Consensus Document on Home Nebulization for Maintenance Treatment of Obstructive Airway Diseases: A Joint Initiative by the National Allergy Asthma Bronchitis Institute (NAABI) and Chest Research Foundation (CRF)

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Abstract
Recent years have seen an increase in the use of nebulizers for delivering maintenance therapy in obstructive airway diseases (OADs) such as asthma and chronic obstructive pulmonary disease (COPD). The probable factors associated with this increase at home are: convenience of drug delivery, technological advances making the nebulizer equipment more efficient and portable, increase in the prevalence of OADs and the ageing population which may impact the optimal use of handheld inhalers such as pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). Although there is increase in the use of maintenance therapy with nebulization, there has been no such increase in the evidence base available for the appropriate use of nebulizers. The last international guidelines were published in 2001. Hence there is a need to address this knowledge gap especially with the widespread use of home nebulization in India. With this objective, we organized a consensus meeting to address certain critical questions pertaining to the use of nebulizers for maintenance treatment in OADs. This article presents the findings of the consensus panel on the use of maintenance treatment of OADs with nebulization at home.

Introduction
Globally, there are an estimated 334 million and 384 million individuals suffering from asthma and chronic obstructive pulmonary disease (COPD), respectively.¹,² The approximate prevalence rate of asthma and COPD in India is around 17.23 million and 15 million, respectively,¹,² which possibly could be under-reported since questionnaire-based data may not reflect the true prevalence. But, when categorized together as obstructive airway diseases (OADs), they account for being the second most commonly diagnosed condition in the primary healthcare practice in India.²-⁵ Although global trends in the asthma mortality rate show a decline, it remains high in the low- and middle-income countries.¹,⁶ More cause for concern is the mortality rate of COPD, both globally and in India. Currently the third most common cause of death worldwide, COPD is the second leading cause of death in India and kills around half a million individuals every year.⁷,⁸

While the increasing mortality rates of COPD are certainly distressing, the morbidity brought forth by this condition is further perturbing. The Global Burden of Disease (GBD) reveals that COPD is among the top ten causes of disability in India, ranking at number five.⁹ With changing demographics in the form of an ageing population coupled with the fact that COPD is a progressive disease often diagnosed in middle age, India is soon going to see vast numbers of individuals disabled by this condition. Additionally, the burden of comorbidities in COPD increases as the disease progresses and many patients suffer from cognitive or manual impairments either due to the disease or ageing¹⁰,¹¹ which may...
Panel 1: Topics identified as a background work to the consensus meeting

1. What should be the appropriate terminology and definition to describe maintenance treatment with nebulization at home?
2. How should one identify/select patients suitable for maintenance treatment with nebulizers?
3. What should be the duration of maintenance treatment with nebulization?
4. Which are the drugs that can be prescribed for maintenance treatment with nebulizers and with which type of nebulizer equipment?
5. What is the long-term safety of maintenance treatment with nebulization at home?
6. Are there any special precautions for OAD patients with comorbid conditions such as cardiovascular diseases (CVDs) and diabetes?
7. What are the cleaning and maintenance recommendations that need to be communicated to patients using long-term nebulization?
8. Should oxygen-driven nebulization be used in COPD patients on maintenance treatment with nebulization at home?
9. At what time intervals should patients using nebulization at home be assessed?
10. How should the success of therapy be assessed and adherence ensured in patients using long-term nebulization?
11. Can home nebulization be prescribed in other chronic respiratory diseases?

In such clinical scenarios, nebulizers could be a useful alternative to handheld inhalers because optimum drug delivery is not completely dependent on patient effort. Nebulization can be used in the home setting, in a long-term care setting, in a hospital setting, and in an emergency room setting. Moreover, there have been several advances in nebulizer technology, making them more patient- and pocket-friendly along with increased availability of nebulized drug formulations. According to crude estimates, such factors have led to an increase in the number of patients being prescribed nebulization in both inpatient and outpatient settings.

Nebulizers, however, are not without drawbacks, particularly that of increased risk of adverse effects (AEs) and acquired infections. Hence, it is imperative that nebulizers be prescribed to patients after careful deliberation.

However, there is insufficient evidence to guide the correct and appropriate use of nebulizers, which is a valid concern amongst many respiratory physicians. The British Thoracic Society (BTS) and European Respiratory Society (ERS) have released guidelines on nebulization in 1997 and 2001, respectively.

The last consensus document, specifically on home nebulization in OADs, by the National Association for Medical Direction of Respiratory Care (NAMDC), USA, was released in 1996 – that is, nearly 20 years ago. There are no recommendations available from India on the correct use of nebulizers (hospital or home) although (anecdotally), the use of nebulizers in increasing in the country.

With the objective of addressing this knowledge gap in the use of home nebulization for the maintenance treatment of OADs, a consensus meeting was jointly organized by NAABI and CRF. The following is a report of this meeting.

Objective

The objective of this consensus meeting was to formulate expert views, using the available evidence,
on the optimal use of maintenance treatment with nebulization at home.

Methodology

The consensus meeting was convened through an expert panel consisting of pulmonologists from different geographies in India as well as different clinical settings (medical colleges, research institutes, private hospitals and private clinics). Prior to the meeting, common questions on maintenance treatment with nebulizers (Panel 1) were identified by the conveners and individual panellists were assigned to research the available evidence with respect to a particular question (Figure 1). At the meeting, the individual panellists presented their findings and a consensus was arrived at through discussion (Figure 1).

Scope of the Consensus Document

This consensus document can have application in the following areas:

1. Physicians treating chronic OADs such as asthma and COPD.
2. Physicians considering prescribing nebulization for long-term use at home.
3. Patients with chronic OADs such as asthma and COPD.
4. Paramedics managing patients with OADs through nebulization at home.

The consensus panel does not intend to promote the use of nebulizers over other handheld devices and urges all physicians treating respiratory diseases to not replace handheld inhalers such as pMDIs and DPIs with nebulizers, and to make all possible efforts to ensure that patients use the pMDIs and DPIs optimally.

