromised adults and were described as bacteremia or sepsis, with no focus of infection reported.[2,5,9-11,13-16,19,22-25,27] No previously reported cases of pneumonia with *B. vesicularis* as causative pathogen were identified.

Because of the high variability in antibiotic susceptibility patterns from the previously reported cases, we were unable to choose an empiric antibiotic with confidence. *Brevundimonas vesicularis* has often been described as susceptible to piperacillin–tazobactam, carbapenems, and aminoglycosides.[2-4,10-15,17,20,22,24,25,27] However, resistance to these antibiotics has also been reported.[4,11,14,15,17,20] We chose piperacillin–tazobactam, to avoid selective pressure on carbapenem-resistant organisms and because this drug has superior lung penetration relative to aminoglycosides. The reported susceptibility to third- and fourth-generation cephalosporins and fluoroquinolones is much less consistent, with the largest case series reporting 0%–86.4% of isolates susceptible to ciprofloxacin and 3%–63.6% of isolates susceptible to ceftazidime.[2,27] There has also been a high degree of variability in the methods used for testing susceptibility in the reported cases, which makes the results difficult to interpret.

CONCLUSION

For the case reported here, we were unable to determine where the patient might have contracted infection with this bacterium or why it caused such a severe infection in a relatively young, healthy adult. Although infections with *Brevundimonas* spp. are uncommon, as revealed by our literature search, this case shows the potential for such an infection to cause bilateral pneumonia and septic shock in an immunocompetent adult. Given the high variability in antibiotic susceptibility that has been reported to date, consideration should be given to initiating empiric therapy with piperacillin–tazobactam or an anti-pseudomonal carbapenem in patients with known or suspected *B. vesicularis* infections.

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Should Medical Cannabis Administered by Inhalation Be Allowed for Hospitalized Patients?

THE "PRO" SIDE

Cannabis has been used medically by many cultures throughout human history.[1] The origins of cannabis prohibition in Canada began mysteriously in 1923. Legislation was passed swiftly by the House of Commons and the Senate, without any debate, discussion, or presentation of supporting evidence warranting prohibition, and despite a strong historical precedent indicating that cannabis was useful for a variety of ailments.[2]

Today's legal landscape regarding cannabis is evolving quickly, driven primarily by grassroots efforts that recognize the medical value of cannabis, as well as the harms of propagating a drug war against its users.[3] The problematic consequences of prohibition have been extensive, and review of them in their entirety is outside this article's scope. For the purposes of this article, however, it is worth mentioning one consequence that is cited by the medical community as an adequate reason for continuing prohibitive policy approaches, and that is the lack of clinical data.[4]

For example, the Canadian Medical Association has recommended against the prescribing of medical cannabis,[5] and cannabinoid prescribing guidelines for Canadian family physicians similarly recommend against prescribing (outside a small subset of conditions refractory to other treatments) because of a lack of high-quality evidence.[6] Furthermore, although Canadian regulations allow the prescribing of medical cannabis, Health Canada has not approved it for therapeutic use for the aforementioned reason. This logic is circular and flawed, because cannabis prohibition predates the era of evidence-based medicine, and the status of prohibition itself is not evidence-based. Additionally, prohibition has directly oppressed and stigmatized medical research involving cannabis, thus lowering the chances that evidence gaps can be filled. However, recent trials have clearly demonstrated the medical utility of inhaled cannabis, especially for chronic pain.[7-17] Meanwhile, there are epidemic harms associated with opioid use for chronic pain, which serve to highlight the relatively favourable safety profile of cannabis.[4]

Cannabis is bioavailable by a number of routes, although about two-thirds of patients prefer administration by inhalation (as either vapour or smoke) over other routes, such as oral administration.[18] Inhalation reduces the latency to onset of action relative to other routes of administration, so patients have faster relief of symptoms and increased control over dose titration.[18] Reduced latency also increases the hedonic value (pleasurable effect) of the experience and subsequent abuse potential. However, the abuse potential of inhaled cannabis must be interpreted in the context of the abuse potential and safety risks of likely medical alternatives.

