

The cost-effectiveness of domiciliary non-invasive ventilation in patients with end-stage chronic obstructive pulmonary disease: a systematic review and economic evaluation

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Scientific summary

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Scientific summary

Background

Chronic obstructive pulmonary disease (COPD) is a chronic progressive lung disease characterised by non-reversible airflow obstruction that mostly affects middle-aged or elderly people who have smoked. Treatment for COPD is based on pharmacotherapy, pulmonary rehabilitation and, in some cases, long-term oxygen therapy (LTOT), and is mainly symptomatic. Many COPD patients experience worsening of symptoms (exacerbations) on a regular basis. Exacerbations are a cause of increased morbidity, mortality and the poor quality of life (QoL) seen in COPD and place a considerable burden on the health-care system, particularly if they result in hospitalisation. Non-invasive ventilation (NIV) is a method of providing ventilatory support via a mask without an endotracheal tube. There is good evidence that patients with hypercapnic respiratory failure during an acute exacerbation will benefit from NIV in hospital; however, the evidence for its use in stable COPD patients is more limited. Suggested benefits are prevention or delay of exacerbations leading to a reduction in hospital admissions and/or increased survival and improved QoL. Previous systematic reviews have not fully considered these outcomes. In the UK, domiciliary NIV is considered on health economic grounds if a patient has had three hospital admissions with acute hypercapnic respiratory failure, although there is only sparse economic evidence to support its use. Therefore, an economic evaluation in a UK context is required. Given that the baseline risk of an exacerbation varies between patients and may affect any potential benefits from NIV, two populations were considered in this report: patients in a stable state of disease (stable population) and those immediately after a period of exacerbation-related hospitalisation (post-hospital population).

Objectives

The aims of this report were to undertake:

- i. a systematic review of randomised controlled trials (RCTs) and non-RCTs comparing domiciliary NIV with usual care, or different types of NIV, in stable/post-hospital COPD patients
- ii. an overview of existing systematic reviews of RCTs comparing domiciliary NIV with usual care, or different types of NIV, in stable/post-hospital COPD patients
- iii. a systematic review of uncontrolled studies (patients on domiciliary NIV only) with the aim of supplementing the findings from controlled studies where evidence was lacking
- iv. a systematic review of the evidence on the cost-effectiveness of domiciliary NIV compared with usual care only in COPD patients
- v. a model-based cost–utility analysis to determine the cost-effectiveness of domiciliary NIV compared with usual care in stable/post-hospital COPD patients.

Methods for the clinical effectiveness review

Studies were eligible for inclusion if they met the following criteria: they were systematic reviews, RCTs, non-randomised controlled studies or uncontrolled studies; the study population comprised adult COPD patients (with or without LTOT or hypercapnia); the intervention was any form of domiciliary NIV added to (any form of) usual care; and the comparator was usual care only or another form of NIV. There were no restrictions on outcomes but, based on the need to inform the economic model, the primary outcomes for the review were considered to be mortality, hospitalisations, exacerbations, QoL, adverse events and adherence to NIV/discontinuations. Other outcomes, such as lung function and blood gases, were considered secondary outcomes.

Bibliographic databases (including MEDLINE, EMBASE, The Cochrane Library and the clinical trials registers) were searched up to September 2014, and citation searching was undertaken. There were no language restrictions.

Study selection was performed in duplicate using predefined criteria, based on full texts where necessary. Disagreements were resolved through discussion and/or referral to a third reviewer. Reference management software was used to document the study selection process.

Risk of bias was assessed using the Cochrane risk of bias tool (for RCTs), with additional criteria considered for crossover trials. For non-randomised controlled studies, risk-of-bias assessment criteria were based on Cochrane Handbook guidelines, and adapted in consultation with the wider review team. Uncontrolled studies were not formally quality-assessed.

Data extraction was performed by one reviewer using a standardised, piloted data extraction form, with a proportion checked by a second reviewer. Data were extracted on study and population characteristics, intervention and comparator characteristics, study quality and results. Formal data extraction was not performed on uncontrolled studies.

For analysis, studies were grouped according to whether the population was stable or post hospital (post exacerbation). Random-effects meta-analysis was undertaken for mortality and some hospitalisation results, with separate analyses for each outcome, population type (stable or post hospital) and study type (RCT or non-randomised controlled). Further subgroup analyses (e.g. based on LTOT or level of hypercapnia) were not feasible. Results for exacerbations and QoL were reported narratively and for secondary outcomes were presented in forest plots without a pooled estimate. Given the small number of trials in each meta-analysis, construction of funnel plots was deemed inappropriate.

