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REVIEW

Recalibrating Perceptions and Attitudes Toward Nebulizers versus Inhalers for Maintenance Therapy in COPD: Past as Prologue

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Abstract: Aerosol therapy administered via handheld inhaler or nebulizer device has long been standard for the treatment of chronic obstructive pulmonary disease (COPD), both for maintenance therapy and for management of acute exacerbations. Of the 2 options for drug delivery, inhaler devices are the most widely used for ambulatory patients with COPD as they are small, portable, and convenient and offer an array of medication options. They are, however, prone to suboptimal inhalation technique and use errors, which decrease the amount of medication delivered, compromise efficacy, and adversely affect clinical outcomes. Nebulizers are less often employed for aerosol delivery than inhalers, particularly in the home environment. Considered bulky and expensive, nebulizers have historically had limited medication options compared with inhalers. Nonetheless, nebulizers may be preferred over inhalers in specific patient populations, such as in patients with poor lung function, lack of hand–breath coordination, or cognitive impairment. Furthermore, technological advances and development of new nebulizer-compatible medications are shifting the benefit equation for nebulizers versus inhalers in a way that merits reconsideration of the role of nebulizers in the maintenance treatment of COPD. Using the available literature, this state-of-the-art review critically evaluates the benefits and limitations of aerosol therapy delivery via inhaler or nebulizer for patients with COPD; describes the factors that may influence the benefit equation, including current advances in nebulizer technology and future developments; and provides insights on implementation of nebulizer therapy in clinical practice.

Keywords: Aerosol therapy, bronchodilator, COPD, exacerbation, inhaler, maintenance

Introduction

Worldwide, there are an estimated 480 million people living with chronic obstructive pulmonary disease (COPD), and this number is anticipated to grow to approximately 600 million by 2050.[1] Although historically considered a disease predominantly caused by tobacco exposure, other factors (eg, air pollution, occupational exposures, poorly controlled asthma, infectious disease, cooking fuel smoke, low socioeconomic status, impaired childhood lung growth due to early-life exposures) are now considered to play a significant role in COPD development.[2] COPD has a tremendous impact on patients' lives, reducing quality of life, causing disability, decreasing social interaction, heightening anxiety and depressive symptoms, increasing risk of acute exacerbations and frequent hospitalizations, and contributing to morbidity and premature mortality.[3,4]

Aerosol therapy—delivered via nebulizer, dry powder inhaler (DPI), pressurized metered-dose inhaler (pMDI), or soft mist inhaler (SMI)—is a mainstay of COPD treatment as well other respiratory conditions such as asthma and cystic fibrosis.[5] Aerosol therapies deliver medication directly to the lungs, providing rapid onset of effect and high local drug concentration, thereby increasing efficacy while reducing the risk for side effects associated with increased systemic exposure after oral or intravenous administration.[6,7] Handheld inhaler devices have long been used more frequently than nebulizers for aerosol therapy delivery.[8–11] Despite the importance and ubiquity of inhaler-based therapies, suboptimal treatment is common because of poor adherence and errors in device use, particularly in patients with COPD who have

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challenges related to advanced age, cognitive impairment, muscle weakness, and/or comorbidities.[12–14] Improper inhaler technique/device use errors are associated with increased exacerbation risk,[15–18] worse health status,[16,17] overuse of inhaled corticosteroids,[19] frequent episodes of emergency care utilization and hospitalizations,[20] and higher costs.[21] By contrast, optimizing inhaler technique reduces the rates of exacerbations and hospital admissions;[22] improves measures of disease control, health status, and quality of life;[23,24] and decreases healthcare resource utilization (hospital admissions, hospital length of stay) and costs.[22] However, providing patients with instruction on proper inhaler technique does not lead to effective use for many patients, including those with physical or cognitive limitations that preclude execution of optimal inhaler technique.[25] Moreover, concern has been raised about inhalers due to propellant restrictions, disposal needs, and a high carbon footprint, particularly for pMDIs.[26–28]

These challenges, along with advances in device technology and a larger array of medication options available, warrant a reconsideration of nebulizers for aerosol therapy delivery in COPD. As a reflection of the changing landscape, Global Initiative for Chronic Obstructive Lung Disease (GOLD) report iterations have expanded their acceptance of nebulizer therapy over the past 2 decades.[29] From 2001 through 2009, GOLD reports did not recommend nebulizer use for maintenance therapy in COPD due their cost and maintenance requirements. In 2010, the GOLD report cautiously included nebulizer therapy within the treatment modalities for COPD, with caveats limiting its use. These caveats were removed in 2017.[30] The 2024 GOLD report lists nebulizer formulation options within the main classes of COPD maintenance medications, with certain medications formulated exclusively for nebulizer use.[5] Nonetheless, nebulizer use has been in decline while inhaler-based therapy use has increased.[10,11] A retrospective analysis of Medicare beneficiaries with COPD from 2008 to 2015 reported decreased nebulizer use, potentially because of increased use of non-nebulized therapies.[10]

Prescriber and patient perceptions of nebulizer therapy may be influenced by previous guidance and experiences with older devices. To provide a balanced view of nebulizer therapy in the current era and beyond, this review seeks to critically synthesize available literature regarding the benefits and limitations of aerosol therapy delivery via inhaler or nebulizer for patients with COPD, identify patient characteristics and clinical scenarios that influence the decision-making process between inhalers versus nebulizers, describe advances in nebulizer technology and future developments on the horizon, and provide insights for successful implementation of nebulizer-based therapy.