Currently, the strongest evidence base for use of cannabis exists for chronic pain syndromes,[17] which are often present in hospitalized patients. Opioids have been the gold standard for treatment of severe pain in acute care settings, and extension of this practice to patients with chronic noncancer pain has led to epidemic morbidity and mortality in North America.[19,20] In hospitals, opioids are frequently administered by the IV route, which has a latency of onset similar to that of inhalation (< 10 seconds), although it has additional risks, including systemic infection and extravasation. IV administration of opioids also carries significant risks for acute toxicity, including respiratory depression and death, as well as the potential for severe physical and psychological dependence. Additional side effects include constipation, pruritus, sedation, nausea, and vomiting.[21] Therefore, on the basis of current practice trends, the increased abuse potential associated with administration routes with a decreased latency of onset has been insufficient to prohibit utilization of other substances with medical utility and abuse potential, such as opioids. That being the case, it is unconvincing to disallow use of inhaled cannabis because of the abuse potential associated with the inhaled route of administration.

Additionally, there is an emerging evidence base supporting certain benefits of cannabis, specifically that it can have opioid-sparing effects, can act as an opioid substitute, and can potentially decrease morbidity and mortality related to opioid use, which together may signal inhaled cannabis as an important medical progression in the care of patients with pain.[22-25] Although the strongest evidence base for cannabis use relates to chronic pain, its effects are myriad and may also decrease the need for other pharmacotherapies. For example, inhaled cannabis can increase appetite, increase the quality and duration of sleep, and decrease nausea, and many patients are using it for mood disorders.[26-28] These effects offer a multitude of potential benefits to hospitalized patients, especially those receiving palliative care.[29]

The significant pharmacokinetic advantages of cannabis delivered by inhalation, evidence supporting patients' preference for inhaled cannabis, and possible clinical advantages over various medical alternatives should naturally lead to extension of its availability to hospitalized patients who are already using medical cannabis. In fact, doing so would be in accordance with best practices for care transitions and compassionate patient-centred care. Each medication that patients use on an outpatient basis should be evaluated by admitting clinicians for appropriateness of continuation upon transfer to the acute care setting. In recent years, there has been a focus on the improvement of medication reconciliation and transitions of care, which has encouraged providers to not abruptly stop or drastically change a patient's medication regimen upon inpatient admission, unless there is a medical rationale for doing so. Negative outcomes associated with poor transitions of care are well documented, and there is no evidence to suggest that medical cannabis should be handled any differently.[30]

There are a number of barriers to implementation of inhaled cannabis in hospitals, as well as unanswered questions about its use, that necessitate flexibility and further study. For example, it appears that vapourization can largely mitigate the risks associated with combustion and the respiratory consequences of smoke inhalation. Potential downsides for other patients or staff in close proximity to cannabis vapour are largely unknown, although they are likely different from those associated with tobacco vapour, given the stark differences in toxicities between the substances. Increasing a building's ventilation and limiting the use of inhaled cannabis to hospitalized patients who can access outdoor or courtyard spaces are potential solutions consistent with current smoking laws.[31]

It is apparent that the medical use of cannabis has been reclaimed by patients and will likely continue to expand in coming years, through both legalization and reduction of stigma associated with cannabis use. Further delaying access to treatment with a therapeutic entity that has been in existence for millennia, that is supported by scientific and public health evidence, and that is widely touted as safe and effective by its users is not compassionate, patient-centred, or evidence-based. In short, it hurts our patients to perpetuate a draconian status quo that prohibits use of cannabis by inhalation. It is time to embrace the medical utility of cannabis fully and in earnest. Barriers and challenges to implementation exist, but they do not represent an adequate rationale for continuing the prohibition of safe and effective treatments involving the inhalation of cannabis inside hospitals.

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THE "CON" SIDE

Although inhaled cannabis is proposed to have benefits as an analgesic, antispasmodic, anticonvulsant, antinauseant, and appetite stimulant, Health Canada has not reviewed data on its safety or effectiveness and has not approved cannabis for therapeutic use.[1,2] Few studies have examined the effects of inhaled cannabis, and the benefits of smoked or vapourized cannabis, based on low- or moderate-quality evidence, have been described only for neuropathic pain and spasticity.[2,3]

Despite the paucity of evidence, Canadian regulations on cannabis for medical purposes permit the authorization of cannabis for patients, who can then purchase it directly from licensed producers.[4] When outpatients who have been using cannabis for medical purposes are admitted to hospital and want to continue their therapy through inhaled delivery routes, there are significant implications for the hospitals. Relevant legislation, quality control, and safety for patients and their families, as well as for hospital staff, are important considerations as hospitals develop policies and procedures to address the use of inhaled cannabis.