Q1: What should be the appropriate terminology and definition to describe maintenance treatment with nebulization at home?

It has been observed that maintenance treatment with nebulization at home is often referred to as ‘home nebulization’. This terminology probably arose from previous studies, reviews and also some consensus statements.14,18,20,22,23 The other terminology observed in the literature was ‘domiciliary use’ of nebulizers.14,24 However, the panel noted that both these terminologies are unclear about chronic use or intermittent use of nebulizers at home. Hence, we suggest that the appropriate terminology should be ‘maintenance nebulization’, which would imply the chronic use of nebulizers for delivering maintenance treatment at home. It can be defined as a physician-prescribed therapy to deliver long-term maintenance drugs (≥3 weeks duration) in carefully selected patients.

Both the terms ‘home nebulization’ and ‘maintenance nebulization’ have been used interchangeably. However, we suggest that acute use and short-term use (<3 weeks) of nebulizers at home be a part of the umbrella term ‘home nebulization’ and be considered different from the term ‘maintenance nebulization’ proposed in this document. Rescue use of nebulization at home should be considered as a part of the maintenance regimen for OADs.

The key terms in the proposed definition are ‘physician-prescribed’, ‘maintenance drugs’ and ‘appropriately selected patients’. These key terms should be considered central to the concept of maintenance nebulization.

Recommendation

Maintenance treatment of OADs with nebulization at home can be referred to as ‘maintenance nebulization’ rather than ‘home nebulization’ to specifically imply long-term chronic use (≥3 weeks).

- Maintenance nebulization can be defined as physician-prescribed therapy to deliver long-term maintenance drugs (≥3 weeks) in appropriately selected patients with OADs.

Q2: How should one identify/select patients suitable for maintenance treatment with nebulizers?

Given the potential for misuse of nebulization in patients with OADs, the consensus panel recommends a careful screening of patients for maintenance nebulization. We reviewed the recommendations available from two guidelines (BTS 1997 and ERS 2001) and one consensus report (NAMDRD 1996).14,20,21 Additionally, we examined original reports and review articles published till March 2015 through PubMed and Google Scholar for identifying the patient categories most suitable for maintenance nebulization. In most of the literature, we observed a descriptive approach for selecting patients for maintenance nebulization, including a clinical review by Dolovich and Dhand (2011),13 which lists the various clinical scenarios in patients with COPD where maintenance nebulization may be preferred over handheld inhalers.

However, we realized that having an algorithmic approach to selecting a patient for maintenance nebulization is more practically relevant. Figure 2 describes the algorithm proposed by the consensus panel after review of the literature at the convened meeting.

Recommendation

Patients should be carefully screened before prescription of maintenance nebulization. More importantly, the screening should focus on the ability to use handheld inhaler devices and every effort should be made to introduce/re-introduce drug administration through handheld inhalers. Patient satisfaction and choice should also be taken into account when considering...
Patient with a confirmed diagnosis of OAD

Prescribe appropriate guideline-based treatment + through a handheld inhaler (pMDI/DPI), taking patient preference into account.

After 2–3 weeks, check clinical improvement * along with device technique. #

Device technique satisfactory and clinical improvement

Continue with regular follow-up every 3 months

Device technique satisfactory but no/suboptimal clinical improvement

Maximize treatment accordingly, based on guideline recommendations

Clinical improvement with satisfactory device technique

Device technique unsatisfactory and no/suboptimal clinical improvement

Switch to the other handheld device (change to pMDI/DPI, based on initial prescription)

Clinical improvement and device technique after 2–3 weeks

No/suboptimal clinical improvement and unsatisfactory device technique

Check the reasons for unsatisfactory device technique/suboptimal improvement:
- Inspiratory flow/breath-holding capacity inadequate?
- Cognitive impairment?
- Physical impairment?
- Comorbidities?
- Need high doses?
Prescribe trial maintenance nebulization for 3 weeks.

If there is clinical improvement, prescribe maintenance nebulization and follow-up every 1 month initially and, later, annually. Check possibility of re-introducing handheld inhalers either alone or concomitantly with nebulizers. If no clinical improvement, then investigate further on the diagnosis.

*Clinical improvement should be assessed as recommended by the respective treatment guidelines.

#Device technique should be assessed as per the patient information literature provided with the device.

+ Unsatisfactory device technique is any deviation from the recommended device technique described in the patient information literature provided with the device.
handheld inhalers versus nebulizers for long-term use. Additionally, the advantages and drawbacks of all inhaler devices, including nebulizers, should be explained to the patients so as to facilitate an informed decision.

Q3: What should be the duration of maintenance treatment with nebulization?

Since the minimum and maximum duration of therapy cannot be defined in the realm of chronic treatment, the panel reviewed the literature with regards to maintenance nebulization. The duration of maintenance nebulization could last from a minimum of 2–3 weeks (ERS guidelines and NAMDRG guidelines)\(^{14,20}\) to an indeterminate period of time. One prospective study by O’Driscoll and Bernstein\(^{25}\) with 49 asthma and COPD patients found the survival rates to be similar amongst patients using maintenance nebulization (n=32) and pMDI + spacer (n=17) over a period of 5 years. Additionally, there have been studies that have assessed the safety of the nebulized long acting beta\(_2\) agonists (LABAs) over a period of 1 year (formoterol and arformoterol studies).\(^{26-28}\) In view of the available evidence, we concluded that the minimum duration for which maintenance nebulization can be safely prescribed in patients with OADs is (but not limited to) 3 weeks. However, we cannot make a similar recommendation for the maximum duration of therapy with maintenance nebulization since it is subject to disease mechanisms and the requirement of the patients, although there are published studies that indicate a 1-year safety period for certain nebulized formulations such as LABAs.