Methods

This critical narrative review was informed by a systematic and structured literature search. A comprehensive search of the MEDLINE database was conducted in May 2024 with terms including those related to the disease state (COPD, emphysema, chronic bronchitis) in combination with treatment modalities (inhaled therapy, aerosol therapy, inhaler, nebulizer) and topics of interest (ease, complexity, technique, impairment, difficulty, acceptance, satisfaction, preference, history, future, emerging, new developments, guidelines, consensus, cost, access, Medicare, Medicaid, coverage, payor, insurance, COVID-19, transmission, education, cleaning, support, caregiver). Results were limited to English-language articles published within the past 10 years. Two hundred thirty-seven abstracts were identified, and 75 articles were found to be responsive to the stated purpose and objectives of the review. Additional relevant publications were identified from reference lists of included articles.

Aerosol Therapy Delivery via Inhaler vs Nebulizer

Inhalers and nebulizers each carry a unique set of advantages and disadvantages. From a class perspective, certain attributes are more favorable for one device or the other (Figure 1). It should be noted, however, that within the broader categories, the different types of inhalers (DPI, pMDI, SMI) and nebulizers (jet, ultrasonic, vibrating mesh) have their own profiles. This section describes the categories in general, with notable specific characteristics highlighted for particular types of devices.

Inhalers

Inhalers have in their favor that they are small (handheld) and self-contained, which makes them convenient and portable.[31,32] They are also widely available, encompass most classes of medications used in the maintenance treatment

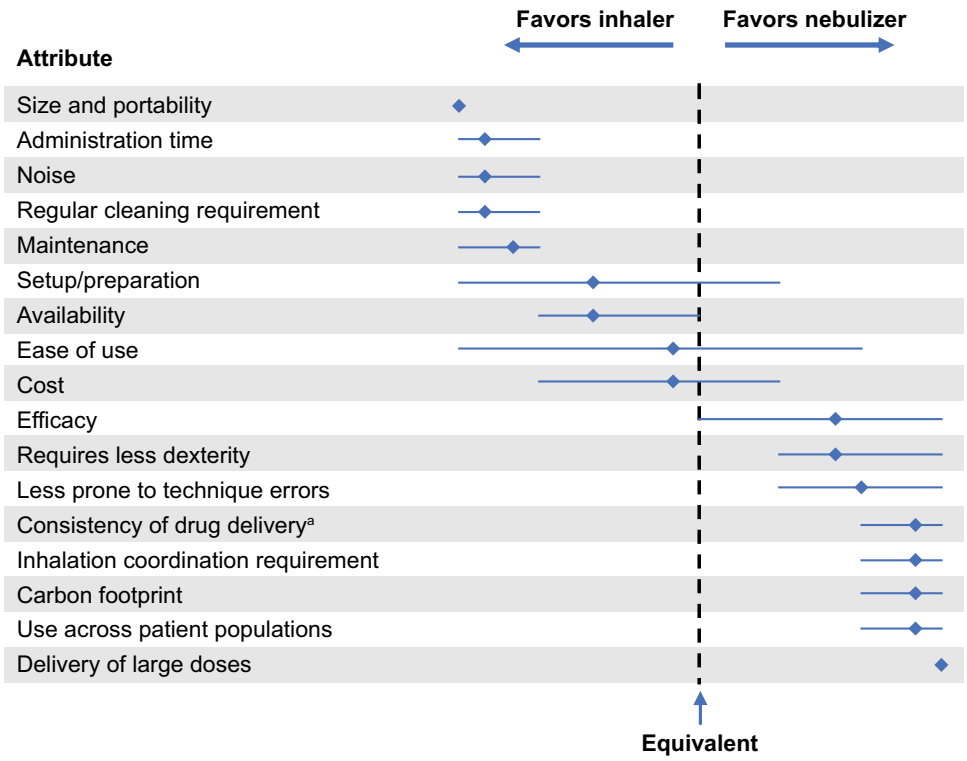

Figure 1 Comparing the attributes of nebulizers and inhalers. Relative ratings represent the opinions of the authors based on literature search results and their knowledge and experience with inhaler and nebulizer devices. Each author independently rated the individual attributes on a 7-point scale that ranged from strongly favors inhalers to strongly favors nebulizers. The resulting score averages and ranges are illustrated on the forest plot. [a]Indicates that drug delivery is less affected by inhalation technique.

of COPD including combination therapies, may come preloaded with medication, include a dose indicator, have a short treatment time, are low maintenance, and can have a cost advantage over nebulizers.[31,32]