Cannabis can be delivered orally, by inhalation, or intranasally. A 2015 survey of adult Canadian medical cannabis users (n = 364) reported smoking as the preferred mode of delivery (37.6%), followed by vapourizing (28.3%) and eating in foods (7.1%).[1] The more recent 2017 Canadian Cannabis Survey found that among respondents using cannabis for medical purposes (n = 1105), 81% reported using dried flower or leaf products (likely smoked or vapourized), and 30% reported using edible products.[5] The advantages of smoking cannabis, as reported by users, include greater enjoyment, greater convenience, more immediate and effective relief of symptoms, and whole-body euphoria.[1] The considerable disadvantages of smoking include increased potential for abuse because of the fast onset,[6] health risks from smoke inhalation (e.g., cancer, emphysema, bronchitis, cough, sputum production, wheezing),[7] and the formation of toxins at the time of combustion, as well as social disapproval of smoking and the associated smell.[1]

Because of the health risks related to smoking, Canada became a party nation to the World Health Organization Framework Convention on Tobacco Control[8] in 2005. This treaty was developed to protect the public's health from the harm caused by tobacco smoke. In Canada, participation in this treaty led to the development of provincial and territorial legislation to ban smoking in many public spaces and workplaces, including hospitals.[9] Although each province and territory developed its legislation independently, there is overall consistency across jurisdictions, with some variations, including the distance from a building entrance at which an individual can smoke or whether smoking is permitted inside a vehicle that is carrying children. In most jurisdictions, smoking of cannabis is not explicitly banned by the legislation; however, New Brunswick and Nova Scotia are adding cannabis to their respective Smoke-free Places Acts.[10,11] These changes mean that provincial health authorities are concerned about the harm that smoking of cannabis poses for the public, much like the smoking of tobacco. Other provinces and territories will likely follow suit to extend the principle of protecting public safety in and around hospitals from not just tobacco, but also cannabis. Vapourization of tobacco is subject to the same smoking regulations in each province, and is not allowed inside many workplaces, including hospitals.[12]

Vapourization of cannabis delivers inhaled tetrahydrocannabinol and other cannabinoids by heating either dry herb (raw plant product) or oil in a non-portable plug-in machine or a portable device. Vapourizing cannabis has been proposed as a harm reduction strategy because without the combustion that occurs with smoking, there is a decrease in toxic byproducts and lower concentrations of exhaled carbon dioxide.[2,13] The 2015 survey of adult Canadian medical cannabis users found that those vapourizing cannabis most frequently used the portable devices.[1] Although overheating can occur with any device, portable devices generally have an increased risk of this problem, and the overheating can lead to some combustion of the product, especially when dry herb is used.[1] This risk would negate any safety benefits of vapourization over smoking. Cannabis vapour produces pharmacokinetic effects similar to those of cannabis smoke, resulting in turn in a similar risk of abuse related to the rapid onset.[5,13] The unique disadvantages of vapourizing include the cost of devices to patients and the difficulty of operating them; for example, some devices require the user to capture the vapour in a bag, then inhale it, whereas other devices use a breathing wand.

Although vapourizing is likely less harmful than smoking,[7] there is still significant risk of vapour escaping into the environment. This vapour may expose hospital staff and neighbouring patients or families to the product. It has a strong scent, yet the hospital setting is an environment where many people may be sensitive to scent, and many hospitals have scent-free policies. In hospitals that use an optical sensor

to detect smoke in the environment, the escape of large amounts of vapour (e.g., through user error or device failure) could conceivably falsely trigger an alarm. The process of administering cannabis to the patient may also present a challenge. If patients are unable to set up the devices themselves or to self-administer the vapourized product, there could be an expectation that hospital staff will support administration using expensive and sometime complex devices, in the absence of industry standards. Hospitals must also consider the large energy requirement of vapourizers, up to 700 W. Devices would likely require assessment by the organization's fire safety group, because these high energy requirements might translate into risks to fuses or breaker issues if the required energy is not properly supplied.

