

Nebulisers: their effectiveness, indications and limitations

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The authors describe the indications and adverse effects of nebulisers and show how careful assessment can identify those patients who will benefit.

Figure 1. Mouthpieces are recommended for nebulisation of steroids and anticholinergics to prevent deposition of these agents on the skin or in the eyes

Nebulisers are devices used to deliver atomised particles of drug to the airways. Atomisation is achieved using either a pressurised gas source (jet nebuliser) or ultrasonic energy (ultrasonic nebuliser). Nebulisers are in common use for a wide range of respiratory conditions.

How nebulisers work

In a jet nebuliser (see Figure 2) a compressor or pressurised gas source generates air or gas that is forced through a narrow hole (venturi) as a high-velocity jet. An area of low pressure occurs immediately

adjacent to this jet that passes over a narrow liquid feed tube. Drug solution is sucked up from a reservoir below the feed tube and atomisation of the solution ensues.¹ The jet, now composed of pressurised gas and atomised solution, impacts on an obstruction known as a baffle; this action generates smaller respirable particles while larger ones fall back into the reservoir of liquid to be reatomised.

Ultrasonic nebulisers (see Figure 3) use a power source to rapidly vibrate an electrically polarised (piezoelectric) crystal within a reservoir of drug solution

or suspension. Standing waves are formed on the surface of the liquid. Small droplets break free from these waves and are released as an aerosol. Ultrasonic nebulisers are more expensive and less able to aerosolise the more viscous drug suspensions. They are, however, faster and maintain a more constant aerosol drug concentration than their jet counterparts.

The size of respirable particles generated by a nebuliser is important, as particles that are too large ($>5\mu\text{m}$) may be deposited in the upper airway and subsequently swallowed, whereas particles that

are too small ($<0.5\mu\text{m}$) may be exhaled without depositing in the lung at all. Nebuliser design is critical to the generation of particles of respirable size. Comparison of available nebulisers confirms that not all are equal either in the time taken to complete nebulisation or in efficacy of lung deposition.²

Choice of nebuliser

A list of available nebulisers and their costs is provided in the *BNF*. Choice must take into consideration effective matching of chamber and compressor, cost, ease of use and ease of maintenance. Currently there are no national recommendations for choice of nebuliser but advice can be sought from the local hospital respiratory

team. Nebulisers are available from a number of major medical suppliers and pharmacies, or can be bought via the internet at very competitive prices.

Unlike the units commonly used in hospitals and driven from cylinder air or wall oxygen, those used in the community are lightweight, portable units with their own integral compressor or ultrasonic device. Most require mains electricity as the power source, but some can be powered from batteries including plug-in adaptors for (ironically) car cigarette lighter sockets.

Nebulised drug can be administered either through a mouthpiece (see Figure 1) or mask, and both are considered to be equally

effective. Face-masks are preferred for infants, young children and in emergency scenarios for ease of use. Mouthpieces are recommended for nebulisation of steroids and anticholinergics to prevent deposition of these agents on the skin or in the eyes where the latter has been linked with exacerbation of glaucoma.

For a standard nebuliser, only about 10 per cent of aerosolised drug may reach the lungs. Metered-dose inhalers and dry powder inhalers are comparable with nebulisers in terms of particle sizes and deposition rates when used optimally. Unlike nebulisers, however, inhaler devices are effort-dependent, and poor technique can render them ineffective. In