For the review of cost-effectiveness studies, economic models, trial-based economic evaluations and costing studies were eligible for inclusion. Relevant outcomes were cost-effectiveness, cost estimates, resource-utilisation estimates and quality-of-life/utility estimates. Included studies were appraised using relevant economic checklists.

A Markov decision model was developed to compare the cost-effectiveness of domiciliary NIV with usual care from a UK perspective for two scenarios (stable and post-hospital populations). This is the first economic model evaluating domiciliary NIV in COPD and potentially the first to differentiate between COPD populations by proximity to a recent exacerbation requiring hospitalisation. The model was structured to consider the short-term increased risk of readmission and subsequent mortality after a hospital admission and the long-term natural history of the disease. The model had a time cycle of 1 month and a lifetime time horizon. All costs and outcomes were considered from a UK NHS perspective for a price year of 2012. Where possible, data to inform the model were taken from the systematic review of clinical effectiveness. Other sources included previously published audit and cohort study data.

Clinical effectiveness results

A total of 31 controlled studies (21 randomised and 10 non-randomised) were identified, on which the main findings were based. Sixty-five uncontrolled studies met the inclusion criteria and were used to supplement data from controlled studies where appropriate. Seven relevant systematic reviews were identified.

For the stable population, there was a moderate amount of evidence to suggest no difference between domiciliary NIV and usual care in terms of survival (up to 24 months' follow-up). There appeared to be a trend towards fewer hospital admissions/days in hospital with NIV in studies reporting this outcome, but this difference was not statistically significant. There was little evidence on exacerbations (not leading to

hospitalisations) and no significant differences were found. For QoL, there appeared to be a trend favouring NIV, but a consistent benefit could not be demonstrated and there was heterogeneity in reporting tools and time points. There was some evidence to suggest a benefit from NIV for improving blood gases (based on mainly unadjusted results) but clinical significance of this potential improvement remains uncertain.

There was less evidence overall for the post-hospital population, and no benefit was evident in terms of survival from RCTs, although non-randomised controlled studies found a statistically significant difference in favour of NIV. Findings for hospital admissions were inconsistent, with one trial finding a statistically significant difference in favour of NIV, one marginally favouring NIV and the largest trial marginally favouring usual care; these findings may be suggestive of population differences but it is not possible to confirm this based on the current data. Quality-of-life data were reported in only one RCT for a post-hospital population, and there were no differences between NIV and usual care. Limited data (from two trials) suggested a potential benefit from NIV in terms of reduction in partial pressure of carbon dioxide in the arterial blood (P_{aCO_2}).

No further subgroup analysis (beyond study design and population) was possible given the small number of trials, the lack of reporting of relevant characteristics and other potential sources of heterogeneity within and between studies. Exploratory analyses suggested a trend towards a correlation between changes in CO_2 and hospital admissions. Such a potential correlation was not observed for mortality. However, the analysis uses aggregate data for change in CO_2 and also for mean difference in hospital admissions, and a causal association therefore cannot be inferred even if there is potential biological plausibility. Further, this was a post-hoc analysis, which is subject to a number of limitations. It does suggest that there needs to be further investigation of the association between CO_2 and clinical outcomes, such as hospital admissions.

There was a lack of reporting of some details relevant to study quality, particularly regarding handling of missing data. Only three RCTs included a 'sham NIV' arm, a lack of which may have led to performance bias and/or bias in patient-reported QoL. The non-randomised studies were more prone to bias overall.

Three small, short-term RCTs comparing different NIV settings were included. No conclusions could be drawn regarding potential differences in QoL. One study found a statistically significant result in favour of higher pressure for reduction of P_{aCO_2} .

Adverse events were inconsistently reported but were in line with those known to affect NIV patients (e.g. mask discomfort, pressure experienced as too high, inability to sleep, etc.) and generally not serious. There was only one potentially more serious adverse event (reported across all studies), which was a suspected barotrauma.

Systematic review of cost-effectiveness

Two cost analyses suggesting that domiciliary NIV may be cost-neutral or cost-saving were identified. However, neither study conducted a full cost-effectiveness analysis. There was, therefore, a need for a de novo model to estimate lifetime cost-effectiveness of domiciliary NIV in a UK COPD population.