Regardless of the delivery system, there remains controversy over the quality control of cannabis products.[14] Therapeutic management in the hospital setting is complicated, since without a biochemical analysis using verified phytocannabinoid standards, patients and health care providers are unable to identify the composition or consistency of the product.[14]

In summary, the inhaled route of administration of cannabis for medical purposes is associated with risks for patients, families, hospital staff, and others in the environment. There are also legislative and operational issues related to smoking and vapourizer devices that hospital administrators would have to consider. From a clinical perspective, pharmaceutical cannabinoids should be considered before cannabis for patients who need this type of therapy.[2] Therefore, cannabis for medical purposes should not be administered by inhalation to hospitalized patients. Other routes of administration, such as the oral route, may be considered by institutions as preferred alternatives.

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Pharmacists' Roles in Critical Care: Environmental Scan of Current Practices in Canadian Intensive Care Units

Clinical pharmacists' practice in critical care has grown and developed independently in different parts of Canada, guided largely by international research and position papers.[1-3] The association of positive patient outcomes with the involvement of clinical pharmacists is well known.[4] An environmental scan of current Canadian practices is not available in the published literature. A non-anonymous survey, consisting of 14 groups of open-form questions, was distributed by e-mail to all members of the Canadian Society of Hospital Pharmacists' Critical Care Practice Speciality Network in March 2017 (see Appendix 1, available from https://www.cjhp-online.ca/index.php/cjhp/issue/view/155/showToc). A follow-up reminder to potential participants working in critical care was conducted by telephone.

Respondents from 31 centres (Table 1), representing 54 of a possible 180 intensive care units (ICUs), provided input. Institution size, setting, region, and pharmacist training levels did not significantly affect any of the survey responses. Most respondents (22 [71%]) practised in a tertiary care centre, 28 (90%) in mixed medical–surgical units, and 27 (87%) in closed intensivist-managed units. The mean ICU size was 21 beds (median 20, range 6–44, interquartile range [IQR] 12–27), and the mean equivalent patient load per full-time equivalent pharmacist[5] was 13 (median 12, range 6–23, IQR 10–17). A group of pharmacists shared ICU coverage in 24 (77%) of the centres, and a tiered team combining advanced-training and entry-to-practice pharmacists was reported for 14 (45%) of the centres. Overall, 9 (29%) of the centres reported that their critical care pharmacy practitioners had received advanced training with either a postbaccalaureate Doctor of Pharmacy (PharmD) or a Master's degree, and 12 (39%) of the centres required an entry-to-practice degree as the minimum educational level to practise in the ICU. Pharmacists had higher credentials in locations where a postbaccalaureate PharmD program had been in existence for longer than 10 years. Clinical pharmacists provided coverage for 8 h/day in 28 (90%) of the centres and for 5 days a week in 26 (84%) of the centres, with a mean of 4 h (range 3–8 h) devoted specifically to rounds. The remaining pharmacist time was devoted to either drug distribution or clinical coverage in non–critical care areas.

Consistent-format patient care rounds were reported by 17 (55%) of the centres, with another 11 (35%) reporting that the specific format of rounds was determined by the attending physician. In 16 (52%) of the units, time was allocated during rounds for the pharmacist to present; in the remainder of the units, pharmacists were expected to support and comment on presentations by other members of the team. Respondents indicated that pharmacists' most common contributions during rounds were reviewing current medications, reviewing antimicrobial therapy, adjusting medication dosing for organ dysfunction, providing therapeutic drug monitoring, and ensuring appropriate prophylaxis (Figure 1). These reported pharmacist activities during rounds aligned with the "fundamental" and "optimal" activities for clinical pharmacists outlined by the Society of Critical Care Medicine and the American College of Clinical Pharmacy.[1,2] Clinical pharmacists transcribed orders from rounds consistently in 3 (10%) of the units (specifically those in the Lower Mainland of British Columbia) and on a dependent basis in another 5 (16%) of the units.