The key challenge associated with inhalers is suboptimal inhaler technique, which is common among patients with COPD.[17,19,22,24,33–55] In the observational, real-world MISMATCH study, which evaluated DPI only or DPI and pMDI use by patients with COPD from 6 countries between October 2022 and May 2021, >90% of the 582 study participants made ≥1 "critical error", defined as an error that can reduce treatment effectiveness and/or decrease medication delivery to the lung.[54,56] Combined data from a multicenter, patient-preference study and an open-label, randomized clinical trial revealed that 91% of the 660 patients did not use correct inhalation technique at baseline despite 85% of patients having received prior inhaler technique instruction.[49] Even after repeated use in either the clinical trial or real-world setting, as many as 4 in 10 patients continue to incorrectly use inhaler devices.[33,36,49,52,57] Part of the challenge may be that inhaler instruction provided is incomplete or inaccurate because of lack of healthcare professional knowledge regarding proper inhaler use.[58] Moreover, "decay" has been observed in inhaler technique, wherein patients who had mastered inhaler technique do not sustain this level of correct use over time.[24,56]

Several factors have been linked to increased risk for inhaler errors, such as use of >1 inhaler device model concurrently.[37,39,47,48] Compared with patients using a single device, the odds of making ≥1 critical error among patients with COPD enrolled in a prospective, cross-sectional, multicenter, observational study were 3 times greater in patients who used 2 devices and almost 9 times higher in patients who used 3 devices.[48] Moreover, the use of single inhaler devices has been shown to improve adherence and persistence and may positively affect healthcare outcomes (eg, decrease exacerbation rates, lower the risk of emergency department visits or hospitalizations, shorten hospital length of stay, and reduce healthcare costs) versus use of multiple separate inhalers.[59–62] This is an important consideration because use of >1 inhaler device is common in COPD, with studies reporting that 45% to 90% of patients are treated with 2 or more inhalers.[38,39,44,55]

The inhaler device itself may contribute to the propensity for errors and the type of errors observed.[24,34,38,39,41,44–49,55] As noted by the GOLD report, inhaler devices with "increased steps reduces the ease of use and likelihood that patients

use the inhaler correctly."[5] It has also been observed that devices with fewer steps to set up the actuation are associated with fewer attempts needed to initially achieve correct technique.[63] Certain devices, such as pMDI and to a lesser extent SMIs, require dexterity and coordination of inhalation with device actuation.[7,25,64] Despite the lesser need for hand–breath coordination with SMI, they are still prone to errors; a 2020 systemic review found that approximately 60% of patients with COPD using SMI made ≥1 error in device use.[64] Hand–breath coordination is not required for DPIs because the patient's inhalation triggers actuation. However, DPIs are not recommended for patients with low inspiratory flow due to the strength of inhalation needed to overcome the device's internal resistance and generate the turbulence necessary for optimal aerosol generation.[65]

Nebulizers

Nebulizers are comparatively easy to use and user friendly.[7,66,67] Nebulizers do not require the inspiratory flow, dexterity, coordination, priming, or breath holding of inhalers.[7,64,66,67] Patients need only to maintain tidal-volume breathing while the nebulizer provides a continuous flow of aerosolized medication.[66] Consequently, nebulizers are less prone to poor inhalation technique, and the consequences thereof, compared with inhalers.[25] In a cohort of 300 consecutive patients with bronchial asthma or COPD, a significantly smaller proportion of nebulizer users (70%) made technique errors compared with users of pMDIs (94%), DPIs (82%), or pMDIs with a spacer (78%; $p = 0.005$).[68] The most common errors observed among nebulizer users in this study were no deep breathing throughout the treatment, poor fitting of mask, and incorrect dose of medication used. Another advantage of nebulizers is that they are suitable for delivery of large volume/high medication doses.[31,66]

A key disadvantage of nebulizers, particularly the older devices, is their size and, for many devices, the requirement for an external power source, which limits their portability.[7,25,31,66] Nebulizer therapy takes longer to use than an inhaler, including the time for setup, medication administration (average administration time, 10–15 min for conventional jet nebulizers), and cleanup.[25,66] The need for regular cleaning and disinfecting is a drawback for nebulizers. A 2021 systematic review of observational studies that assessed knowledge, attitudes, and practices regarding nebulizer therapy in the home environment reported that cleaning and disinfecting was often inadequate, resulting in pathogen contamination retained on nebulizer components.[69] The review also noted that patients failed to service nebulizer components that require routine replacement and that instruction or training on nebulizer use and maintenance is lacking. Nebulizer cleanup and maintenance are recognized by patients with COPD as areas of educational need.[70] In a 2023 qualitative study of the transition from hospital to home in 21 patients with COPD receiving nebulizer therapy, no difficulties were noted in nebulizer setup and utilization; however, a need for additional education regarding nebulizer cleanup and maintenance was identified.[70] In general, patients did not view portability of their nebulizer as an issue. The perspective about portability may reflect the time frame of the study (2020–2022) and the more frequent use of newer, more portable nebulizers.

