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Optimising the non-invasive ventilation pathway for patients with amyotrophic lateral sclerosis/motor neuron disease: A systematic review

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Abstract

Objective: To systematically review quantitative and qualitative literature on optimal provision of non-invasive ventilation for patients with amyotrophic lateral sclerosis/motor neuron disease.

Methods: A systematic search of electronic databases, together with supplementary search methods was used to identify relevant literature from the last 20 years. Studies of any empirical design with an English abstract were eligible for inclusion. Data from documents meeting our criteria were extracted and synthesised using narrative and thematic synthesis. A patient pathway of care model was used to integrate data and provide a process perspective to the findings.

Results: While the importance of individualising care was highlighted, factors optimising use for all patients include: specialised multi-disciplinary team service provision; determining need using respiratory function tests in addition to symptom report; providing adequate information for patients and their family; paying attention to the role of carers in decision-making; adequately managing secretions; considering the most advantageous place of initiation; optimising the interface, machine mode and settings for patient comfort and effectiveness; providing supportive interventions where appropriate; regular monitoring and adjustment of settings; and providing opportunities for ongoing discussion of patient wishes.

Conclusions: Optimising use of NIV in people with motor neuron disease requires consideration of multiple factors as part of a process throughout the patient pathway. Current guidelines predominantly focus on the initiation of NIV and may underplay psychosocial factors. We have made evidence-based recommendations for each step in the pathway, which may help improve optimal uptake, usage, quality of life, and survival outcomes in patients with MND.

Keywords: Motor neuron disease; amyotrophic lateral sclerosis, non-invasive ventilation; systematic review; respiratory failure

Introduction

Non-invasive ventilation (NIV) is known to improve quality of life (QOL) and survival in patients with amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND) (1). Usage of NIV to alleviate symptoms is becoming commonplace, with a documented 2.6-fold increase in the number of patients referred for NIV, and 3.4-fold increase in patients using, NIV, between 2000 and 2012 (2). Authors of a recent study (3) concluded that use of NIV can extend life by a factor of 2.25 compared to no intervention in ALS patients. They also highlighted that if usage of NIV is “optimised”, that this could further extend life by a factor of up to 2 compared to a standard NIV protocol (3).

Not all patients become successfully established on NIV, with studies reporting varying rates of tolerance. Typical rates described are around 28% of patients not achieving at least four hours of usage (4). Oliver and Turner (5) highlighted that use or non-use of NIV was one of many decisions to be faced by an individual ALS patient on their journey of care. Authors have called for the removal of potential obstacles to use of NIV for ALS patients (6), and there have been demands for a greater understanding of the personal and socio-economic factors which determine access (7).

In order to increase understanding of optimal NIV provision, we conducted a systematic review to identify available research evidence from the last 20 years. We aimed to summarise the evidence on factors influencing optimal use of NIV in people with ALS/MND, at different stages of the patient journey from initial decision-making, initiation, and establishing use, to ongoing management, and end of life choices.

Materials and methods

The review protocol was registered with PROSPERO: CRD42018094394. Table 1 details the inclusion criteria.

Insert Table 1 around here

Relevant literature was identified via a systematic search of key health, medical and social care databases (see Table 2). Search terms included a combination of MeSH subject headings and free-text terms and were recorded in detail as per PRISMA guidelines (8). We also searched reference lists and reviews, and accessed websites of relevant organisations.

Insert Table 2 around here

Retrieved citations were uploaded to EndNote (Version 7), with title and abstracts independently screened by two reviewers. Full copies of potentially relevant citations were retrieved, and documents excluded were noted (supplementary material). Studies meeting

the inclusion criteria were read in full and data from each were systematically extracted by one reviewer and checked by a second.

Assessment of risk of bias

Appraisal of study quality was based on the established hierarchy of study design, together with use of checklists for each design type (9). [See Supplementary Material 1. Study appraisal checklists.](#)

Methods of synthesis

Due to heterogeneity meta-analysis was not appropriate. Therefore narrative synthesis and thematic synthesis (10) were used to analyse and compare quantitative and qualitative data. A conceptual pathway model (11) provided a process perspective to the findings (12).

Results

We included 193 documents in the review, representing 129 unique studies. Figure 1 illustrates the process of study selection. For papers excluded at full document screening [see Supplementary Material 2. List of studies excluded at full paper screening.](#)

Insert Figure 1 around here

The largest proportion of studies were of quantitative or mixed-method design. Included studies originated from a wide range of countries, although much of the qualitative literature was from the UK (Figure 2). Only six studies reported in 11 documents were of comparative design (Figure 3).