Respondents reported that pharmacists prepared for rounds using checklists in 10 (32%) of the centres, with FASTHUG[6] being the most common checklist. The majority of pharmacist documentation occurred as shadow charting, with 25 (81%) of respondents reporting that this documentation was not included in the medical record; for example, 17 (55%) of the centres reported use of a standardized patient monitoring form. In 27 (87%) of the units, pharmacists relied on the progress notes of other team members to record their contribution during rounds in the medical record, and 57% (17/30) of respondents reported that they would supplement those notes if they were discordant with the care decision made or if the pharmacist determined that further detail was necessary. Pharmacists spent much effort creating shadow charting, which is shared solely among pharma-

Table 1. Locations of Centres Responding to Survey

Province	No. of Respondents
Newfoundland	1
Nova Scotia	1
New Brunswick	2
Quebec	1
Ontario	10
Within Toronto	4
Outside Toronto	6
Manitoba	2
Saskatchewan	2
Alberta	5
British Columbia	7
Within Lower Mainland	3
Outside Lower Mainland	4
Total	31

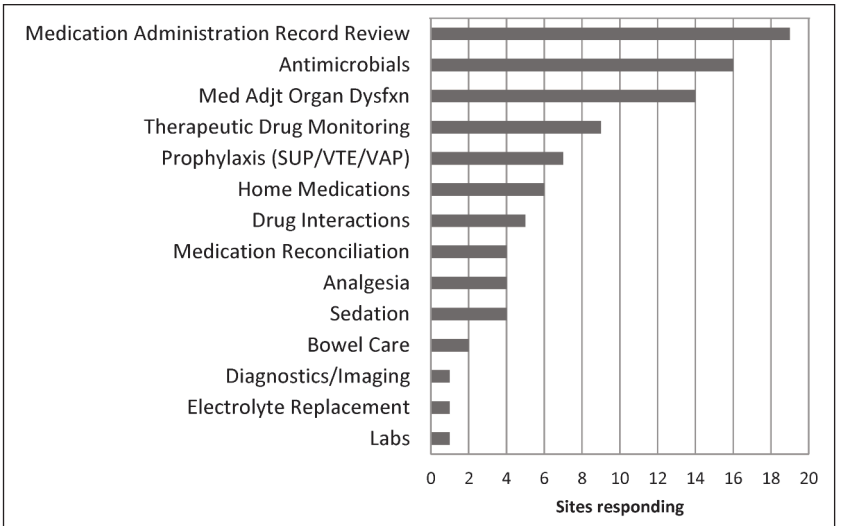

Figure 1. Topics to which pharmacists contributed during rounds (n = 31 centres responding to the survey). Med Adjt Organ Dysfxn = medication adjustment in context of organ dysfunction, SUP = stress ulcer prophylaxis, VAP = ventilator-associated pneumonia, VTE = venous thromboembolism.

cists. Shadow charting may be leftover from a time before computer information systems, when pharmacists rarely attended the ward and conducted consultations over the telephone. Institutions should review the efforts expended on shadow charting, with a view to ensuring that pharmacists' assessments and actions are included in the formal medical record.

These results show that Canadian pharmacists' self-description of their practice in the ICU is variable and poorly defined, with clinicians often describing their practice as being dependent on specific patient requirements. Clinical coverage models, patient load, and pharmacist training levels also differ. Documentation of drug therapy decisions largely relies on physicians' progress notes, and the majority of pharmacist documentation occurs outside the legal record. However, clinical pharmacists are commonly expected to document their interventions, and doing so has been shown to have benefits in terms of cost avoidance.[1,7,8] Work, research, and programming to decrease barriers to pharmacist documentation are ongoing.[9,10] The sample in this survey study may have been too small to show statistically significant practice differences in relation to centre characteristics. This sample may also not be reflective of all centres in Canada, as there was likely selection bias among the participants; however, the findings may serve as a baseline for future environmental scans of ICU practice in Canada.

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Cotrimoxazole-Induced Tremor

Cotrimoxazole (sulfamethoxazole–trimethoprim) is an anti-infective agent infrequently associated with neurotoxicity.[1] However, the potential for this medication to cause new symptoms of central nervous system irritability or alteration should not be overlooked, as illustrated by the following case.

A middle-aged patient, weighing 67 kg, was admitted to the intensive care unit (ICU) for respiratory failure.* Cotrimoxazole (1200 mg sulfamethoxazole and 240 mg trimethoprim) IV every 12 h was initiated for treatment of potential *Pneumocystis jirovecii* pneumonia. The patient had received a deceased-donor renal transplant 12 years before the current admission to overcome end-stage renal impairment due to immunoglobulin A nephropathy. The patient had been receiving tacrolimus monotherapy as immunosuppression therapy up to the time of admission. The patient had also been receiving oral cotrimoxazole (800 mg sulfamethoxazole and 160 mg trimethoprim) 3 times a week for prophylaxis before the admission, with concurrent renal function consistent with an estimated glomerular filtration rate of 57 mL/min.