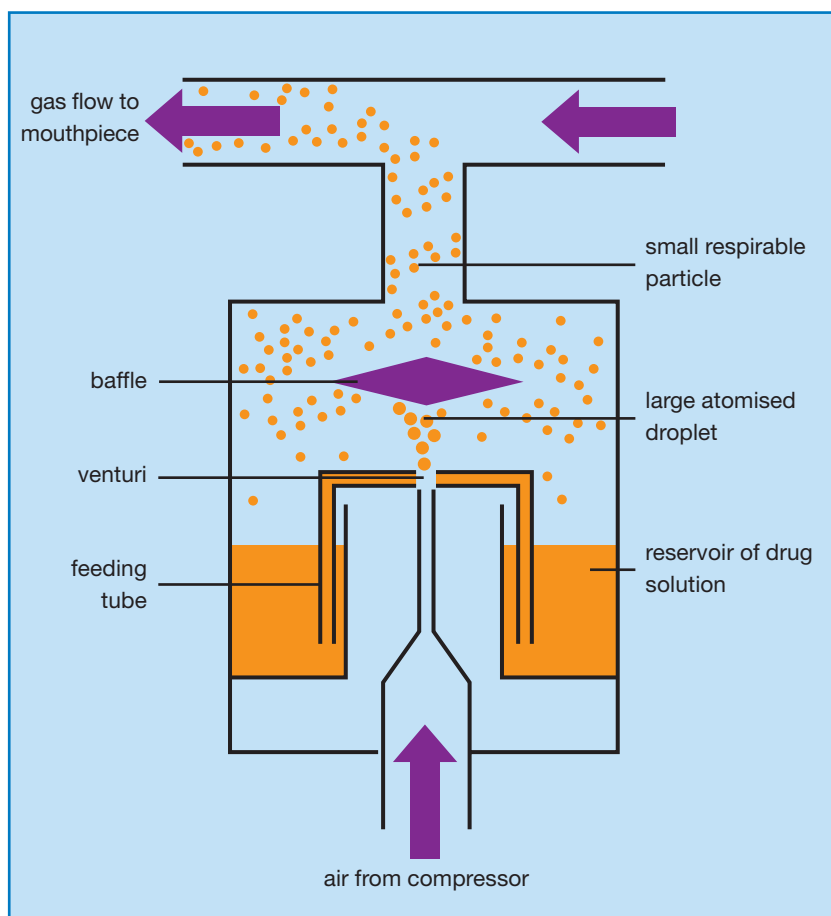


Figure 2. Jet nebuliser design. Compressed air or pressurised gas is forced through a narrow hole (venturi). Negative pressure adjacent to this fast-flowing jet sucks liquid up from a reservoir into the jet via feeding tubes. The liquid is atomised into large particles that impact on a baffle to generate smaller respirable particles

circumstances when inhalers cannot be used effectively, nebulisers can deliver guaranteed larger doses of drug to the lungs.

Indications for nebulisers

Nebulisers can be used to administer a number of drugs for specific conditions, as listed in Table 1. The only categorical indications for nebuliser use are when the drug needed is not available in any other form or when the patient is unable to use alternative delivery devices, *eg* some children and older patients, and in emergency department patients *in extremis*. Relative indications are when large volumes of drug need to be delivered or when convenience dictates.

The evidence for the beneficial use of nebulisers in other settings is extremely limited. Even within the emergency room, where nebulisers are routinely used to deliver large doses of bronchodilators, there is no benefit compared to similar doses delivered via spacer devices in terms of hospital admission rates and time to discharge.³

It remains conventional practice to administer bronchodilators via nebuliser to extremely ill patients who may not be able to easily use a spacer device and where equal dose delivery may be impractical. To deliver an equivalent amount of nebulised salbutamol (5mg) would require 50

separate actuations of a 100µg metered-dose inhaler.