With older conventional jet nebulizers, there was variability in drug output and, hence, lung deposition—a problem that is less common with newer, high-efficiency nebulizers.[66] The noise associated with operation of conventional jet nebulizers can be an issue for some patients, whereas newer ultrasonic nebulizers and mesh nebulizers run more quietly.[67]

Cost Considerations

Although nebulizer therapy is viewed as more expensive,[25] the cost of inhalers can exceed that of nebulizer therapy in the US.[71] A key driver of cost in the inhaler market is the development of branded devices that extend patent exclusivity, a strategy that has been used to great effect to maintain revenue after the active ingredient is off patent.[71,72] In contrast, many of the nebulizer solutions are generic.[71] Feldman et al[71] note that 2020 Medicare Part D spending for a month's supply of the branded Combivent® Respimat® (albuterol-ipratropium) inhaler averaged $207, whereas spending for generic albuterol and ipratropium as a nebulizer solution was $21. The cost of the nebulizer itself must be factored into the equation, although the device can last for years. These findings are significant because a large proportion of Medicare recipients have COPD (16.5% as of 2018).[73] Moreover, cost-related nonadherence, wherein patients intentionally miss doses, take lower than the prescribed dose, or delay filling prescriptions to lower the cost of treatment, affects an estimated 1 in 6 US adults with COPD.[74]

After implementing a protocol to reduce medication waste associated with unused drug by switching from inhaler-based therapies to nebulizer therapies during hospital stays in patients with COPD, a US-based hospital system reported a $1.56 million (38.5%) reduction in system-wide drug expenditures in year 1 and a $1.65 million (40.6%) reduction in year 2.[75] In the year prior to implementation of the nebulizer switch protocol, inhalers accounted for approximately 18% of respiratory drug delivery, yet were responsible for nearly 80% of total drug costs. A limitation of the cost analysis is that the study did not measure the effect of the switching protocol on respiratory therapy labor, which is an important consideration, as the time needed for delivery and documentation is longer for nebulizers than inhalers. Importantly, no negative effects on COPD-related hospital length of stay or 30-day readmissions were observed with the switch to nebulizer therapy.[75]

From a patient perspective, although some patients report barriers to access related to insurance coverage and acceptance by suppliers, many patients with COPD who participated in a qualitative survey described their COPD medications and nebulizer device as affordable.[70] Notably, the majority of patients surveyed (95%) had primary insurance coverage through Medicare, Medicaid, or both, which may have influenced their experience with nebulizer cost. Medicare or dual-enrollment beneficiaries are likely to pay lower coinsurance amounts compared with the general population and may also have low cost-sharing, depending on the type of plan (Original Medicare [OM], OM with a supplemental plan, OM with a Part D plan, or Medicare Advantage).

Patient Experiences and Preferences

Patient satisfaction with or acceptability of inhalers is generally moderate to high, although it does vary among individual devices.[33,34,36,57,76–81] Patient satisfaction with their inhaler has been linked to better medication adherence,[80,82,83] greater compliance with prescribing instructions and advice,[84] higher health-related quality-of-life scores,[84] fewer exacerbations,[84] and lower error rates. Indeed, an increased risk of errors has been observed among patients with COPD and lower device satisfaction.[46]

Although the data are limited, patients with COPD report high levels of satisfaction, confidence, and ease of use with nebulizer delivery of aerosol therapy.[85–87] In a survey of patients hospitalized with asthma or COPD during the COVID-19 era that compared nebulizer therapy versus a pMDI with a spacer, the majority of patients reported that nebulizer therapy was subjectively more effective, easier to use, and more comfortable.[88] The side effect profile was considered by the patients to be similar between the 2 devices, although there was a greater perceived infection risk with nebulizer therapy. Perceived infection risk influenced preference for future treatment, with those patients who believed there to be a greater infection risk with nebulizer therapy less likely to prefer it compared with a pMDI with a spacer.

Experiences with aerosol therapy may differ between patients with COPD compared with those who have asthma because of inherent differences in the patient populations. Patients with COPD are generally older, are more likely to use 2 or more different inhaler devices, receive less training on inhaler technique, take a longer time to learn correct inhaler technique, are more likely to make critical errors, and are less satisfied with inhaler devices than patients with asthma.[42,47,63,78,83] With these differences in experience come differences in device preferences between the 2 patient groups.[63,78]

Factors That Influence the Benefit Equation for Inhalers Vs Nebulizers

Citations in the literature suggest that, when proper inhalation technique is used, aerosol therapy has equivalent efficacy whether delivered via inhaler or nebulizer—a conclusion based on the results of systematic reviews.[89–91] The actual benefit derived from aerosol therapy, however, hinges on its appropriate use, which is influenced by a number of factors. It is, therefore, recommended that device choice should weigh elements related to:[5,90] the device, including drug and device availability, convenience (size, portability), administration time, cost (for the patient and the healthcare system); the patient, including age, capacity to use the device correctly, number and type of concurrent aerosol therapies, preference, clinician recommendation; and the clinical setting, including the inpatient, outpatient, and home environment.

Among these elements are factors that shift the balance of device attributes in favor of nebulizers (Table 1).[5,66,92] Poor health status, in general, has been linked to more inhaler errors in patients with COPD.[39] Mental health conditions and negative changes in mood can also influence adherence to aerosol therapy.[70] However, the most prevalent patient-related factors that compromise the ability to use inhaler devices correctly and warrant consideration of nebulizer therapy

Table 1 Patient Characteristics or Clinical Scenarios That Favor COPD Maintenance Aerosol Therapy Delivered via Nebulizer[a]