In the ICU, the patient received 2 IV doses of cotrimoxazole before the medication was switched to oral cotrimoxazole (1600 mg sulfamethoxazole and 320 mg trimethoprim) twice daily. This approximates doses of 48 mg/kg daily sulfamethoxazole and 9.6 mg/kg daily trimethoprim, representing doses lower than usually prescribed for treatment of *P. jirovecii* pneumonia because of an acute decline in renal function (estimated glomerular filtration rate 19 mL/min at the time of admission).

Twenty-four hours after receiving the first IV dose, the patient was described as having new-onset twitching of both arms and both legs. By 48 h of therapy, after the switch to an oral formulation, the twitching had progressed to shaking of the limbs, predominantly the arms. By the fourth day of therapy, the symptoms had progressed to full body tremor. The possible contribution of cotrimoxazole was considered, and the drug was stopped at this point. Tremors of both the upper and the lower extremities subsequently declined, although complete resolution did not occur until 48 h after the last dose of cotrimoxazole.

No concurrent drug therapy, electrolyte imbalance, new therapy, or nutritional deficiency could be identified that would have accounted for the onset and offset of the tremor. Concurrent drug therapy included amlodipine, apixaban, acetylsalicylic acid, bisoprolol, hydralazine, insulin, mirtazepine, nitroglycerin, prednisone, and tacrolimus. None of these medications had been initiated recently. Tacrolimus concentrations measured before and subsequent to the symptoms of tremor were 3.7 and 3.3 µg/L, respectively (pre-dose measurements), which suggests that tacrolimus was unlikely to have contributed to the symptoms. No computed tomography of the head or electroencephalopathy studies were conducted. The patient was not rechallenged with cotrimoxazole, because other pathogens were isolated from sputum samples, rendering cotrimoxazole therapy unnecessary. The Naranjo score for a potential drug adverse effect was 6 (consisting of 1 point for a previous report of the same effect [as described below], 2 points for symptoms appearing after initiation of the drug, 1 point for improvement with discontinuation, and 2 points for no alternative cause), which suggested a probable cause–effect relationship. No alternative cause, such as drug withdrawal, structural neurological change, or metabolic toxicity, could be found.

Cotrimoxazole has been reported to cause tremor in a wide range of patient populations, from young to elderly patients,[2-11] and from immunocompetent[2] to immunosuppressed.[3-10] Reported associated daily doses have typically been sulfamethoxazole 75–100 mg/kg daily and trimethoprim 15–20 mg/kg daily, commonly initiated for treatment of *P. jirovecii* pneumonia[3-11] or other infections with pathogenic gram-negative bacteria.[2] No reports are available describing tremor associated with lower doses, as reported in this case. The observed toxicity may be concentration-dependent, given previously described resolution of symptoms with dose reduction.[6,8,10]

Onset of the tremor occurs soon after drug initiation; lag periods are reportedly as short as 2 days[2,8,11] or as long as 8 days,[4] with 3–5 days being the most common.[3-7,9,10] Symptoms resolve within 2–3 days following drug discontinuation,[3,5-11] although

*The patient's consent for publication of this report could not be obtained because of subsequent death from other causes. Personal details not pertinent to understanding of the case have been omitted to protect confidentiality.

full resolution has been infrequently reported as taking up to 8–10 days.[2,4] No additional treatment, beyond simple discontinuation of cotrimoxazole, has been reported as being utilized to quicken the recovery.

The mechanism by which cotrimoxazole causes neurotoxicity is unknown, and which moiety of the combination product causes the toxicity cannot be delineated. Potential mechanisms include accumulation of toxic metabolites due to a glutathione deficiency[5]; inhibition of the enzyme dihydrofolate reductase by trimethoprim, resulting in decreased concentrations of tetrahydrobiopterin, a naturally occurring pteridine that is a cofactor required for the production of catecholamines and serotonin[11]; or inhibition of phenylalanine metabolism resulting in toxic concentrations.[8]

