Standardized Orders for Salbutamol and Ipratropium: Do They Lead to Waste and Irrational Prescribing?

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INTRODUCTION

In the context of climate change, the use of pressurized metered dose inhalers (pMDIs) to deliver medications is particularly concerning, because the hydrofluoroalkane (HFA) propellants are potent greenhouse gases.[1] The HFA most commonly used today has 1300 times the potency of carbon dioxide (CO_2).[1] Globally, it is estimated that 18 million pMDIs are prescribed yearly, contributing to the equivalent of 13 billion tons of CO_2 released into the atmosphere.[1] To place this impact in perspective, a 100-dose pMDI has a carbon footprint equivalent to a 280-km car trip.[2] Among all inhaler devices, pMDIs have the greatest global warming potential—the ability for greenhouse gases to retain heat in the atmosphere—relative to nebulizers, soft-mist inhalers, and dry-powder inhalers (DPIs).[2] Within the Fraser Health Authority (FHA) of British Columbia, large quantities of pMDIs for short-acting bronchodilators (specifically salbutamol and ipratropium) are prescribed through standardized order sets (SOSs).

SOSs should encourage best practice that also reduces negative impacts on the environment.[1,3] However, if poorly thought out, they may lead to the standardization of suboptimal medication use and inadvertently lead to medication waste. We were curious as to whether any SOSs for pMDIs might be contributing to irrational prescribing and the generation of unnecessary medical waste.

DESCRIPTION OF CURRENT USE OF STANDARDIZED ORDER SETS

In FHA, which has 12 hospitals with a total of approximately 3600 beds,[4] 28 000 ipratropium and 46 000 salbutamol pMDIs were dispensed in 2022/23 (FHA Medication Use Evaluation [MUE] Group, personal communication, October 26, 2023).A recent FHA audit showed that approximately 80% of inhaler doses are wasted.[5,6] which prompted the MUE Group to investigate factors contributing to excessive waste, starting with an audit of SOSs with salbutamol and ipratropium orders. None of the organization's SOSs contained soft-mist formulations, because there are none on the formulary.

EVALUATION OF THE STANDARDIZED ORDER SETS

In October 2023, we identified 36 SOSs that contained orders for pMDI salbutamol and/or ipratropium, of which we assessed 22. Eleven SOSs were excluded because they involved clinical situations requiring special dosing, where the inhalers were not used for relief of respiratory symptoms (i.e., pediatrics, patients receiving mechanical ventilation, and hyperkalemia protocols). An additional 3 SOSs were excluded because a copy of the SOS could not be obtained. The 22 included order sets covered indications such as asthma, chronic obstructive pulmonary disease (COPD), pre- and post-operative care, general hospital admission, ward transfers, and IV infusion protocols. One pharmacist (L.L.) sorted the SOSs according to order type (mandatory, optional), frequency (scheduled, as needed [PRN], one-time), and dosage form offered (pMDI, nebules, DPI). A second pharmacist (A.M.T.) confirmed the results. The key findings of our inventory are summarized in Table 1.

To assess the appropriateness of orders, 2 pharmacists (L.L., A.M.T.) searched the available literature for information about optimal inhaler prescribing, using key terms in the Google search engine. No meaningful guidance was found. A pragmatic review of the following reference types was then performed: official product monographs, direct contact with the manufacturer, relevant guidelines, guideline citations, and tertiary resources (Lexicomp and UpToDate databases). The pharmacists used the available information to develop criteria for how to structure salbutamol and ipratropium orders so they would be practical and evidence-based and would minimize medication waste. The following aspects were considered: optimal doses, appropriate frequencies, dose–response effect, onset of action, and when to escalate therapy. These criteria were applied to the 22 SOSs included in our audit, and recommendations for improvement were developed (Table 2).

IDENTIFYING AREAS FOR IMPROVEMENT OF STANDARDIZED ORDER SETS

Our analysis of SOSs revealed a concerning array of suboptimal ordering. The prevalence of multiple inhaler formats, unclear regimens, excessive dosing, and inconsistencies in how medications are ordered suggests that our current SOSs are contributing to medication waste, financial loss, and potential risks to patients. The details are summarized below.

Implementing Evidence-Informed Therapy

SOSs for patients who did not have exacerbations were within the standard dosing guidelines set out in product monographs, although some used the higher end of the suggested range. For example, we found orders for salbutamol by pMDI written as "200 µg inhaled every 4 hours PRN". However, this medication may be given as "100–200 µg every 4–6 hours PRN" for acute episodes of bronchospasm.[7,8] Similarly, variable ranges were seen for SOSs for patients with exacerbations, such as "6–8 puffs of salbutamol pMDI given 20 minutes apart in the first hour" in cases of acute asthma.