There is some limited evidence to suggest that corticosteroids might be more effective in chronic asthma or chronic obstructive pulmonary disease (COPD) when administered via nebuliser. In one study in patients with asthma, budesonide (Pulmicort) given by jet nebuliser was associated with increased peak expiratory flow rate, reduced symptom scores, and reduced use of rescue beta-agonists compared to inhaler and spacer.⁴

In a separate retrospective cohort study of 2178 patients with asthma or COPD who were over 50 years of age, administration of steroids via nebuliser was associated with less visits to the emergency department and less use of systemic steroids than the period prior to their use.⁵

A Cochrane review of the evidence in asthma, however, concludes there is insufficient evidence to make a recommendation for use of nebulised steroids,⁴ and no evidence for benefit with nebulised beta-agonists in either acute³ or chronic asthma.⁶

The more justifiable use of nebulisers may be in the administration of drugs that cannot otherwise be delivered directly to the lungs. For example, nebulisers are employed to administer mucolytic and antimicrobial agents in bronchiectasis and cystic fibrosis. In this setting, they are particularly useful in being able to administer large volumes of drug, and to aerosolise agents that are often in viscous solutions.

Nebulised hypertonic saline has been shown to improve mucociliary clearance and lung function in patients with cystic fibrosis.⁷ Nebulised antibiotics are useful in reducing exacerbation rates in both patients with cystic fibrosis

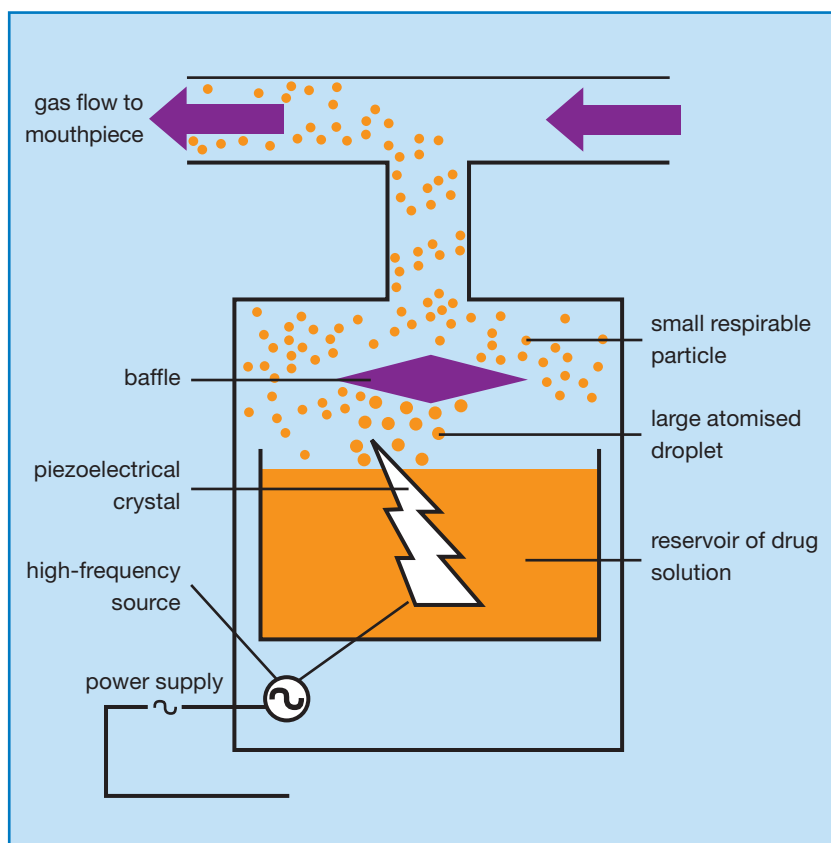


Figure 3. Ultrasonic nebuliser design. A power supply is used to drive a high frequency source that vibrates a piezoelectrical crystal within a reservoir of liquid. Large droplets break free from standing waves that form on the surface of the liquid, and these impact on a baffle to create smaller respirable particles

and those with bronchiectasis colonised with *Pseudomonas*.⁸ Nebulised recombinant human DNase/dornase alpha (Pulmozyme) breaks down DNA in viscid sputum and is used to improve sputum clearance and pulmonary function in both conditions.

For patients with HIV, nebulised pentamidine (Pentacarinat) may be effective as secondary prophylaxis against *Pneumocystis* pneumonia.⁹ It is, however, less effective than oral co-trimoxazole, with higher relapse rates mainly in the relatively poorly ventilated upper lobes. Nebulised hypertonic saline helps provide deep cough-induced sputum for the diagnosis of *Pneumocystis*.