Clinicians should consider the presentation of new-onset tremors, or other neurologic manifestations, as a potential indicator of drug toxicity if cotrimoxazole is being used at the doses considered necessary for treatment of *P. jirovecii*, *Stenotrophomonas maltophilia*, or *Nocardia* pneumonia, or if there is significant impairment of renal function. Discontinuation of the drug should result in quick resolution of symptoms without the need for additional corrective therapy. Clinicians should also consider alternative pathogen-directed antimicrobial therapy, because rechallenge of cotrimoxazole at an equivalent dosage has been reported to reproduce the symptoms of tremor.[4]

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La crise des opioïdes au Canada : l'engagement de la SCPH

par Patrick Fitch

On ne peut ignorer les manchettes. Le Canada est aux prises avec une crise des opioïdes. On compte plus de 2 900 décès apparemment liés à la consommation d'opioïdes en 2016 et près de 3 000 au cours des neuf premiers mois de 2017 (https://www.canada.ca/fr/sante-canada/services/toxicomanie/abus-medicaments-ordonnance/opioides/deces-lies-opioides.html). Selon l'Organe international de contrôle des stupéfiants, le Canada affiche l'un des taux les plus élevés de consommation d'opioïdes au monde (https://www.incb.org/incb/en/narcotic-drugs/Availability/availability.html). Cet enjeu de santé publique nécessite l'action de plusieurs parties prenantes.

La Société canadienne des pharmaciens d'hôpitaux (SCPH) a participé à des conférences sur les opioïdes organisées par le Gouvernement du Canada (en novembre 2016) et par l'Association des pharmaciens du Canada (en juin 2017) et s'est engagée à prendre certaines mesures pour aider à résoudre cette crise (https://cshp.ca/opioid-crisis). Voici des rapports d'étape sur plusieurs d'entre elles.

La SCPH a sondé ses membres pour savoir quelles ressources leur sont nécessaires en matière de prévention, d'éducation, de traitement, de suivi et de surveillance et pour connaître les mécanismes de mise en application relatifs aux substances contrôlées. L'analyse des résultats est en cours. Attendez-vous à pouvoir bientôt consulter les résultats complets.

La SCPH milite pour que les pharmaciens soient désignés en vertu du *Règlement sur les nouvelles catégories de praticiens*. Dans les provinces où les pharmaciens peuvent déjà prescrire, cette désignation étendrait ce droit aux substances contrôlées.

La SCPH dirige l'élaboration de lignes directrices sur la prévention et la détection de détournement de substances contrôlées dans les hôpitaux et autres organismes de soins de santé et sur les mesures à prendre à cet effet. Nos principaux partenaires sont Santé Canada, SoinsSanté*CAN*, l'Association des infirmières et infirmiers du Canada et la Société canadienne des anesthésiologistes. D'autres groupes occupent des rôles de contributeurs ou d'experts consultants, notamment l'Institut pour la sécurité des médicaments aux patients du Canada, l'Association des paramédics du Canada, la Canadian Association of Emergency Physicians, des organismes réglementaires de professionnels de la santé et des chercheurs dans le domaine. Nous cherchons à prendre contact avec des parties prenantes importantes du milieu des soins de longue durée, de l'agrément des hôpitaux et des organismes d'application de la loi. Les lignes directrices finales, qui comprendront les meilleures données probantes disponibles, devraient être publiées en décembre.

Nous recueillons et publions des ressources éducatives et en lien avec la pratique sur l'utilisation des opioïdes dans la section Pharmacy 365 de notre site Web (https://cshp.ca/pain-management).

À titre de praticien en pharmacie, chacun d'entre nous doit faire sa part. Les taux élevés de consommation d'opioïdes au Canada laissent croire qu'un changement de paradigme ou un changement culturel est nécessaire en ce qui touche à notre façon de traiter la douleur aiguë et la douleur chronique non cancéreuse. D'ailleurs, le public est de plus en plus informé sur le sujet. Récemment, un chroniqueur du *Globe and Mail* a attiré l'attention sur une étude examinant les conséquences inattendues de la grande disponibilité de la naloxone (chronique disponible au https://www.theglobeandmail.com/opinion/article-does-naloxone- really-save-lives/, article disponible au https://ssrn.com/abstract=3135264). Par exemple, se croyant moins à risque de mourir de surdose à cause de la disponibilité de la naloxone, les toxicomanes pourraient commencer à consommer plus souvent, à forcer les doses ou à prendre des substances plus puissantes. De plus, le nombre de vols liés aux médicaments et de visites aux services des urgences a augmenté.