Patient-Related Factors	Treatment-Related Factors
• Cognitive impairment (eg, Alzheimer's disease, intellectual disabilities, altered consciousness)	• Inadequate symptom relief despite appropriate inhaler use
• Impaired manual dexterity (eg, arthritis, Parkinsonism, or stroke)	• Frequent exacerbations despite inhaler use[92]
• Severe pain or muscle weakness caused by neuromuscular disease	• Use of respiratory medications that are not available in inhaler formulations
• Long-term care resident with cognitive decline, physical limitations, or poor adherence[92]	• Need for higher bronchodilator or corticosteroid doses for symptom control
• Inability to use an inhaler in an optimal manner despite instruction ○ Inability to coordinate breathing needed for a pMDI or SMI[5] ○ Inadequate inspiratory flow needed for a DPI	• Need for multiple aerosol therapies to be coadministered
• Lack of compliance with inhaler therapy	• Lack of affordable pMDI or DPI options[b]
• Patient preference for nebulizer use	

Note: [a]Based on consensus of the authors' expert opinions and clinical experience. [b]For Medicare-eligible patients. Adapted from Dhand et al,[66] with additional citations as noted.

Abbreviations: COPD, chronic obstructive pulmonary disease; DPI, dry powders inhalers; pMDI, pressurized metered-dose inhalers; SMI, soft mist inhaler.

for patients with COPD are advanced age, cognitive impairment, and physical limitations such as muscle weakness, impaired hand dexterity, and insufficient inspiratory flow.

Advanced Age

As noted earlier, patients with COPD are on average older than patients with other obstructive respiratory diseases that frequently use aerosol therapy such as patients with asthma or cystic fibrosis.[63,93] Advanced age brings with it the increased propensity for comorbidities, including those that impair cognition, impose physical limitations, and reduce dexterity.[5] Data have shown that older patients with COPD are more prone to inhaler use errors than younger patients.[41,43,45,47,51] In clinical practice, clinicians weigh ease of use and device suitability more heavily in treatment selection for older versus younger patients.[79]

Cognitive Impairment

A 2017 systematic review that included 14 observational studies with data from 23,116 patients reported pooled prevalences of 25% (95% CI: 23%–42%) for mild cognitive impairment and 32% (95% CI: 18%–38%) for any cognitive impairment in patients with COPD.[94] The likelihood of cognitive deficits is enhanced among those with poor lung function, who require supplemental oxygen, or who are experiencing or recovering from an acute exacerbation of COPD.[95] In a small cohort of patients with a recent hospitalization or emergency department visit for a COPD exacerbation, 62% met the criteria for mild cognitive impairment or dementia.[95] Notably, patients with mild cognitive impairment or dementia were significantly more likely to demonstrate incorrect pMDI inhaler technique than patients with normal cognitive function even after adjustment for potential confounders (odds ratio, 18.94 [95% CI: 2.65–401.99]). These data align with overall findings that lower cognitive score/cognitive impairment impedes the ability to use inhaler devices correctly.[24,41,96] The presence of cognitive impairment also predicts decay of inhaler technique (ie, an increase in errors) over time.[24]

Although a nebulizer may be beneficial for successful delivery of aerosol therapy in patients with cognitive impairment, it is important to note that not all patients will be able to independently set up a nebulizer device and would, therefore, require family or caregiver assistance.

Muscle Weakness and Hand Dexterity

The presence of comorbid conditions such as severe pain or muscle weakness due to neurologic/neuromuscular conditions (eg, Parkinsonism, stroke) or musculoskeletal conditions (eg, arthritis) that affect hand dexterity can compromise a patient's ability to properly use an inhaler device.[7,66] A small observational study reported that measures of hand grip strength and endurance were, respectively, 15% and 28% lower in patients with stable COPD than in volunteers without respiratory problems.[97] Moreover, a positive correlation has been observed between cognitive scores and hand grip strength and dexterity in patients with COPD.[98] Low handgrip strength has also been shown to predict 30-day readmissions after an acute exacerbation of COPD.[99] Decreased hand strength has been identified as a predictor of incorrect pMDI use in older patients.[99,100] With DPI, the presence of hand tremors or shaking could lead to partial loss of the administered dose.[7]

As with cognitive impairment, the presence of muscle weakness or hand dexterity challenges may favor nebulizer use; however, individual patients may require family or caregiver assistance to set up and maintain the device.

Insufficient Peak Inspiratory Flow Rate

Peak inspiratory flow rate (PIFR) may be low in patients with COPD because of an acute exacerbation, lung hyperinflation, hypoxemia, and/or muscle wasting. The inspiration flow rate required for effective medication delivery varies among inhalers, from approximately 20 L/min for pMDIs to 30 L/min for high-resistance DPIs and >100 L/min for low-resistance DPIs.[101,102] Due to their mechanism of action, SMI delivery is generally independent of inspiratory flow rate. In a small observational study, 40% of patients with stable COPD had insufficient PIFR to meet the specifications of their inhaler device.[103] Among patients hospitalized for an acute exacerbation of COPD, a separate study reported that 52% of patients had suboptimal PIFR (≤60 L/min).[104] Of patients aged >65 years, the proportion with suboptimal PIFR increased to 60%. For patients with low PIFR, discharge with aerosol therapy via a nebulizer versus a DPI was associated with significantly lower rates of all-cause (30-day: 0% vs 50%; 90-day: 17% vs 70%) and COPD-related (30-day: 0% vs 50%; 90-day: 17% vs 70%) readmissions, respectively ($p < 0.05$).