Insert Figure 2 and Figure 3 around here

In a mixed-method approach, rather than separating the quantitative and qualitative data into separate sections, we have integrated and drawn upon findings from each, to synthesise and summarise key evidence relating to each step of the NIV pathway: (i) the decision to trial NIV; (ii) initiation; (iii) ongoing usage; and (iv) withdrawal (Figure 4). For full details of each study [see Supplementary Material 3. Individual study extractions.](#)

Insert Figure 4 around here

i) Decision to trial NIV

Studies highlighted the influence of service delivery model on patient access to NIV. Specialised multidisciplinary units increase referrals and usage (6, 13-17). Integrated services facilitate comprehensive assessment, particularly joint palliative and respiratory

clinics (18, 19). Having a respiratory therapist on a team increases patient access to NIV, numbers trialling it, and achieving at least four hours usage (20, 21).

Assessment of need

Patient symptoms alone were not recommended as the basis for NIV trial, given the considerable variation in clinician assessment of NIV need based on symptoms (22, 23). The literature discussed the use of a range of respiratory function tests, although there was no clear evidence regarding which might be of most value. Regular assessment of forced vital capacity (FVC) was recommended to predict declining lung function (24). While established guidelines (13, 14, 25) recommend that a FVC or vital capacity (VC) of less than 50% of predicted value, or a FVC or VC less than 80% of predicted value plus any symptoms or signs of respiratory impairment (particularly orthopnoea), are criteria for NIV consideration, the literature contained criticism of these recommendations. Concerns included: their application to patients with bulbar symptoms; the threshold value set; the method of testing; and the association between FVC and other symptoms (26).

Other assessments such as nocturnal oximetry were suggested as being useful, and potentially more sensitive than FVC measurement (13-15, 26-30). Sniff nasal inspiratory pressure (SNIP) and maximal inspiratory pressure (MIP) were also reported as valuable to monitor early respiratory insufficiency (28-32). Although, it was highlighted that SNIP assessment may not be accurate for those with significant bulbar involvement (13-15). Another paper echoed the potential limitations of FVC measurement, suggesting that MIP (together with nocturnal oximetry) may have greater sensitivity than FVC (33).

There was a lack of consensus in the literature regarding the use of polysomnography. Some authors reported it to be a useful method of assessment (34-36) particularly where spirometry cannot be performed.(37) Other reports in contrast found it to be frequently inconclusive (38). Home based unattended sleep study using peripheral arterial tonometry was suggested as valuable by one team, as it incurred only small cost and was found to increase identification of need for NIV (39-41). A further study recommended transcutaneous carbon dioxide monitoring as a useful clinical tool for detecting respiratory failure (42, 43).

While assessment of diaphragmatic function was recommended as important in several good quality studies (13-15, 44-47), the relevance of this tool in clinical practice was questioned (48). One study reported concerning findings, by identifying preserved diaphragmatic function in patients who had established respiratory insufficiency (28-30).

Timing of NIV

While there was no clear evidence regarding the optimal timing of NIV (13-15), the literature emphasised that early timely referral is important and many patients are referred too late (49-52). Optimal timing of NIV is important, as late initiation may be associated with reduced compliance (22, 53), reduced survival, shorter ALS duration and worse ventilator capacity/arterial blood gas values (24, 54).

Authors suggested that discussion about NIV should begin shortly after diagnosis (55, 56). They emphasised that discussion should not be rushed (57), but should occur as "a process" including end of life considerations (58), with re-discussion taking place every six months (13-15).

The literature emphasised that optimal timing can vary for each patient (59). For some, initiating NIV can be perceived as the start of decline, death, and a threat to the self (60, 61). In contrast, for other patients starting NIV can signal hope for the future (60-63). Authors highlighted that discussion should take into account that patients might focus on the current position, while carers and health care professionals prefer to plan for the future (64, 65).

Patient and carer-related factors

Severity of bulbar symptoms was recognised to be a challenge to successful usage (66, 67), and to gaining maximal survival benefit from NIV (68, 69). However, not all studies found bulbar symptoms to be an obstacle to NIV initiation, and bulbar patients could still have significant increases in survival (3). Authors recommended that bulbar patients should be given a trial of NIV (70, 71-75) although enhanced care, and intensive monitoring may be required (67, 76, 77). Cognitive impairment was highlighted as a potential challenge (66).