Recommendation

The minimum duration of maintenance therapy that can be prescribed in a patient with OAD is 3 weeks. However, no recommendation can be made on the maximum duration of therapy.

The decision to end/continue maintenance nebulization lies with the prescribing physician after taking into account the subjective and objective improvement along with ensuring that there are no concerns regarding AEs with the prescribed nebulized formulations.

Q4: Which are the drugs that can be prescribed for maintenance treatment with nebulizers and with which type of nebulizer equipment?

In keeping with the advances in the nebulizer design and technology, there has been an exponential increase in the approvals for nebulized drugs available in the market. Table 1 lists the approved nebulized drugs that can be prescribed for maintenance nebulization in OADs. This list contains the drugs that can be used on an as-needed, short-term or long-term basis.

Since compatibility of the nebulizer and the drug formulation is important for optimum drug deposition, selecting the right nebulizer is equally important. Various factors such as output rate, performance variability, effect of nebulization on drug formulation and cleaning and maintenance should be considered when selecting a nebulizer for the patient (Table 3).\(^{11}\)

Recommendation

Selecting the right drug and the right nebulizer is important for the success of maintenance nebulization in OADs. Prescribers are advised to refer to the exact indications, posology and administration available in the prescribing information of the available drugs.

Q5: What is the long-term safety of maintenance treatment with nebulization at home?

There is a paucity of data in terms of the long-term safety of maintenance nebulization. This is probably due to the logistical difficulties in conducting long-term, randomized, controlled trials with maintenance nebulization.\(^ {20}\) Moreover, most of the long-term clinical trials with maintenance nebulization, which have been published (to our knowledge), involved drugs in respect of which there are some concerns about AEs with long-term use, such as LABAs. In a 1-year, open-label study with 569 COPD patients receiving either nebulized formoterol (20 mcg b.i.d.) or DPI formoterol (12 mcg b.i.d.), no differences were observed between the dosage forms in terms of AEs, cardiac and laboratory parameters.\(^ {27}\) The only published study (to the best of our knowledge), which has assessed the long-term safety of maintenance nebulization for more than a year, is the 5-year survival study by O’Driscoll and Bernstein\(^ {25}\) mentioned previously. Table 3 reviews the safety evaluation performed across various published studies with nebulized formulations of steroids and bronchodilators.

Looking at the limited evidence base available, the panel recommends a regular review of the patients on maintenance nebulization for local and systemic AEs and, possibly (at least annually, based on the 1-year safety studies with LABAs),\(^ {27,28}\) also of the laboratory and cardiac parameters (Table 4). Baseline ECG and an echocardiography and a close follow-up after 1 month (may be with an ECG) in association with a cardiologist is recommended for patients with known heart disease.

Recommendation

To ascertain long-term safety in patients with OADs, it is recommended to perform a regular review (at least every 6 months).

Q6: Are there any special precautions for OAD patients with comorbid conditions such as CVDs and diabetes?

Although there is some theoretical concern about the use of nebulized drugs in OAD patients with comorbid conditions such as
CVD and diabetes, the panel did not come across any study specifically evaluating the effect of nebulized drugs in such specific populations. The safety trials of nebulized LABAs such as formoterol and arformoterol generally exclude COPD patients with underlying cardiac conditions.\textsuperscript{26,27,44} However, it is possible that high doses of drugs such as beta-agonist bronchodilators may be harmful in COPD patients with underlying cardiac disease.\textsuperscript{21} In a recently published randomized controlled trial by Donohue et al.\textsuperscript{28} involving 841 COPD patients (age ≥40 years, baseline FEV\textsubscript{1} ≤65\%) receiving either nebulized arformoterol or placebo for 1 year, there was no conscious effort made to exclude patients with an underlying CVD. Although there were numerically more serious cardiac AEs in patients taking arformoterol (3.1\%) than placebo (2.4\%), no significant differences were observed between the treatment groups in terms of time to the first serious cardiac AE.\textsuperscript{28} The BTS guidelines on the use of nebulizers in COPD recommends ECG monitoring as a precaution after the first dose of nebulized bronchodilator is administered to the COPD patient with an underlying cardiac condition.\textsuperscript{21}

Just as is the case with nebulized beta\textsubscript{2}-agonists, there are no studies that have evaluated the effects of nebulized corticosteroids in OAD patients with underlying comorbid diabetes. One study by Faul et al.\textsuperscript{45} assessed the effects of high-dose fluticasone (880 mcg/day) on asthma or COPD patients with comorbid type 2 diabetes mellitus for 12 weeks and did not find any significant effect of the treatment on glycosylated haemoglobin. However, the authors recommended monitoring blood glucose levels in patients taking high-dose ICS with concomitant diabetes.

One of the concerns with the use of nebulized beta\textsubscript{2}-agonists is the transient and dose-dependent decrease in serum potassium levels, as noted by a few studies.\textsuperscript{46-48} There are no recommendations available to suggest what intervals should the serum potassium levels be monitored in patients using beta\textsubscript{2}-agonists through maintenance nebulization.

In view of the available evidence, the present panel realizes that although monitoring blood glucose in OAD patients with diabetes is possible, regular monitoring of patients for cardiac events may not be practically feasible. As recommended previously,