A multicenter, randomized, double-blind, active-comparator clinical trial compared bronchodilation with the long-acting muscarinic antagonist (LAMA) revefenacin delivered via nebulizer with that of the LAMA tiotropium delivered via DPI for patients with moderate to very severe COPD and PIFR <60 L/min against resistance of the Diskus® inhaler.[105] For the overall study population, changes in trough forced expiratory volume in 1 second (FEV_1) and trough forced vital capacity (FVC) were not significantly different between the 2 LAMA delivery mechanisms; however, in patients with baseline FEV_1 <50% predicted, treatment with nebulized revefenacin resulted in a greater change in trough FEV_1 and trough FVC than treatment with DPI tiotropium.[105]

Nebulizer Therapy and Respiratory Infection Transmission

In 2020, the COVID-19 pandemic brought to the forefront concerns about infectious respiratory disease transmission during aerosol-generating procedures.[106–112] Clinicians and professional organization opinions differed with regard to whether drug administration via nebulizer qualifies as an aerosol-generating procedure and if it was safe in light of the ongoing pandemic.[112] Recommendations to reduce virus transmission with nebulized therapy during the COVID-19 pandemic have been interpreted by some to mean that nebulizers are not recommended for the management of COPD.[113] Consequently, many clinicians switched their patients from nebulizer therapies to inhalers[112] and nebulizer use during hospitalization for acute exacerbations of COPD decreased.[111]

In 2024, the COPD Foundation Nebulizer Consortium (CNC) published guidance on mitigating the risk of transmitting respiratory infections during nebulization.[112] Based on the available published literature, the CNC report concluded that the current evidence is insufficient to classify nebulizer therapy as an aerosol-generating procedure; data are inconclusive regarding a direct relationship between nebulizer use and infection transmission; and "nebulizer use should not be discouraged when clinically indicated."

The CNC report further provides guidance on strategies for mitigating infection transmission risk and increasing the safety of aerosol drug delivery in both the healthcare and home environments.[112] The home environment

recommendations are consistent with the 2024 GOLD report, which suggests that spread of infection can be limited by implementing precautions such as avoiding nebulizer use in the presence of others and using the nebulizer near an open window or in a space with increased air circulation.[5] The CNC recommendation for continued use of nebulizer therapy when clinically indicated is also consistent with the 2024 consensus panel on the utilization of nebulized budesonide for managing asthma and COPD in both stable and exacerbation stages in Thailand, which recommends continuing nebulization in patients with COPD for whom it may be beneficial as long as appropriate COVID-19 transmission safety measures are applied.[114]

Taken together, the current recommendations indicate that nebulizer use remains a viable option for aerosol therapy delivery in the inpatient, outpatient, or home settings as long as appropriate safety precautions are utilized.

Nebulizer Options and Advances

The predominant categories of nebulizers used in treatment of COPD include jet nebulizers, ultrasonic nebulizers, and vibrating mesh nebulizers (Table 2).[66,67,112,115] Among these, jet nebulizers are the least expensive and most commonly used.[116,117] Jet nebulizers use compressed air or oxygen to force air through a constricted outlet at high velocity, thereby generating a vacuum that draws liquid up from the reservoir, which collides with the air "jet" in the chamber resulting in aerosol creation.[115] Jet nebulizers can produce aerosol continuously or preferentially during inspiration (ie, breath-enhanced and breath-actuated jet nebulizers). The latter design reduces medication waste and environmental contamination due to the release of fugitive aerosols into the environment during exhalation. Waste with jet nebulizers is also generated by retention of medication in the nebulizer and tubing, resulting in reduced lung deposition.[117] With breath-enhanced jet nebulizers, the release of medication is greater during inhalation than exhalation.[115] Breath-actuated jet nebulizers have the ability to sense a patient's inspiratory flow and limit aerosol release to inhalation.

Ultrasonic nebulizers generate aerosols by producing high-frequency vibrations that create oscillation on the surface of the liquid.[115] Compared with jet nebulizers, the aerosol particles produced by ultrasonic nebulizers are more consistent in size, the output rate is higher, and the administration time is lower. Ultrasonic nebulizers are less widely used,

Table 2 Attributes by Type of Nebulizer

Features	Jet	Ultrasonic	Vibrating mesh
Power source	Compressed gas, electric, or battery	Electric or battery	Electric or battery
Portability	Limited	Limited	Portable
Treatment time	15–20 min	4–10 min	<1–5 min
Output rate	Low	Intermediate	High
Residual volume	0.5–2.0 mL	Low and variable	Low and variable
Performance variability	Low to high[a]	Intermediate	Low
Efficiency with suspensions	Low	Poor	Variable
Environmental contamination Continuous Breath actuated Breath enhanced	 High Low Medium[b]	 High NA NA	 High NA NA
Cleaning	Required after every use	Required after several uses	Required after every use
Cost	Very low	High	High
Sound	Noisy	Silent	Low/silent

Note: [a]Depends on the type of jet nebulizer. [b]Low with a filtered mouthpiece. Data from these studies[66,67,112,115].
Abbreviation: NA, not applicable.

however, because of their cost, size, propensity for mechanical issues, and inefficiency when used for nebulizing suspensions and other viscous solutions.