We wanted to see if there was evidence that lower doses were as effective as higher doses or if there was a known dose ceiling. We consulted the product monographs for

TABLE 1. Selection of SOS Findings

Finding[a]	Example from SOS[b]
Mandatory 200-dose pMDI dispensed for a one-time dose	• Salbutamol 100 µg/puff MDI, inhale 2 puffs with aerochamber × 1 dose PRN for dyspnea or bronchospasm
Two inhaler formats offered at the same time[c]	• Salbutamol 2.5–5 mg by nebulizer q4h PRN OR • Salbutamol 200 µg (2 puffs) by inhaler q4h PRN
Inconsistencies in dosing regimens across indications	Orders within the same SOS for postoperative bronchospasm
No stop date for a temporary indication No guidance on monitoring for response to an initial low dose (before giving another dose)	Choose one or both of the following: ❑ Salbutamol 5 mg by nebulizer q2h PRN for bronchospasm ❑ Ipratropium 0.5 mg by nebulizer q2h PRN for bronchospasm *and* • Salbutamol 2.5–5 mg by nebulizer or 200 µg by MDI q4h PRN
No indication listed for PRN puffers, opportunity to provide 2 dosage forms for the same medication (salbutamol), high starting dose for salbutamol in non-exacerbation setting, doses exceeding maximum allowable dose	General admission SOS for any Fraser Health Authority Hospital Choose from the following: ❑ Salbutamol 4 puffs by MDI q4h PRN ❑ Salbutamol 2.5–5 mg by nebulizer q4h PRN ❑ Ipratropium 250–500 µg by nebulizer q4h PRN
Variation in dosing regimen (dose, frequency, duration) and multiple inhaler formats offered to patients at the same time	*For COPD exacerbation in setting of long-term care* Hold all current regularly scheduled orders for 3 days, as well as current PRN treatment for 7 days, and restart upon completion of treatment below: ❑ Salbutamol 100 µg by inhaler with spacer, 2 puffs QID × 3 days and salbutamol 100 µg by inhaler, 2 puffs q2h PRN for 7 days ❑ Salbutamol 2.5 µg by nebulizer QID × 3 days and salbutamol 2.5 µg by nebulizer q2h PRN for 7 days ❑ Ipratropium 20 µg by inhaler with spacer, 2 puffs QID × 3 days and ipratropium 20 µg by inhaler, 2 puffs q2h PRN for 7 days ❑ Ipratropium 0.5 mg by nebulizer QID × 3 days and ipratropium 0.5 mg by nebulizer q2h PRN for 7 days *For COPD exacerbation in general adult population* Bronchodilators: • Salbutamol ▪ 100-µg inhaler: inhale 4 puffs q4h while awake and 2 puffs q1h PRN with spacer for 48 h, then 2 puffs q4h PRN with spacer (if not nebulized) ▪ 5-mg nebulizer q4h while awake and q1h PRN for 48 h, then 2.5 mg by nebulizer q4h PRN (if not given by inhaler) • Ipratropium ▪ 20-µg inhaler: inhale 4 puffs QID with spacer while awake for 48 h (if not nebulized) ▪ 0.5-mg nebulizer QID while awake for 48 h (if not given by inhaler)

COPD = chronic obstructive pulmonary disease, MDI = metered dose inhaler, pMDI = pressurized metered dose inhaler, SOS = standardized order set.
[a]Each row in the table represents the finding(s) from and contents of a single SOS.
[b]A solid circular bullet indicates a mandatory order.
[c]Both orders shown as mandatory and active on the medication administration record.