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**Table 1: Approved or recommended nebulized drugs in India for use in home nebulization**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Molecule</th>
<th>Recommended use (in adults)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting beta\textsubscript{2}-agonist (SABA)</td>
<td>Salbutamol</td>
<td>As-needed use in OADs</td>
</tr>
<tr>
<td>Long-acting beta\textsubscript{2}-agonist (LABA)</td>
<td>Formoterol</td>
<td>Long-term maintenance in COPD</td>
</tr>
<tr>
<td>Short-acting muscarinic antagonist (SAMA)</td>
<td>Ipratropium bromide</td>
<td>Long-term maintenance in COPD</td>
</tr>
<tr>
<td>Inhaled Corticosteroids (ICS)</td>
<td>Fluticasone</td>
<td>Long-term maintenance in asthma</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Long-term maintenance in COPD/ as-needed use in maintenance regimen in COPD</td>
<td></td>
</tr>
<tr>
<td>SABA + SAMA</td>
<td>Salbutamol + ipratropium</td>
<td>Long-term maintenance in asthma</td>
</tr>
<tr>
<td>ICS + SABA</td>
<td>Budesonide + levosalbutamol</td>
<td>Long-term maintenance in asthma</td>
</tr>
<tr>
<td>ICS + LABA</td>
<td>Budesonide + formoterol</td>
<td>Long-term maintenance in OAD</td>
</tr>
<tr>
<td>Mucolytics</td>
<td>N-acetylcysteine</td>
<td>Short-term adjuvant use in OAD in case of mucus hypersecretion</td>
</tr>
</tbody>
</table>

*For exact indications, posology and administration, please refer to the prescribing information available from the manufacturer of the respective products.

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**Table 2: Characteristics of different types of nebulizers**

<table>
<thead>
<tr>
<th>Features</th>
<th>Jet</th>
<th>Ultrasonic</th>
<th>Vibrating mesh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power source</td>
<td>Compressed gas or electrical mains</td>
<td>Electrical mains</td>
<td>Batteries or electrical mains</td>
</tr>
<tr>
<td>Portability</td>
<td>Restricted</td>
<td>Restricted</td>
<td>Portable</td>
</tr>
<tr>
<td>Treatment time</td>
<td>Long</td>
<td>Intermediate</td>
<td>Short</td>
</tr>
<tr>
<td>Output rate</td>
<td>Low</td>
<td>Higher</td>
<td>Highest</td>
</tr>
<tr>
<td>Residual volume</td>
<td>0.8-2.0 mL</td>
<td>Variable but low</td>
<td>≤0.2 mL</td>
</tr>
<tr>
<td>Environmental contamination</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Continuous use</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Breath-activated</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Performance variability</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>Formulation characteristics</td>
<td>Temperature</td>
<td>Increases*</td>
<td>Increases†</td>
</tr>
<tr>
<td>Concentration</td>
<td>Increases</td>
<td>Variable</td>
<td>Minimum change</td>
</tr>
<tr>
<td>Suspensions</td>
<td>Low efficiency</td>
<td>Poor efficiency</td>
<td>Variable efficiency</td>
</tr>
<tr>
<td>Denaturation</td>
<td>Possible‡</td>
<td>Probable‡</td>
<td>Possible‡</td>
</tr>
<tr>
<td>Cleaning</td>
<td>Required, after single use</td>
<td>Required, after multiple use</td>
<td>Required, after single use</td>
</tr>
<tr>
<td>Cost</td>
<td>Very low</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

*For jet nebulizers, the temperature of the reservoir fluid decreases about 15°C during nebulisation because of evaporation; †For ultrasonic nebulizers, vibration of the reservoir fluid causes a temperature increase during aerosol generation, which can be as high as 10–15°C.; ‡Denaturation of DNA occurs with all the nebulisers; (With permission from Dolovich M, Dhand, R; The Lancet 2011)
for the purpose of long-term safety with nebulized drugs, OAD patients with comorbidities such as CVD and diabetes should be reviewed regularly (at least annually) for blood glucose and cardiac parameters. Since it is practically difficult to measure serum potassium in patients taking long-term nebulized beta₂-agonists, it is prudent to advise the patient and the carers to be aware of the general signs and symptoms of hypokalaemia and report to the emergency department if noticed.

**Recommendation**

OAD patients with complicating comorbidities such as CVD and diabetes should be reviewed regularly (every 6 months) for blood glucose and cardiac parameters.

**Q7: What are the cleaning and maintenance recommendations that need to be communicated to the patients using long-term nebulization?**

Nebulizers require regular cleaning and maintenance. Ideally, nebulizers should be cleaned after every use; however, since this may not be practically possible, we recommend cleaning and disinfecting the nebulizer at least once a day. Many manufacturers of nebulizers also recommend cleaning and disinfecting the nebulizer before using for the first time and if the nebulizer has not been used for a long time.

Since it depends on the nebulizer and the frequency of use, the instructions for cleaning and maintenance of the nebulizer should follow the recommendations made by the respective manufacturers since nebulizers are of different types and manufactured by different companies. Table 5 lists the general instructions for the cleaning and maintenance of jet, ultrasonic and mesh nebulizers.

**Recommendation**

Patients should be educated on the cleaning and maintenance of their nebulizers, and a periodic review of the nebulizer should be performed by the prescribing physician. Patients should be advised to clean the nebulizer accessories at least once a day.

**Q8: Should oxygen-driven nebulization be used in COPD patients on maintenance treatment with nebulization at home?**

Long-term oxygen therapy (LTOT) for more than 15 hours is recommended by the guidelines as a treatment to improve survival in patients with COPD and a patient with COPD being treated with maintenance nebulization may have been prescribed LTOT. Drugs can be administered to patients requiring oxygen through nebulization by converting an air-driven jet nebulizer into an oxygen-driven jet nebulizer. However, such an arrangement should not be recommended for home use because of the risk of carbon dioxide retention, especially with bronchodilators, in such patients.

** Recommendation**

Patients (especially those with COPD) should not be prescribed maintenance nebulization with oxygen-driven jet nebulizers because of the risk of carbon dioxide retention, especially with bronchodilators.

**Q9: At what time intervals should patients using nebulization at home be assessed?**

Regular follow-up is key to the successful management of any chronic disease. Patients who have been prescribed maintenance nebulization should be assessed for the following:

1. Effectiveness of the prescribed treatment
2. Adherence to the treatment
3. Need for continuing maintenance nebulization
4. Possibility of re-introducing handheld inhalers

The European Respiratory Society Task Force, which has formulated guidelines on the use of nebulizers, recommends initiating follow-up approximately 1 month after the start of maintenance nebulization. A re-assessment of the need for and effectiveness of maintenance nebulization, along with adherence, can be made annually. The present panel endorses these recommendations because of their feasibility in clinical practice.