Nebulised morphine has been utilised to palliate breathlessness

in terminally ill patients with lung cancer, COPD and interstitial lung disease. Similarly, nebulised local anaesthetics such as lidocaine have been used to palliate dyspnoea and cough. The evidence for effectiveness is poor outside of a few trials in cancer patients, and a recent Cochrane review concluded that there was little benefit of nebulised morphine on the perception of dyspnoea associated with severe interstitial lung disease.¹⁰

Nebuliser assessment

The decision to consider nebulised therapy in primary care is most likely to occur within the context of COPD and occasionally chronic severe asthma. The National Institute for Health and Clinical

Excellence (NICE) guideline concerning management of COPD¹¹ is clear and suggests that nebulisers should only be considered in patients with distressing or disabling breathlessness despite maximal therapy.

Continued prescription of medication is only justified if its use is associated with a reduction in symptoms, an increase in the ability to undertake activities of daily living, an increase in exercise capacity, or an improvement in lung function. While the measurement of FEV₁ (forced expiratory volume over one second) is critical to the diagnosis of COPD it varies little with bronchodilator administration but sometimes functional improvement may be demonstrated with an increase in vital capacity or forced vital capacity.

The key judgement for most is the patient's perceptions of benefit, including reduced symptoms and fewer visits to their GP or hospital.¹² To best estimate any benefits or otherwise of nebulised therapy, a formal trial with recording of symptoms and functional changes, together with lung function, is advised.

An example of a nebuliser trial for bronchodilator therapy is shown in Table 2. Peak flow readings are measured twice daily (with additional spirometry at the start and end of the trial in COPD patients) over four weeks. During the first week bronchodilators are administered via inhaler plus large volume spacer. During the subsequent three weeks, different combinations of bronchodilator are used via nebuliser to identify the most effective agents.

There are no independently validated outcomes for a positive trial, so each case should be taken individually with reference to the NICE parameters above. One practical

ABBREVIATED PRESCRIBING INFORMATION

(Please consult the Summary of Product Characteristics (SPC) before prescribing.)