TABLE 2. Summary of Recommendations

Category	Recommendation or Consideration
Evidence-informed recommendation	• Use the lower end of the suggested dosing range, and reassess response after the expected onset of action before administering further doses
Environmental considerations	• Offer DPI or nebules over pMDIs; reserve pMDIs for patients who cannot use the preferred inhalers (e.g., because of poor inspiratory capacity) • When terbutaline is listed on the SOS or order string, include "low carbon footprint" as a reminder • Furthermore, for patients who have scheduled and standing PRN orders for the same medication, offer only one type of inhaler device, to minimize wastage of doses where possible • Use nebules for patients anticipated to have a short hospital stay, those with a temporary indication (with stop date), and those with one-time dose orders
Practical considerations	• Include indications and maximum number of allowable doses on all PRN orders • Provide details on the frequency and parameters of medication efficacy assessment

DPI = dry-powder inhaler, pMDI = pressurized metered dose inhaler, SOS = standardized order set.

details regarding evidence for a dose response, but found no information. We also contacted the various manufacturers, but received no answers. However, a drug approval document from the US Food and Drug Administration described a single study analyzing salbutamol HFA dose response in patients with stable asthma.[9] There was a significant change in peak forced expiratory volume in the first second (FEV_1) between the 100- and 200-µg doses, but not between the 200- and 400-µg doses.[9] However, the COPD guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) indicate that dose–response curves are mostly flat, and increasing the dose of β_2-agonist or anticholinergics may provide subjective benefit in acute distress but not in stable disease.[10] The authors of the GOLD report cited small dose–response studies, but some were irrelevant to our analysis, as they did not involve salbutamol or ipratropium.[10] Only one study demonstrated a flat dose–response curve for increasing doses of nebulized ipratropium in patients with stable COPD.[11]

According to pharmacokinetic principles, patients should be reassessed after the expected onset of action of the medication before a decision is made about administering further doses. Implementing rational regimens, with titration to the lowest effective dose based on response, can reduce waste and decrease the risk of medication harm.

Applying an Environmental Lens to Prescribing

The SOSs in our audit featured only salbutamol and ipratropium pMDIs and nebules; no orders included an option for the lower-carbon-footprint terbutaline DPI, although that medication is on the institutional formulary. Four of the SOSs had mandatory PRN orders for pMDI and nebules, and 5 had optional PRN orders, although pMDI and nebules were always coprescribed.

The Global Initiative for Asthma (GINA) and GOLD guidelines state that no inhaler format is preferred over another in maintenance therapy for asthma or COPD, respectively.[10,12] In the acute care setting, a CADTH review suggested that nebulizers are as effective as pMDIs with spacers for patients with asthma or COPD.[13] With no differences in efficacy among inhaler formats, environmental considerations should be incorporated into the ordering process. This approach is listed as a priority for both the UK National Institute for Health and Care Excellence (NICE) and the British Thoracic Society.[14] Use of pMDIs should be minimized, as they contain HFA.[15] One pMDI dose has a carbon footprint 18 times greater than an equivalent DPI dose.[16] The more environmentally preferable DPIs should be selected wherever possible, and this approach can be encouraged through SOSs.[1]

The patient's expected inhaler use should also be considered. In 2021/22, the average length of stay in an acute care hospital in Canada was 7.2 days.[17] As a result, only a small fraction of doses in multidose inhalers will be used by the time of discharge.[2] Therefore, we believe nebules should be given for short hospital stays and for patients who have a temporary need (e.g., for anaphylaxis or postoperative bronchospasm), with specification of a stop date to allow for reassessment. Furthermore, when patients have scheduled and standing PRN orders for the same medication, only one type of inhaler device should be offered to minimize wasted doses where possible. Using nebules has certain negative environmental impacts, such as waste from the plastic tubing, mouthpiece, and personal protective equipment; however, there is some evidence to suggest the net negative environmental impact of nebules is lower than that of MDIs.[18] Goulet and others[18] conducted a "cradle-to-grave" analysis comparing the environmental impact of albuterol by pMDI and albuterol nebules; the nebules had one-fifth to one-third the global warming potential of the pMDI (measured in terms of kilogram CO_2 equivalents).

Practical Considerations

To prevent inadvertent administration of unnecessary doses, orders should include the indication and maximum number of PRN doses allowed. Orders should also include

details about when to monitor for a response and the potential need for additional doses.[3] Only one inhaler format should be offered to the patient at a time, and a thorough assessment of the patient's adherence and technique should be performed before deeming the patient's disease control or the product itself as being suboptimal.[10,13]

FHA is now starting to implement computerized prescriber order entry (CPOE), and efforts should be made to capitalize on this opportunity to leverage the platform's capabilities for structuring rational orders. For example, the CPOE system may allow implementation of an interactive prescribing tool that guides prescribers to select a DPI rather than a pMDI (e.g., terbutaline DPI vs salbutamol pMDI) or to choose nebulized rescue medications when only PRN orders are needed; the system might also list the relative carbon footprint of all inhalers so that prescribers can consider this factor at the point of prescribing to minimize environmental impact. The "playbook" developed by Stoynova and Culley[1] lists the changes that could be made and suggests a process for doing so.