**Recommendation**

Initial follow-up should be performed 1 month after the start of maintenance nebulization and, later, at least annually.

**Q10: How to should the success of therapy be assessed and adherence ensured in patients using long-term nebulization?**

Adherence to medication is a well-known challenge in any chronic pharmacotherapy and is defined as “the extent to which a person’s behaviour (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice”.

In case of the inhalation technique, the ease of use of a device may impact adherence to medication. Although patients have shown a preference to nebulizers in surveys, there are no established means to identify and ensure adherence in patients who have been prescribed maintenance nebulization. In a study of 985 patients (aged 30–74 years) with moderate-to-severe COPD who were prescribed maintenance nebulization (with beta₂-agonists), the adherence to treatment was observed to be 50.6%, as measured objectively. The predictors of adherence were older age, better education, having a stable lifestyle, report of therapy making the patient feel better, marital status, history of emphysema and more breathlessness, poorer lung function, and having little smoking and alcohol history.

The present panel believes that, in clinical practice, adherence to any treatment can only be judged by
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study duration</th>
<th>Patients</th>
<th>Intervention</th>
<th>Safety evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grzelewska-Rzymowska et al.</td>
<td>Double-blind, double-dummy, multicentre, randomized, parallel-group</td>
<td>12 weeks</td>
<td>N=124 (age: 18–70 years), moderate–severe asthma, on high-dose ICS</td>
<td>Nebulized BDP suspension for nebulization b.i.d. 3,000–4,000 mcg/day + 3–4 puffs b.i.d. of placebo (n=63) or BDP pMDI (3–4 puffs) b.i.d. 1,500–2,000/day with spacer + placebo nebulization b.i.d. (n=61) Rescue: salbutamol</td>
<td>Both treatments well tolerated. Treatment-related AEs were seen in 9.5% of patients in the BDP nebulization group versus 8.2% in the BDP pMDI group. Number of treatment-related AEs in the BDP nebulization group versus the BDP pMDI group: 20.6% versus 11.5%.</td>
</tr>
<tr>
<td>Bousquet et al.</td>
<td>Double-blind, double-dummy, randomized, placebo-controlled, parallel-group</td>
<td>3 weeks</td>
<td>N=40 (age: 18–60 years), intermittent (as per GINA) asthma</td>
<td>Nebulized BDP (1,600 mcg/day) (n=10) or nebulized BDP (3,200 mcg/day) (n=10) or BDP pMDI + spacer (800 mcg/day) (n=10) or placebo (n=10)</td>
<td>All treatments well tolerated. AEs were reported by 5 patients each in the three groups (nebulized BDP 1,600 mcg/day, BDP pMDI, and placebo) and 7 patients in the nebulized BDP 3,200 mcg/day group. Number of AEs: 13 in nebulized BDP 1,600 mcg/day, 34 in nebulized BDP 3,200 mcg/day, 19 in BDP pMDI and 15 in placebo. AEs were mild-to-moderate in severity, with the most commonly reported being headache and sore throat. With respect to change in mean random morning cortisol levels, no significant differences from pre-treatment levels, and between groups.</td>
</tr>
<tr>
<td>Terzano et al</td>
<td>Randomized, active-controlled, parallel-group</td>
<td>12 weeks</td>
<td>N=205 (age: 18–65 years), moderate persistent asthma</td>
<td>Nebulized BDP b.i.d. (2,400 mcg/day) (n=103) or nebulized FP b.i.d. (2,000 mcg/day) (n=102)</td>
<td>Both treatments were well tolerated. Up to 22.5% of patients in the BDP group and 32% of patients in the FP group reported one or more AEs. Number of AEs was 30 in the BDP group and 46 in the FP group. All AEs were mild in severity.</td>
</tr>
<tr>
<td>Delacour et al</td>
<td>Randomized, controlled, open-label, parallel-group</td>
<td>12 weeks</td>
<td>N=120 (age: 6 months to 6 years) severe persistent asthma</td>
<td>Nebulized BDP b.i.d. (800 mcg/day) + oral ketotifen (n=58) or nebulized BUD b.i.d. (750 mcg/day) + oral ketotifen (n=62)</td>
<td>Urinary cortisol and urinary cortisol/creatinine ratios not significantly affected. Of 338 AEs observed in the randomized treatment period, 168 were reported in the BDP group and 170 in the BUD group. Overall, the frequency and profile of AEs were equivalent for the two treatments, with side effects generally being associated with the ear, nose and throat, and respiratory system.</td>
</tr>
<tr>
<td>Bisca et al</td>
<td>Double-blind, double-dummy, multicentre, randomized, parallel-group</td>
<td>4 weeks</td>
<td>N=151 (age: 6–16 years), having moderate-to-severe asthma exacerbation at entry</td>
<td>Nebulized BDP b.i.d. (1,600 mcg/day) (n=75) or BDP pMDI + spacer b.i.d. (800 mcg/day) (n=76)</td>
<td>Number of patients reporting AEs: 25 in nebulized BDP versus 26 in BDP pMDI. Number of AEs: 43 in nebulized BDP and 48 in BDP pMDI.</td>
</tr>
<tr>
<td>Study</td>
<td>Study design</td>
<td>Study duration</td>
<td>Patients</td>
<td>Intervention</td>
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<tr>
<td><strong>Nebulized steroids: Budesonide</strong></td>
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<tr>
<td>Shapiro et al.34</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group</td>
<td>12 weeks</td>
<td>N=178 (age: 4–8 years), diagnosed with asthma, taking daily ICS</td>
<td>Nebulized BUD 0.25 mg or 0.50 mg or 1.0 mg b.i.d. or placebo</td>
<td>Dropouts due to asthma worsening were significantly fewer (p&lt;0.015). AEs and basal and ACTH-stimulated cortisol responses not different between groups. Change in ACTH-stimulated cortisol levels from baseline to end of treatment: –9.1 nmol/L in placebo (n=8); and 41.2, 54.7 and –56.3 nmol/L in the 0.25 mg (n=14), 0.50 mg (n=11) or 1.0 mg (n=13) nebulized BUD groups, respectively.</td>
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<tr>
<td>Murphy et al.35</td>
<td>Randomized, partially blinded, active-controlled, parallel-group</td>
<td>12 weeks + 2 weeks’ follow-up</td>
<td>N=60 (age: ≥12 years), moderate-to-severe asthma</td>
<td>Nebulized BUD 0.5 mg o.d. or nebulized BUD 1.0 mg b.i.d. or nebulized BUD 2 mg b.i.d. or BUD pMDI 400 mcg b.i.d.</td>
<td>AEs and severity of AEs were similar across all groups. The most common AE: upper respiratory tract infection (6.9%).</td>
</tr>
<tr>
<td>Cetinkaya et al.36</td>
<td>Randomized, controlled trial</td>
<td>12 weeks</td>
<td>N=31 (age: 6–24 months), recurrent or persistent wheezing</td>
<td>Nebulized BUD 0.25 mg or nebulized FP 0.25 mg b.i.d. for 6 weeks and at half the dose for another 6 weeks</td>
<td>Mean pre-treatment morning cortisol was lower in FP than in BUD. No difference in ACTH, serum HbA1C, sodium, chloride, potassium levels, weight and height between groups.</td>
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<tr>
<td>Szefer et al.37</td>
<td>Open-label, randomized, active-controlled, multicentre</td>
<td>52 weeks</td>
<td>N=395 (age: 2–8 years), mild asthma or recurrent wheezing</td>
<td>Nebulized BUD 0.5 mg o.d. (n=197) or montelukast (4 mg or 5 mg) o.d. (n=198)</td>
<td>Similar AEs between groups Most AEs were mild to moderate in intensity. Similar increases in height from baseline to end of treatment.</td>
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<td><strong>Nebulized steroids: Fluticasone</strong></td>
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<tr>
<td>Westbroek et al.38</td>
<td>Multicentre, randomized, double-blind, parallel-group</td>
<td>12 weeks</td>
<td>N=301 (age: ≥17 years), oral steroid-dependent asthma</td>
<td>Nebulized FP 2 mg (n=102) or 0.5 mg (n=103) b.i.d. or placebo (n=96)</td>
<td>Both treatments well tolerated. Oral candidiasis most commonly reported: 12% in FP 4 mg/day group, 14% in FP 1 mg/day, and 8% in placebo. Serious AEs: 14% in placebo, 9% in FP 1 mg/day, and 6% in FP 4 mg/day. Serum cortisol lower in FP 4 mg/day than FP 1 mg/ day or placebo, albeit within the normal range. No laboratory abnormalities.</td>
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<tr>
<td><strong>Nebulized bronchodilators: Formoterol</strong></td>
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<tr>
<td>Gross et al.39</td>
<td>Randomized, double-blind, double-dummy trial</td>
<td>12 weeks</td>
<td>N=351 COPD (FEV1 44% predicted)</td>
<td>20 mcg/2 ml FFIS b.i.d. or 12 mcg FF DPI b.i.d. or placebo solution or placebo DPI</td>
<td>Drug-related AEs in the FFIS arm with a frequency &gt;1% and exceeding placebo were dry mouth, nausea, and insomnia.</td>
</tr>
<tr>
<td>Nelson et al.40</td>
<td>Randomized, double-blind, double-dummy trial</td>
<td>12 weeks</td>
<td>N=351 COPD (smoking history of ≥10 pack-years)</td>
<td>20 mcg/2 ml FFIS b.i.d. or 12 mcg FF DPI b.i.d. or placebo solution or placebo DPI</td>
<td>No clinically meaningful effects of FFIS or FF DPI treatment on mean or maximum HR, ventricular premature beats, or incidence. Treatment-emergent cardiac AEs occurred in 4.1%, 3.5% and 4.4% of patients in the FFIS, FF DPI and placebo groups, respectively; withdrawals due to possible cardiac AEs occurred in 1 patient per treatment group. No deaths or serious cardiac AEs occurred during the treatment period. Mean changes from baseline in HR, PR interval, QRS complex, QT interval, and RR interval were comparable between the three treatment groups at each time point.</td>
</tr>
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Table 3: Review of studies evaluating the safety of nebulized steroids and bronchodilators