Authors highlighted that carer/family roles in decision-making are important to consider, as there is potential for differing attitudes to NIV (65, 72, 73, 78, 79). Patients may fear becoming a burden to their family (64), or could reject NIV in order to maintain their identity and independence (59, 62, 64). Patient autonomy in decision-making was recognised to be important (65) and health professionals should take care to avoid leaving patients with "no choice" regarding NIV (60, 61, 80).

Information provision

Studies reported evidence that there could be limited understanding regarding the effects of NIV amongst patients and carers (55, 56). There were reports of NIV being initiated without clear information and discussion beforehand with patients and carers (58, 81). Studies described how an absence of information could lead to a lack of informed decision-making (59, 64, 82). There were recommendations of training programmes for family and caregivers to increase adherence and tolerance (83). Patient information sessions were also suggested

to reduce uncertainty in decision-making (84). Authors particularly highlighted the importance of sufficient information regarding the impact of NIV on QOL. Achieving improved QOL rather than prolonging life, was often more important for patients when making decisions about NIV (59).

ii) Initiation of NIV

Control of secretions/airway clearance

Studies emphasised the value of addressing excess secretions prior to NIV initiation (4). Pharmacological interventions could be used,(85) and the value of mechanically assisted cough devices was emphasised (13-15, 47, 86, 87).

Place

There was debate regarding the optimal place of NIV initiation. There were reports of concordance being greater and more rapid in hospital than at home (88). Although other studies found that home initiation of NIV was safe and effective (18, 19, 47). Out-patient initiation could be as effective, and less problematic, than inpatient initiation (89, 90). One study reported that out-patient initiation could reduce waiting time for NIV, which could be important in terms of survival outcomes (91, 92).

Interface, machine, mode and settings

Optimising mask fitting during initiation was described as being imperative (93-95), with a need for there to be varied interfaces available to trial (4, 74, 96, 97). Humidification should be fully considered (94, 98, 99), and optimisation of ventilation settings was considered to be crucial. The use of lowest possible NIV pressure settings was linked to improved survival in one study (98), and other authors emphasised that having incorrect settings was linked to NIV failure (100, 101). While ventilator mode was not considered important (102, 103), it was noted that there could be advantages for some patients of differing modes (36, 104).

Patient and carer experiences of initiation

One study outlined how patients could change their views about NIV once it had been initiated (60). Although it was emphasised that shifting toward a positive response could take time and perseverance (65, 105). Any initial negative impacts for carers may lessen as they became more familiar with the machine (80).

iii) Ongoing support

Monitoring

Regular monitoring was found to be of key importance, although it was emphasised that the optimal interval for a patient would vary by the stage and severity of disease (106). While NIV use may commonly be judged in terms of hours of usage, the literature emphasised the need to monitor adequacy of ventilation in addition to hours of usage. Analysis of both compliance data and machine data was highlighted as vital to evaluate ongoing efficiency (107-109). Authors in particular recommended examining data regarding patient-ventilator asynchrony (71, 110, 111).

Adjustment

Periodic adjustment based on comfort, symptoms, downloaded ventilator data, and carbon dioxide level was described as essential (53, 97, 98). One study found that 78% of patients required at least one change, 33% at least two, 11% at least three, and 6% of patients required at least four changes in NIV settings (4).

Service delivery

Tele-monitoring was recommended to support the need for regular monitoring and adjustment, with evaluations finding it to be user-friendly for patients, and cost effective in terms of reduced contacts and admissions (112-116).

iv) Withdrawal

Timing of discussion

The literature recommended that end of life issues should be discussed early in the course of the disease, with re-discussion every six months as patient views regarding life-extending treatments may change over time (117). Patients, family and staff all may require support in this discussion (118). Authors reported that patients often wish to keep NIV in place to the end, in which case planning regarding withdrawal is not required (119).

Pharmacological support

Administration of medication (mainly subcutaneous morphine or diamorphine and midazolam) was recommended to avoid/relieve distressing symptoms such as breathlessness and anxiety at end of life (82, 120). Health care professionals however, may need support to overcome concerns that high doses of medication will be regarded as hastening death (82, 118, 120).

Patient and carer factors

Decision-making regarding end of life might take several months (121), and the literature emphasised individual variation in wishes (122, 123). Authors highlighted the need for a

sensitive holistic evaluation of NIV use and withdrawal (62), with discussion including the patient, family and medical staff, as well as support from end of life specialists. During discussion there should be care not to override patient wishes (120).

Service delivery factors

Uncertainties and challenges for doctors when withdrawing NIV were described (124), with reports of practitioners often feeling professionally vulnerable (82,118). Studies called for clearer guidelines and an ethical statement of conduct, as the professional and legal situation regarding withdrawal could be uncertain (120).