Au cours de la Conférence sur la pratique professionnelle de 2018 de la SCPH, j'ai plusieurs fois entendu le terme « gestion responsable des opioïdes ». Les conférenciers avançaient que les pharmaciens peuvent agir de bien des façons pour promouvoir l'utilisation rationnelle des opioïdes, notamment en offrant d'autres stratégies de traitement de la douleur lorsque cela est adéquat. Par exemple, les opioïdes ne sont pas toujours le meilleur traitement de la douleur chronique non cancéreuse.

Ainsi, tout comme les pharmaciens ont déjà pris la responsabilité de la gestion responsable des antibiotiques, j'invite l'ensemble des membres de la SCPH à prendre aussi en main la gestion responsable des opioïdes et à en faire un élément central dans leur pratique.

[Traduction par l'éditeur]

Patrick Fitch, B.S.P., A.C.P.R, est président et agent de liaison interne pour la Société canadienne des pharmaciens d'hôpitaux.

The Canadian Opioid Crisis: CSHP's Commitment

Patrick Fitch

There is no escaping the headlines. Canada is in the midst of an opioid crisis. More than 2900 apparent opioid-related deaths occurred in 2016 and nearly 3000 in the first 9 months of 2017 (https://www.canada.ca/en/health-canada/services/substance-abuse/prescription-drug-abuse/opioids/apparent-opioid-related-deaths.html). Canada has one of the highest rates of opioid use in the world (according to the International Narcotics Control Board; https://www.incb.org/incb/en/narcotic-drugs/Availability/availability.html). This public health issue requires action from multiple stakeholders.

The Canadian Society of Hospital Pharmacists (CSHP) participated in opioid conferences hosted by the Government of Canada (November 2016) and the Canadian Pharmacists Association (June 2017), and committed to a number of actions to help resolve the crisis (https://cshp.ca/opioid-crisis). Here are progress reports on several of them.

CSHP surveyed members about their needs for resources on prevention, education, treatment, monitoring, and surveillance, as well as enforcement practices concerning controlled substances. Analysis of the results is underway. Expect the full results shortly.

CSHP is advocating for the designation of pharmacists under the New Classes of Practitioners Regulations. In provinces that already allow pharmacist prescribing, this designation would extend prescribing authorization to controlled substances.

CSHP is leading the development of guidelines for preventing, identifying, and responding to diversion of controlled substances in hospitals and other healthcare organizations. Our core partners include Health Canada, HealthCare*CAN*, the Canadian Nurses Association, and the Canadian Anesthesiologists' Society. Other groups serving as contributors or expert consultants include the Institute for Safe Medication Practices Canada, the Paramedic Association of Canada, the Canadian Association of Emergency Physicians, health professional regulatory bodies, and researchers in the field. We are reaching out to important stakeholders in long-term care, hospital accreditation, and law enforcement. The final guidelines, which will incorporate the best available evidence, should be ready for publication in December.

We are gathering and posting educational and practice-related resources on opioid use in the Pharmacy 365 section of our website (https://cshp.ca/pain-management).

We as individual pharmacy practitioners must also play our part. Canada's high rate of opioid use suggests the need for a paradigm or cultural shift in how we treat acute pain and chronic noncancer pain. The public is taking note as well. Recently, a *Globe and Mail* columnist highlighted a study looking at the unintended consequences of widespread naloxone availability (see https://www.theglobeandmail.com/opinion/article-does-naloxone-really-save-lives/ and https://ssrn.com/abstract=3135264). For example, as drug users realize they are less likely to die from an overdose through the availability of naloxone, they may start to use more often, use higher doses, or switch to more powerful drugs. Drug-related theft has increased, as have emergency department visits.

During the 2018 CSHP Professional Practice Conference, I heard the term "opioid stewardship" several times. Speakers suggested that pharmacists can act in many ways to promote rational use of opioids, including provision of alternative pain control strategies when appropriate. For example, opioids are often not the best choice for chronic noncancer pain.

Just as pharmacists have taken on the mantle of antibiotic stewardship, I challenge all CSHP members to adopt opioid stewardship as a core element of their practice.

Patrick Fitch, BSP, ACPR, is President and Internal Liaison for the Canadian Society of Hospital Pharmacists.

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