KEPPRA® film-coated tablets 250 mg, 500 mg, 750 mg, 1000 mg

KEPPRA® 100 mg/ml oral solution

KEPPRA® 100 mg/ml concentrate for solution for infusion

Active Ingredient: Tablets: levetiracetam 250, 500, 750 and 1,000 mg. *Oral Solution:* levetiracetam 100 mg per ml. *Infusion:* levetiracetam 100 mg per ml. **Uses:** Monotherapy for partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy. Adjunctive therapy for partial onset seizures with or without secondary generalisation in adults and children from 4 years of age and for myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. *Infusion:* an alternative for patients when oral administration is temporarily not feasible. **Dosage and Administration:** *Oral solution* should be diluted prior to use. *Infusion:* Keppra concentrate must be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15-minute infusion. **Monotherapy (adults and adolescents from 16 years):** Recommended starting dose of 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily. **Adjunctive therapy: Adults and adolescents older than 12 years or weighing 50 kg or more:** 500 mg twice daily can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks. **Elderly:** Adjustment of the dose is recommended in patients with compromised renal function. **Children aged 4 to 11 years and adolescents (12 to 17 years) of less than 50 kg:** 10 mg/kg twice daily, increased up to 30 mg/kg twice daily. Do not exceed increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used. (For full dosage recommendations see SPC.) **Patients with renal impairment:** Adjust dose according to creatinine clearance as advised in SPC. **Patients with hepatic impairment:** No dose adjustment with mild to moderate hepatic impairment. With severe hepatic impairment (creatinine clearance <70ml/min) a 50% reduction of the daily maintenance dose is recommended. **Contraindications, Warnings etc.:** **Contraindications:** Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients. **Precautions:** If discontinuing treatment reduce dose gradually as advised in SPC. Due to its excipients, the *oral solution* may cause allergic reactions (possibly delayed). *Infusion:* Keppra concentrate contains 7.196 mg of sodium per vial. To be taken into consideration by patients on a controlled sodium diet. **Interactions:** Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1,000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. **Pregnancy and lactation:** Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. **Driving, etc:** Caution recommended when performing skilled tasks, e.g. driving vehicles or operating machinery. **Adverse Effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: **Very common** (≥10%): asthenia/fatigue, somnolence. **Common** (between 1%–10%): GI disturbances, anorexia, weight increase, accidental injury, headache, dizziness, hyperkinesia, tremor, ataxia, convulsion, amnesia, balance disorder, disturbances in attention, memory impairment, emotional lability, hostility, depression, insomnia, nervousness/irritability, agitation, personality disorders, thinking abnormal, vertigo, rash, eczema, pruritus, diplopia, vision blurred, myalgia, infection, nasopharyngitis, cough increased, thrombocytopenia. Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** **Tablets:** None. **Oral solution:** Store in original container. After first opening use within 2 months. **Infusion:** Use immediately after dilution. **Legal Category:** POM. **Marketing Authorisation Numbers:** 250 mg x 60 tabs: EU/1/00/146/004. 500 mg x 60 tabs: EU/1/00/146/010. 750 mg x 60 tabs: EU/1/00/146/017. 1,000 mg x 60 tabs: EU/1/00/146/024. **Solution x 300 ml:** EU/1/146/027. **Infusion (500 mg/5 ml) x 10 vials:** EU/1/00/146/030. **NHS Cost:** 250 mg x 60 tabs: £29.70. 500 mg x 60 tabs: £52.30. 750 mg x 60 tabs: £89.10. 1,000 mg x 60 tabs: £101.10. **Solution x 300 ml:** £71.00. **Infusion (500 mg/5ml) x 10 vials:** £135.00. **Name and Address of PL Holder:** UCB S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium. **Further information is available from:** UCB Pharma Ltd., 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformationuk@ucb-group.com

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Information about adverse event reporting can be found at www.yellowcard.gov.uk Adverse events should also be reported to UCB Pharma Ltd

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Indication	Common disease setting	Nebulised drug	Drug effect
bronchial narrowing	asthma/COPD	salbutamol/terbutaline	bronchodilator
bronchial narrowing	asthma/COPD	ipratropium bromide	bronchodilator
airway inflammation	asthma/COPD	budesonide/fluticasone	anti-inflammatory
airway inflammation	asthma	cromoglicate	anti-inflammatory
viscous/retained secretions	cystic fibrosis/bronchiectasis	normal saline (0.9%)	loosens secretions
viscous/retained secretions	cystic fibrosis/bronchiectasis	hypertonic saline (3-7%)	loosens secretions
viscous/retained secretions	cystic fibrosis	DNase/dornase alpha	liquifies secretions by DNA lysis
airspace <i>Pseudomonas</i> colonisation/infection	cystic fibrosis/bronchiectasis	colistimethate sodium/tobramycin	reduces exacerbations
<i>Pneumocystis</i> pneumonia prophylaxis	HIV	pentamidine	reduces relapse rates
(terminal) dyspnoea	COPD/lung cancer	morphine	may relieve dyspnoea
(terminal) cough and dyspnoea	COPD/lung cancer	lidocaine	may relieve cough and dyspnoea

Table 1. Potential indications for nebuliser therapy

approach is for the patient to maintain a symptom diary with daily entries that may reveal a pattern of use and response, or otherwise, to

treatment. Nebuliser prescription should then only be recommended if the patient also perceives potential benefit.