Discussion

The review has synthesised a substantial volume of literature relating to use of NIV in people with ALS/MND. While there was little evidence from studies using high quality comparative designs, data from both quantitative and qualitative literature provide valuable insights into optimal NIV provision. Table 3 provides a summary of findings from the literature, and recommendations for optimising the NIV patient pathway.

Insert Table 3 around here

The review highlights the need to recognise individuality, with decision-making needing to be based on adequate respiratory function test data, but also patient wishes. Studies cautioned against over-reliance on symptom report, and the value of a range of tests for evaluating respiratory insufficiency was suggested. The limitation of many of these assessments in patients with bulbar symptoms was highlighted. There was no conclusive evidence regarding which might be superior to the others, although use of established FVC guideline thresholds was criticised. While some of the literature we included precedes the introduction of NIV guidelines, it nonetheless presents a picture of variance in practice between different clinicians in terms of pulmonary function testing and recommendation for NIV commencement. Given the evidence regarding the benefits of early initiation in terms of increased compliance and survival (24, 53, 54), a key question remains regarding how the need for NIV should be best determined. Further comparative studies would be beneficial to aid clinical decision-making. There are many studies using neurophysiology to investigate the role of the diaphragm in respiratory failure, with this literature contributing important insights to the field.

A recent study highlights that the timing of initiation may be based on historical international and USA insurance standards (87). The authors concluded that earlier access to NIV and cough assist, prior to precipitous respiratory decline, is needed to gain maximal survival benefit. The challenges in achieving optimal timing of NIV however, were emphasised in the

literature. While the evidence suggested the benefits of early introduction, there were potential tensions in the triangle between clinician, patient and family (125), and studies reported that patient preference was often to delay. The review indicated the importance of information provision for patients and families in the decision-making process. The suggestion was made that focusing on improved quality of life, rather than extending life may be helpful in encouraging NIV trial. Further qualitative work exploring the process of decision-making from clinician, patient and family perspectives may help to identify optimal communication strategies.

The importance of managing secretions before initiation was highlighted in the review, together with the need to consider enhanced care for people with bulbar symptoms. A paper published since we completed the review, emphasises the potential positive effect of NIV on survival of patients with severe bulbar dysfunction who are NIV users, and reported high levels of tolerance in these patients when respiratory secretions were managed (126). Another recent paper confirms that use of cough assist alongside NIV provides additional survival benefits over NIV alone (87).

An area of variance between clinicians and between countries is in regard to the site of NIV initiation. The common practice in some countries of in-patient initiation may need reconsidering in light of reported benefits from alternative models due to more rapid scheduling of initiation. Further work to determine whether different patients respond better to different settings would be beneficial; for example it could be possible that patients with bulbar symptoms benefit from an in-patient initiation. The optimal place of initiation is a key unanswered question requiring further study.

The availability of multiple options for interfaces was emphasised, which may have cost implications for service delivery. Also in terms of service delivery, the benefits of joint palliative and respiratory clinics were indicated. Greater involvement of palliative services may support regular and ongoing discussion regarding end of life wishes. Studies suggested that patients and carers may not always receive adequate information prior to NIV initiation, and discussion should encompass all stages of the NIV pathway.

The review highlights the importance of not only monitoring the number of hours of use of NIV (quantity), but also whether the settings are optimised (quality). While some NIV is better than none, there may be patients who could be achieving enhanced benefits if ventilator settings were adjusted. One study worryingly found that only around half of patients were correctly ventilated (based on symptoms and blood gases) in the first month after initiation (93).

Limitations

This review was limited to studies published in English, which may account for the over-representation of papers from the UK using qualitative methods. Our search terms may have missed relevant papers, although we believe our use of supplementary searching techniques will have mitigated any limitations in database indexing. Included evidence spans the last 20 years, and practice reported in earlier studies may have changed considerably, particularly given the constantly evolving NIV technologies. We recognise that the use of tracheostomy versus NIV can be a key dilemma, and this would be a useful focus for a separate review.

Conclusions

Optimising use of NIV in people with motor neuron disease requires consideration of multiple factors as part of a process across the patient pathway. While the importance of individualising care is highlighted, factors optimising care for all patients include: a specialised multi-disciplinary team; determining need using respiratory function tests in addition to symptom report; providing adequate information for patients and their family; paying attention to the role of carers in decision-making; adequately managing secretions; considering the most advantageous place of initiation; optimising the interface, machine mode and settings for patient comfort and effectiveness; regular monitoring and adjustment of settings; and providing opportunities for ongoing discussion of patient wishes. Current guidelines predominantly focus on the initiation stage of NIV, and may underplay psychosocial factors in the process. We have made evidence-based recommendations for each step in the pathway, which may help improve optimal uptake, usage, quality of life, and survival outcomes in patients with MND.