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>Donohue et al.(^{27})</td>
<td>Open-label safety extension</td>
<td>52 weeks</td>
<td>N=569 COPD</td>
<td>FFLS 20 μg b.i.d. inhalation solution or 12 μg FF DPI</td>
<td>Results of safety monitoring for AEs, laboratory values, and cardiac changes were similar between treatment groups. There were no clinically important changes from baseline in laboratory tests, including serum potassium and glucose, or vital signs and no treatment-related increases in cardiac arrhythmias, heart rate or QTc prolongation.</td>
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<td>Nebulized bronchodilators: Arformoterol</td>
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<td>Baumgartner et al(^{41})</td>
<td>Multicentre, randomized, double-blind, double-dummy, placebo- and active-controlled trial</td>
<td>12 weeks</td>
<td>N=717 (age: ≥35 years) COPD, FEV(_1) predicted ≤65% (n=143), and FEV(_1)/FVC ≤70%</td>
<td>ARF 15 mcg b.i.d. (n=141), ARF 25 mcg b.i.d. (n=143), ARF 50 mcg q.d. (n=146)</td>
<td>The AEs in the ARF groups were similar to SAL and placebo, including serious AEs and COPD AEs. Frequency of COPD exacerbations during the first 3 weeks: 6.4% in ARF 15 mcg, 6.3% in 25 mcg, and 2.1% in 50 mcg; 5.6% in SAL; and 4.9% in placebo. During the last 3 weeks, the rates were 4.0%, 5.2%, 3.2%, 3.3%, and 6.1%, respectively. Dose-related decrease in the ARF groups in potassium concentrations at week 12 ranged from -0.05 to -0.19 mEq/L at 2 hours and -0.12 to -0.18 mEq/L at 6 hours after administration; SAL ranged from -0.02 to -0.14 mEq/L and placebo ranged from 0.00 to -0.10 mEq/L, respectively. The mean increases in glucose concentrations in the ARF groups at week 12 ranged from 6.2 to 26.0 mg/dL at 2 hours and 9.1 to 18.8 mg/dL at 6 hours after administration; SAL was 14.7 and 8.0 mg/dL; and placebo was 3.8 and 4.7 mg/dL, respectively. At week 12, dose-related increases in heart rate, measured 2 hours after study drug administration, were found with increasing doses of ARF (range, 1.2–3.5 bpm); SAL (2.1 bpm); and, placebo (0.6 bpm). Cardiovascular AEs: chest pain (ARF: 3.4–6.6%; placebo: 6.6%), palpitation (ARF: 0–1.4%; placebo: 1.0%), and tachycardia (ARF: 0.3–1.0%; placebo: 1.4%). Increases in the beta-mediated events such as tremor, nervousness, and insomnia occurred with increasing doses of ARF.</td>
</tr>
<tr>
<td>Donohue et al(^{28})</td>
<td>Multicentre, double-blind, randomized, placebo-controlled study</td>
<td>52 weeks</td>
<td>N=841 (age: ≥40 years) moderate-to-severe COPD, 15 pack-year smoking history, baseline mMRC ≥2</td>
<td>ARF (15 mcg) (n=420) or placebo (n=421) b.i.d. via nebulization</td>
<td>Risk of cardiovascular AEs was low. No meaningful difference in mean pre-dose glucose and potassium serum concentrations; change in ventricular heart rate at 2 hours post-dose</td>
</tr>
<tr>
<td>Hanania et al(^{42})</td>
<td>Double-blind, double-dummy, multicentre, randomized, parallel-group, active-controlled</td>
<td>26 weeks</td>
<td>N=444 (age: ≥35 years), physician-diagnosed COPD</td>
<td>Nebulized ARF 15 mcg (n=149) or nebulized ARF 25 mcg (n=147) or FF DPI 12 mcg (n=147) b.i.d.</td>
<td>Occurrence of dizziness, tremor, nervousness, insomnia, and paraesthesia was low. No meaningful difference in mean pre-dose glucose and potassium serum concentrations; change in ventricular heart rate at 2 hours post-dose</td>
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<tr>
<td>Nebulized bronchodilators: Combination</td>
<td>Randomized, double-blind, parallel-group, multicentre</td>
<td>~12 weeks</td>
<td>moderate-to-severe COPD</td>
<td>Nebulized SAL 3.0 mg (n=216) or IB 0.5 mg (n=214) or combination (n=222)</td>
<td>Up to 56.8% in the combination therapy group, 52.3% in the IB group, and 57.4% in the SAL group had at least one AE. Worsening of lower respiratory tract symptoms was the most frequently reported event in all three groups. Upper respiratory tract events were also common. Also, 24 patients in the combination group, 17 in the IB group, and 24 in the SAL group possibly had drug-related AEs.</td>
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</table>