CONCLUSION

This examination of existing SOSs determined that they potentially do lead to waste and suboptimal medication use. We encourage readers to assess their own SOSs or order sentences within their CPOE system. It is evident that rational inhaler prescribing practices, including principles of waste reduction, practicality, and evidence-informed management, should be simultaneously considered.

References

1. Stoynova V, Culley C. *Climate conscious inhaler practices in inpatient care*. CASCADES Canada [Creating a Sustainable Canadian Health System in a Climate Crisis]; [cited 2023 Nov 8]. Available from: https://cascadescanada.ca/resources/climate-conscious-inhaler-practices-in-inpatient-care-playbook/
2. *Environmentally sustainable opportunities for health systems primer series: inhalers.* CASCADES Canada [Creating a Sustainable Canadian Health System in a Climate Crisis]; [cited 2023 Nov 8]. Available from: https://view.publitas.com/5231e51e-4654-42c2-accd-b722e21f3093/environmentally-sustainable-opportunities-for-health-systems-primer-series-inhalers/page/1
3. *Guidelines for standard order sets.* Institute for Safe Medication Practices; 2022 [cited 2023 Nov 8]. Available from: https://www.ismp.org/guidelines/standard-order-sets
4. *Fraser Health: About us* [web page]. Fraser Health; 2023 [cited 2023 Nov 9]. Available from: https://www.fraserhealth.ca/about-us
5. Aeng ESY, McDougal KC, Allegretto-Smith EM, Tejani AM. Hidden costs of multiple-dose products: quantifying ipratropium inhaler wastage in the hospital setting. *Can J Hosp Pharm.* 2021;74(2):117-21.
6. Aeng ESY, Dhaliwal, MM, Tejani AM. A cautionary tale of multiple dose products: fluticasone and salmeterol combination inhaler waste. *J Eval Clin Pract.* 2020;26(6):1699-702.
7. APO-salbutamol HFA [product monograph]. Apotex Inc; 2019 Aug 8.
8. Salbutamol HFA [product monograph]. Sanis Health Inc; 2014 Nov 7.
9. *Ventolin-HFA (albuterol sulfate) drug approval package: medical review part 4.* Food and Drug Administration (US); 2001 [cited 2023 Nov 8]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/20-983_Ventolin-HFA_medr_P4.pdf
10. *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease.* Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2023 [cited 2023 Nov 8]. Available from: https://goldcopd.org/2023-gold-report-2/
11. Gross N, Petty T, Friedman M, Skorodin M, Silvers G, Donohue J. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease: a three-centre study. *Am Rev Respir Dis.* 1989;139(5):1188-91.
12. *Global strategy for asthma management and prevention.* Global Initiative for Asthma (GINA); updated 2023 [cited 2023 Nov 8]. Available from: https://ginasthma.org/2023-gina-main-report/
13. Wells C, Loshak H. Standardized hospital order sets in acute care: a review of clinical evidence, cost-effectiveness, and guidelines [CADTH rapid response report: summary with critical appraisal]. CADTH; 2019 Jul.
14. *Asthma inhalers and climate change.* National Institute for Health and Care Excellence (UK); updated 2022 Sep [cited 2023 Nov 8]. Available from: https://www.nice.org.uk/guidance/ng80/resources/inhalers-for-asthma-patient-decision-aid-pdf-6727144573
15. Myrdal PB, Sheth P, Stein SW. Advances in metered dose inhaler technology: formulation development. *AAPS PharmSciTech.* 2014;15(2):434-55.
16. *NHS Dorset green inhaler prescribing guidance – support pack.* NHS Dorset; 2022 [cited 2023 Nov 8]. Available from: https://nhsdorset.nhs.uk/Downloads/aboutus/medicines-management/Other%20Guidelines/Dorset%20Green%20Inhaler%20Guidance%20DMAG%20version%20v2%20%282%29.pdf
17. *Hospital stays in Canada, 2021–2022.* Canadian Institute for Health Information; 2023 [cited 2023 Nov 8]. Available from: https://www.cihi.ca/en/hospital-stays-in-canada#:~:text=The%20age%2Dadjusted%20average%20length,heart%20failure%20(9.2%20days
18. Goulet B, Olson L, Mayer BK. A comparative life cycle assessment between a metered dose inhaler and electric nebulizer. *Sustainability.* 2017;9(10):1725.

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