Week 1	bronchodilators via inhaler plus large volume spacer
Week 2	salbutamol 5mg 4 times daily (nebuliser)
Week 3	ipratropium bromide 500mg 4 times daily (nebuliser)
Week 4	combined salbutamol and ipratropium 4 times daily (nebuliser)

Table 2. Nebuliser trial for bronchodilator therapy

Problems with nebuliser therapy

Nebulisers not only have limited beneficial effects but also some less appreciated dangers. High doses of salbutamol may cause tremor, tachycardia, hypokalaemia, hyperglycaemia, and prolongation of the QT interval that can precipitate tachyarrhythmias. Administration of bronchodilators in hypoxic patients may lead to pulmonary venous shunting and exacerbate hypoxia.¹³ Nebuliser use in acute severe asthma and COPD should therefore include simultaneous oxygen administration.

Nebulised ipratropium bromide has been linked to worsening narrow-angle glaucoma, and high-dose nebulised corticosteroids with

cataract formation and systemic steroid side-effects. The anti-pseudomonal antibiotic colistimethate sodium may cause bronchospasm and should be preceded by administration of salbutamol and initiated at a low dose.

Funding

Nebulisers can be provided by secondary-care units free to patients after specialist recommendation and this should be the usual mechanism of supply. The advent of primary-care airways clinics and general practitioners with a special interest in respiratory disease challenges primary care organisations to provide alternative supply mechanisms.

Some patients opt to buy their own nebuliser machine without

seeking guidance on the type or delivery characteristics. The costs of drugs used in nebulisers far outweigh those of the nebuliser purchase itself so should only be provided if assessment suggests benefit. While maintenance of the unit itself is relatively simple, written guidance should be provided to patients on cleaning and the need for an annual service.

Conclusions

Nebulisers are devices able to effectively deliver a variety of aerosolised drugs to the lung. They are indicated when there are no alternative delivery systems for a particular drug or when a patient is unable to use an alternative delivery system such as inhalers. Nebulisers are

most commonly used in airways disease when a larger dose of drug may be delivered more quickly.

In many, but not all, instances, however, nebulisers offer little benefit over simple inhalers and may have significant adverse consequences. Careful assessment should therefore be made of individual response to nebulised therapy to identify those few patients who will obtain meaningful benefit from long-term treatment.

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InfoPOEMs



SSRIs effective for depression after one week

Bottom Line:

Treatment of unipolar depression in adults with SSRIs significantly improves symptoms in as quickly as one week. (LOE = 1a-)

Reference:

Taylor MJ, Freemantle N, Geddes JR, *et al*. Early onset of selective serotonin reuptake inhibitor antidepressant action. *Arch Gen Psychiatry* 2006;63: 1217-23.

Study Design: Systematic review **Funding:** Industry and government **Setting:** Various (meta-analysis)

Synopsis:

Most clinicians believe that it takes two to three weeks of therapy with SSRIs before patients with depression improve. These investigators thoroughly searched multiple databases including MEDLINE, EMBASE, PsychLIT, The Cochrane Registry of Controlled Trials, reference lists of identified articles and other systematic reviews, and conference proceedings for randomised trials comparing SSRIs with placebo for the treatment of unipolar depression in adults. No language restrictions were applied. Where possible, standardised treatment effect sizes were calculated for each study at weekly intervals.

From an initial search yielding 500 citations, 50 trials comprising 6153 participants receiving SSRIs and 3968 receiving placebo met inclusion criteria. The methodologic quality of the individual trials was of moderate to high quality. Only one individual performed the search. Twenty articles provided data that could be analysed for symptom scores at multiple periods. Various methods were used to rate treatment effects. Overall, a statistically significant positive treatment effect of SSRIs compared with placebo was evident in as early as one week. In one model, the degree of improvement was greatest in the first week with a gradual decline in the magnitude of incremental benefit in later weeks. In a different model, the effect was evident in the first week, with stronger effects occurring in later weeks. No formal assessment was performed to check for publication bias or whether the results of the independent trials were homogeneous.

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