Vibrating mesh nebulizers produce aerosol by passing liquid through holes in a vibrating mesh.[115] Vibrating mesh nebulizers are smaller and quieter than jet nebulizers and are more portable and have a shorter treatment time than either jet or ultrasonic nebulizers.[66,67,115] A 2024 systematic review and meta-analysis that included 10 studies comparing vibrating mesh nebulizers with jet nebulizers in a total of 314 patients with COPD reported that the former is associated with greater dose of drug delivered compared with the latter.[117] The analysis also found that more aerosol was emitted with vibrating mesh nebulizers than with jet nebulizers. No differences were observed with respect to lung function or lung capacity. In a real-world assessment, patients with COPD rated the eFlow® vibrating mesh nebulizer high in portability, ease of cleaning, size, weight, administration time, and relative noise.[86] Among patients who had previously used a nebulizer, 80% reported an increase in satisfaction with eFlow versus their previous nebulizer. Drawbacks of vibrating mesh nebulizers include high cost, the potential for viscous solutions and suspensions to clog the mesh, and difficulty cleaning.[117] Vibrating mesh nebulizers typically require cleaning after every use. However, assessment of a disposable vibrating mesh nebulizer (Aerogen® Solo) found that it could be used 3 times per day for 28 days without rinsing or washing with no degradation in performance.[118] The aperture plates became partially occluded within the first week of use, but this change did not appear to harm device performance.

Overall, nebulizers have become quieter, more portable, and more efficient, thereby increasing the feasibility for nebulizer use to move from the hospital/clinic setting to the home environment.

Medications Compatible with Nebulizer Delivery

Development has also advanced on the medication side of nebulizer therapy, with the main classes of COPD maintenance aerosol therapies now available in nebulizer formulations, including short-acting beta-agonists (SABAs), long-acting beta-agonists (LABAs), short-acting muscarinic antagonists (SAMAs), and LAMAs, as well as combinations of SABA and SAMA (Table 3).[5,7,119,120] The nebulizer formulation of the LAMA revefenacin is a comparatively newer addition to the aerosol therapy armamentarium.[7,121] The corticosteroid budesonide is available as a nebulizer formulation and is recommended as an

Table 3 Nebulized Therapies for Maintenance Treatment of COPD

Class	Drug
Short-acting beta-agonists (SABA)	Fenoterol[b] Levalbuterol Albuterol
Long-acting beta-agonists (LABA)	Arformoterol (*nebulizer only*) Formoterol (*nebulizer only in US*)
Short-acting muscarinic antagonist (SAMA)	Ipratropium bromide
Long-acting muscarinic antagonist (LAMA)	Revefenacin (*nebulizer only*)
Combination SABA + SAMA	Fenoterol/ipratropium[b] Albuterol/ipratropium
Inhaled corticosteroids	Budesonide
Antibiotics[a]	Colistin Gentamycin[b] Tobramycin Aztreonam
Dual PDE3/PDE4 inhibitor	Ensifentrine (*nebulizer only in US*)

Notes: PDE3/PDE4, phosphodiesterase 3/phosphodiesterase 4. [a]Nebulized antibiotics with clinical data evaluating their efficacy in patients with COPD who have chronic bronchial infection. [b]These formulations are not approved by the US Food and Drug Administration. Data from these studies[5,7,119,120].

alternative to systemic corticosteroids for select patients with an acute exacerbation of COPD.[5,114] A 2024 expert consensus panel from Thailand also recommended nebulized budesonide as an alternative to inhaled corticosteroids in stable patients with COPD, particularly those with frequent exacerbations or who are unable to correctly use a DPI or pMDI.[114] However, as budesonide is formulated as a suspension, it cannot be used in an ultrasonic nebulizer.[122]

There are currently limited data for use of nebulized antibiotics in patients with COPD.[119] An advantage of the aerosol route for antibiotic administration is that it limits systemic exposure versus oral antibiotics.[119] There is preliminary evidence supporting use of nebulized antibiotics for the prevention of acute exacerbations in patients colonized with *Pseudomonas aeruginosa*, but further investigation is needed to determine the utility of nebulized antibiotics in COPD.[7,119,120]

The next iteration of nebulizer therapies is likely to involve additional fixed-dose combination agents such as LAMA/LABA,[7] as well as development of new medications such as the dual phosphodiesterase 3/phosphodiesterase 4 (PDE3/PDE4) inhibitor, ensifentrine.[7,106] Ensifentrine (previously called RPL554) is described by Cazzola et al[123] as a "'first-in-class' drug having bifunctional bronchodilator and anti-inflammatory activity in a single molecule" that acts on 3 mechanisms involved in the pathogenesis of COPD: bronchoconstriction, inflammation, and dysfunctional mucociliary clearance. Ensifentrine has been evaluated in clinical trials as an adjunct to LAMAs or LABAs,[124] but there are limited data on use when added to LAMA/LABA combination therapy or triple therapy.[123] Notably, ensifentrine does not have the tolerability issues that have limited the utilization of other PDE inhibitors.[123,125,126] Ensifentrine (Ohtuvayre™, Verona Pharma) was approved by the US Food and Drug Administration for the maintenance treatment of COPD in adult patients in June 2024.