BDP=beclomethasone propionate; FP=fluticasone propionate; BUD=budesonide; ICS=inhaled corticosteroids; FF=formoterol fumarate; FFIS=formoterol fumarate inhalation solution; mMRC=modified Medical Research Council; ARF=arformoterol; SAL=salmeterol; IB=Ipratropium bromide

Q11. Can home nebulization be prescribed in other chronic respiratory diseases?

Establishing a strong and participative doctor-patient relationship may help to identify and ensure adherence to maintenance nebulization. However, it is not clear as to whether nebulized antibiotics have also been studied in bronchiectasis. Nebulizers have been used for a fairly long time to deliver drugs to patients with respiratory disease. The benefits and drawbacks of antibiotic nebulization have been compared with traditional oral antibiotic delivery. Various factors should be considered in deciding whether to prescribe home nebulization. Factors include the disease severity, the duration of treatment, the likelihood of adherence, the effectiveness of the treatment, and the possibility of reintroducing handheld inhalers.

Although nebulization is used for the administration of antibiotics in other chronic respiratory diseases such as cystic fibrosis, the prescriber has to be careful about the associated risk of antibiotic resistance. With active research going on in the field of more efficient, portable, and patient-friendly nebulizers, the future of nebulization looks interesting.

Recommendation

1. Maintenance treatment in OADs with nebulization at home can be referred to as ‘maintenance nebulization’ rather than ‘home nebulization’ to specifically imply chronic use.
2. Patients must be carefully screened before prescription. The minimum duration of nebulization therapy that can be prescribed in a patient with OAD is 3 weeks. However, no recommendation can be made on the maximum duration of therapy. The decision to end/continue maintenance nebulization lies with the prescribing physician after taking into account the subjective and objective improvement along with the possibility of reintroducing handheld inhalers.
3. The minimum duration of maintenance therapy that can be prescribed in a patient with OAD is 3 weeks. However, no recommendation can be made on the maximum duration of therapy. The decision to end/continue maintenance nebulization lies with the prescribing physician after taking into account the subjective and objective improvement along with the possibility of reintroducing handheld inhalers.

Summary of the Recommendations

1. Maintenance treatment in OADs with nebulization at home can be referred to as ‘maintenance nebulization’ rather than ‘home nebulization’ to specifically imply chronic use.
2. Patients must be carefully screened before prescription. The minimum duration of nebulization therapy that can be prescribed in a patient with OAD is 3 weeks. However, no recommendation can be made on the maximum duration of therapy. The decision to end/continue maintenance nebulization lies with the prescribing physician after taking into account the subjective and objective improvement along with the possibility of reintroducing handheld inhalers.
3. The minimum duration of maintenance therapy that can be prescribed in a patient with OAD is 3 weeks. However, no recommendation can be made on the maximum duration of therapy. The decision to end/continue maintenance nebulization lies with the prescribing physician after taking into account the subjective and objective improvement along with the possibility of reintroducing handheld inhalers.