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Declaration of interest

The authors report no conflict of interest

Data availability statement

Any additional data is available from the corresponding author if required.

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Table 1. Inclusion criteria for the review

Population	Studies with participants who have a diagnosis of MND/ALS, or the families/caregivers of these patients, or staff delivering services to these patients.
Intervention	Studies relating to any form of long-term, domiciliary non-invasive ventilation (administration of ventilatory support using any form of removable mask/mouthpiece and without using an invasive artificial airway).
Study design	Studies of any empirical design including conference abstracts and guidance and standards regarding NIV for patients with MND.
Outcomes	Studies which outline any outcome related to patients or delivery of NIV services.
Other criteria	Studies published since 1998 Citations with an English abstract

Table 2. Sources searched

MEDLINE via OvidSP (1998-May 2018)
MEDLINE In-Process & Other Non-Indexed Citations & Epub Ahead of Print & MEDLINE ® without Revisions via OvidSP (1998 - May 2018)
Embase via Ovid SP (1998-May 2018)
CINAHL via EBSCO (1998 – May 2018)
PsycINFO via OvidSP (1998 – May 2018)
Cochrane Database of Systematic Reviews (CDSR) via The Cochrane Library (2005-May 2018)
Database of Abstracts of Reviews of Effects (DARE) via The Cochrane Library (1998 -April 2015 – no longer updated, archive only)
Cochrane Central Register of Controlled Trials (CENTRAL) via The Cochrane Library (1998-May 2018)
Health Technology Assessment (HTA) Database via The Cochrane Library (1998- May 2018)
Science Citation Index via Web of Science (1998 – May 2018)
Social Sciences Citation Index via Web of Science (1998 – May 2018)

Table 3. Summary of factors associated with optimal non-invasive ventilation at different stages of the care pathway

Stage of the pathway	Optimising factors
Decision to trial NIV	<p>Specialised units</p> <p>Joint respiratory/palliative clinics</p> <p>Respiratory therapist</p> <p>Recognition of limitations of symptom report to evaluate need</p> <p>Consideration of a suite of tests to assess respiratory insufficiency</p> <p>Early initiation</p> <p>Timely, ongoing decision-making</p> <p>Recognition that decision-making should be individualised</p> <p>Ensuring decision-making is active patient choice/patients are in control</p> <p>Emphasis on impact on quality of life rather than survival</p> <p>Ensure information provided is sufficient, consider need for education sessions</p> <p>Recognise potential for differing patient and family perceptions regarding the role of NIV, patient focus on present, family wish to plan for future</p> <p>Patients may require information at different times to carers</p> <p>Consider support systems required, reassurance regarding impact/burden on self and family</p>
Initiation	<p>Address excess secretions prior to initiation</p> <p>Supplementary use of assisted cough device</p> <p>Consider location of initiation - patients prefer home and less costly but varying evidence regarding success/concordance. There is evidence regarding positive outcomes from outpatient rather than inpatient initiation</p> <p>Importance of optimising mask fitting, variety of interfaces, combine with mouthpiece interface for high hours of use</p> <p>Explore use of humidification</p> <p>Consider machine modes</p> <p>Recognise the importance of optimising settings</p> <p>Provide enhanced care for patients with bulbar symptoms</p>

Ongoing support	<p>Ensure regular monitoring of adequacy of ventilation</p> <p>Recognise the importance of analysing ventilator data</p> <p>Provide readjustment of pressure settings as required</p> <p>Consider use of tele-monitoring in light of evidence that tele-monitoring enables patient involvement, and reduces time and costs</p>
Withdrawal	<p>Regularly review and re-discuss end of life wishes as part of a process</p> <p>Recognise the individual variation in decision-making</p> <p>Recognise that professionals find withdrawal challenging</p> <p>Provide opportunities for early discussion and holistic evaluation</p> <p>Consider use of medication to reduce symptoms, but provide support where professionals find this ethically challenging</p>

Figure 1. PRISMA diagram illustrating the process of study selection

Figure 2. Summary of countries of origin of the included studies

Figure 3. Summary of types of study design

Figure 4. Non-invasive ventilation pathway model