Results of economic evaluation

Base-case results for the stable population suggest that domiciliary NIV may be cost-effective at a threshold of £30,000 per quality-adjusted life-year (QALY) gained, with an incremental cost-effectiveness ratio (ICER) of £28,162 per QALY gained. Probabilistic sensitivity analysis suggested that domiciliary NIV had a 55% probability of being cost-effective at the above threshold, demonstrating the uncertainty around the

impact of domiciliary NIV on hospital admission in this population. The effectiveness estimate for a reduction in hospital admissions applied was not statistically significant. Key drivers of the model were clinical effectiveness (hospital admissions and utility), duration of effect and elements of the cost of domiciliary NIV provision. NIV was found to be more cost-effective (approaching an ICER of £20,000 per QALY gained) when the benefits were assumed to last a lifetime, but there is currently no clinical evidence to support this. Speculative modelling found that, for NIV to be cost-effective in the stable population, there would need to be a 24% (or greater) reduction in the rate of hospital admissions per patient per year with NIV or an increased utility score of 2.5%. The population expected value of perfect information (EVPI) was £596M, which reflects the value of removing all uncertainty regarding the decision to adopt domiciliary NIV at a willingness-to-pay threshold of £30,000 per QALY gained. This value is high because of the large population potentially affected by this decision and should be considered indicative owing to uncertainties regarding the prevalence of COPD and the proportion considered end-stage and stable.

For the post-hospital population, cost-effectiveness findings reflected the disparity of effectiveness findings from the three available RCTs. As pooling of effectiveness results was not appropriate, base cases were generated incorporating the individual effectiveness estimates from the three RCTs. Results ranged from usual care being dominant to ICERs below £10,000 per QALY gained, depending on the base case. The probabilities of NIV being cost-effective at a threshold of £20,000 per QALY gained were 0%, 72% and 100% for the three base cases. Speculative modelling found that, for NIV to be cost-effective in the post-hospital population, there would need to be a 15% (or greater) reduction in the rate of hospital admissions per patient per year with NIV. The results from the EVPI conducted for each case also gave very mixed values for perfect information to inform the decision to offer domiciliary NIV to this population.

In both stable and post-hospital populations, the model was sensitive to risk of admission and death. This highlights the importance of collecting more robust data on patient characteristics that determine these risks.

The model results must be viewed as speculative because of the uncertainty around effect estimates and some parameter inputs, a lack of long-term data and a lack of quality-of-life/utility data.

Conclusions

Overall, the evidence from RCTs could not consistently demonstrate a benefit from NIV compared with usual care in either stable or post-hospital populations, although there was a trend towards fewer hospital admissions and, to a lesser extent, towards improved QoL for the stable population. A benefit in terms of survival for the post-hospital population was shown in non-randomised controlled studies only, and the findings for hospital admissions (from RCTs) were inconsistent.

There was also too little evidence to draw any conclusions on the potential benefits of higher-pressure NIV settings. In line with the clinical findings, a speculative economic model found that NIV may be cost-effective in a stable population at a threshold of £30,000 per QALY gained, but this is associated with a large amount of uncertainty. It is not possible to draw any overall conclusions regarding cost-effectiveness in a post-hospital population, as the results based on three different base cases are too disparate and are also based on limited evidence. It is likely that the broad categorisation into stable and post-hospital patients has not been able to capture more subtle differences between patients, who may derive more or less benefit from NIV. The findings of the report based on aggregate study-level (RCT) data are sensitive to the emergence of future study data. Further evidence, potentially from currently ongoing trials but more probably from individual patient data (IPD) analyses, is required to determine whether or not there are any other patient characteristics or equipment settings that are predictive of a benefit of NIV and to establish optimum time points for starting (and potentially discontinuing) NIV.

Recommendations for future research

A number of currently ongoing studies may add to the evidence base. The results from this report will need to be re-examined in the light of any new trial results, particularly in terms of reducing the uncertainty in the economic model. Given this, recommendations for additional RCTs would be premature, but any new RCTs should consider including a sham NIV arm and/or a higher- and lower-pressure arm in order to evaluate effects of different settings. An appropriately conducted IPD analysis of all study data may be more useful in informing some of the outstanding questions about the type of patient who might benefit most from NIV. The feasibility of IPD to examine potential effect modifiers should be explored but will be dependent on sufficiently high event rates and availability of information on effect modifiers for all patients.

Study registration

This study is registered as PROSPERO CRD42012003286.

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