Recommendation

1. Establishing a strong and participative doctor-patient relationship may help to identify and ensure adherence to maintenance nebulization. However, we believe that the best way to ensure adherence is to establish a strong and participative doctor-patient relationship.
2. Patients must be carefully screened before prescription. The minimum duration of maintenance therapy that can be prescribed in a patient with OAD is 3 weeks. However, no recommendation can be made on the maximum duration of therapy. The decision to end/continue maintenance nebulization lies with the prescribing physician after taking into account the subjective and objective improvement along with the possibility of reintroducing handheld inhalers.
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Although nebulization is used for the administration of antibiotics in other chronic respiratory diseases such as cystic fibrosis, the prescriber has to be careful about the associated risk of antibiotic resistance. With active research going on in the field of more efficient, portable, and patient-friendly nebulizers, the future of nebulization looks interesting.

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Although nebulization is used for the administration of antibiotics in other chronic respiratory diseases such as cystic fibrosis, the prescriber has to be careful about the associated risk of antibiotic resistance.
Table 4: The safety check list

Safety measures for equipment used
1. Checking the filter: Filter should be checked every month as a routine. Blackening of the filter should be reported to the manufacturer and blackened filter should be changed immediately.
2. Every 6-12 months filter should be changed routinely [or as suggested by the information brochure provided by the manufacturer].
3. No liquids, even for cleaning purposes should be applied to compressor.

Safety of Accessories
- Safety in regard to nebulizer accessories is for microbiological perspective (Infection/Contamination).
- The tubing and the nebulizer chamber should be replaced every 4-6 weeks. They should be cleaned on a daily basis (see cleaning section).
- If a patient develops an LRTI and has a sputum test which shows a positive culture, it would be prudent to do swabs for culture from the nebulizer and the accessories.

Safety of common drugs used in home nebulization
Safety precautions for Long Acting β2 Agonist (LABA), Short Acting β2 Agonist (SABA), Short Acting Anti-muscarinic (SAMA)
- A baseline Echocardiogram (ECG) should be recorded for all patients initiating Home Nebulization.
- Any baseline ECG abnormality should be investigated further. Ideally with a cardiology consultation.
- Any prolongation of QT interval should preclude the use of LABA & SABA.
- A baseline K+ (Potassium) level should be checked in patients receiving Salbutamol or Levosalbutamol.
- K+ level should be rechecked at the end of one month and again at 3 months in patient on long term Home Nebulization.
- Patients complaining of intermittent palpitation should be advised to undergo ECG and if normal a 24 hours Holter monitoring should be performed.
- Inspection of the oral cavity and oropharynx should be done regularly in patients on nebulized steroids to check for fungal (Candida) infection.
- Regular stringent mouth washing and cleaning of nebulizer & accessories daily should be advocated at each contact by a trained health personnel.

Table 5: General instructions for cleaning and maintenance of different nebulizers

<table>
<thead>
<tr>
<th>Jet nebulizers</th>
<th>Ultrasonic nebulizers</th>
<th>Mesh nebulizers</th>
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<tbody>
<tr>
<td>Wash all accessories except the tubing in warm water/mild detergent solution. Rinse with warm water to remove detergent residue and leave to air-dry. Wipe the outer surface of the tubing and the compressor with a clean cloth. If there is some water in the tubing, connect it to the compressor and blow air through the tubing for a few seconds. Change the air filter as soon as it changes colour.</td>
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<tr>
<td>Wash all the accessories such as mouthpiece/mask, extension tube, medication cap and air filter with a mild detergent or a commercially available disinfectant. Wipe the main body with a damp, soft cloth.</td>
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<tr>
<td>Medication container, mesh cap, mask adapter and mouthpiece/mask should be washed in warm soapy solution and later left to air-dry. Do not touch/remove the mesh cap. The remaining medication in the mesh holes can be removed by nebulizing clean water after re-assembling the unit. Wipe the main unit with a clean cloth.</td>
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</table>

5. To ascertain the long-term safety in patients with OAD, especially those with complicating comorbidities such as CVDs and diabetes, it is recommended to perform a regular review (at least annually).

6. Patients should be educated on the cleaning and maintenance of nebulizers, and an occasional review of the nebulizer should be performed by the prescribing physician. Patients should be advised to clean the nebulizer accessories at least once a day.

7. Patients (especially those with COPD) should not be prescribed maintenance nebulization with oxygen-driven jet nebulizers because of the risk of carbon dioxide retention, especially with bronchodilators.

8. Initial follow-up should be performed 1 month after the start of maintenance nebulization and, later, at least annually.

9. Success of maintenance nebulization should be assessed on, i) effectiveness of the treatment (objective and subjective); ii) adherence to treatment; iii) need for continuing maintenance nebulization; iv) Adverse effect of home nebulization; and v) the possibility of reintroducing handheld inhalers.

10. Establishing a strong and participative doctor-patient relationship may help to identify and ensure adherence to maintenance nebulization.

11. Although nebulization is used for the administration of antibiotics for other chronic respiratory diseases such as cystic fibrosis, the prescriber has to be careful about the associated risk of antibiotic resistance.

Conclusion

Maintenance nebulization for OADs is and should be considered as an alternative for drug administration and not as a substitute for handheld inhaler devices. These recommendations should be viewed as a reference and not as guidelines for prescribing maintenance nebulization. There is a definite need for more evidence on the long-term safety of maintenance nebulization in patients with OADs.
Acknowledgements

We thank Cipla Ltd. for the unrestricted educational grant and logistical support provided for the consensus meeting.

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