Clinical Pearls for Nebulizer Use in Clinical Practice

Implementing effective aerosol therapy is a multistep process that involves communication and shared decision-making between the patient and the clinician. The first step in the process is choosing a suitable medication and device for administration of that medication. There is no device that is universally appropriate for all patients; it is imperative to ensure that the device aligns with the patient's needs, abilities, preferences, and access.[5,112] As data have shown, in clinical practice a prescribed inhaler regimen often does not align with patient needs due to divergence from guideline recommendations and/or lack of insurance coverage.[127]

Tools are available to assist in determining a patient's suitability for a particular inhaler device. In-Check DIAL™ (Clement Clarke), which measures a patient's inspiratory effort, is a multipatient device with a disposable, single-use mouthpiece.[128] The device's resistance can be adjusted to approximate different types of inhalers. In-Check DIAL can also be used for instructional/training purposes. The Aerosol Inhalation Monitor (Vitalograph® AIM™) is a single-use disposable inhaler simulator that assesses multiple aspects of a patient's inhaler technique, including canister activation, inspiratory flow rate, breath hold time, and inhalation time.[129] Like In-Check DIAL, it can be used for initial assessment and training. Both devices are suitable for use in clinic or pharmacy settings. Instructional videos demonstrating how to use these devices as well as many other inhaler and nebulizer devices are freely available online, produced by the device manufacturers or by professional organizations such as the COPD Foundation (COPDFoundation.org).

Although there is no comparable assessment tool for determining nebulizer suitability, the characteristics shown in Table 1 are a helpful guide for patient types and clinical scenarios that favor COPD maintenance aerosol therapy delivered via nebulizer rather than inhaler.

Once the choice of aerosol therapy has been determined, patient education and training are key to ensuring appropriate device use. Based on the available literature for inhaler devices, it is known that reading the patient information leaflet is insufficient for many patients to master inhaler technique; face-to-face instruction by a trained professional is recommended.[34] Moreover, training is associated with higher patient satisfaction with an inhaler device,[83] which in turn is linked to better adherence and patient outcomes.[112] For nebulizers, training in general and cleaning and maintenance in particular have been identified by patients as areas of educational need.[70,87,130] In a survey of 254 patients with COPD, only 47% recalled having been trained on how to use their inhaler or nebulizer device and few patients remembered discussing cleaning of the device.[87] In a separate study, 31 of 50 patients with COPD surveyed did not feel adequately informed about nebulizer use, and only 7 recalled being taught how to use and clean the device.[130] These findings are consistent with a survey of 205 pulmonologists in which only 9% indicated that they discuss device cleaning and storage at a patient's first visit.[131] This lack of education and training could explain why a large proportion of patients

with COPD fail to wash nebulizer components after use and to disinfect the device.[130] Patients should also be made aware of any nebulizer maintenance needs, such as periodic replacement of the air filter for jet nebulizer compressors. If a patient depends on a caregiver to assist with nebulizer use, the caregiver should be included in the education and training.[132]

As described in this review, aerosol therapy is prone to suboptimal technique and use errors, which can adversely affect treatment efficacy and outcomes. Incorrect use of nebulizers by patients in the home environment can range from errors in assembling and operating the device through cleaning, drying, and maintaining the nebulizer.[130] It is, therefore, important to assess that patients are using their devices correctly at the outset and periodically thereafter.[5]

It is important to note that although this review sought to present an unbiased assessment of both handheld inhalers and nebulizers for the maintenance treatment of COPD, there are limitations that influence the ability to draw conclusions from the data. For example, the breadth and depth of clinical research, particularly in regard to technique errors, patient satisfaction, and ease of use, is greater for inhalers than for nebulizers. Moreover, criteria used to define technique errors, critical errors, and patient satisfaction varied among studies, making it difficult to compare findings. The studies themselves were heterogeneous with regard to patient populations (eg, disease severity, prior aerosol therapy experience) and the training provided to patients. There was also often a lack of detailed information on the relationship between device error rates and clinical outcomes. Last, as noted when describing propensity to errors, not all devices within a category have the same attributes and should ideally be considered on an individual basis. Greater insight into matching the right patient to the right device could be gained through prospective, randomized controlled trials and additional research evaluating nebulizer devices within different subsets of patients with COPD.

Conclusions

Nebulizers of the modern era represent a significant advance over their predecessors, with newer versions that provide more consistent and efficient medication delivery and have greater portability. With these features and a wider range of medication options, nebulizers warrant consideration as an alternative to handheld inhalers. The most important consideration for choosing an aerosol therapy delivery method is that the patient is able to access and use it correctly. For many patients with COPD, including those with cognitive impairment or physical limitations that preclude optimal inhaler use, the benefit equation favors nebulizers. With appropriate education and training, nebulizer therapy is a viable option for the maintenance treatment of COPD.

Abbreviations

CNC, COPD Foundation Nebulizer Consortium; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; OM, Original Medicare; PDE3, phosphodiesterase 3; PDE4, phosphodiesterase 4; PIFR, peak inspiratory flow rate; pMDI, pressurized metered-dose inhaler; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonist; SMI, soft mist inhaler.

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Author Contributions

All authors were involved in the manuscript's conception and execution; participated in the analysis and interpretation of the data; critically reviewed and revised manuscript drafts; agreed on the journal to which the manuscript was submitted; and provided approval of manuscript versions throughout the development process. All authors agree to be accountable for the contents of the article.

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