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The optimisation of non-invasive ventilation in amyotrophic lateral sclerosis: A systematic review

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Take home message

We report a systematic review that identifies factors associated with the optimal initiation and ongoing monitoring of NIV in patients with ALS. We make recommendations to optimise the use of NIV in ALS to improve patient outcomes.

Abstract

Background

Non-invasive ventilation (NIV) prolongs survival and quality of life in amyotrophic lateral sclerosis (ALS); however, its benefits depend upon the optimisation of both ventilation and adherence. We aimed to identify factors associated with effective initiation and ongoing use of NIV in ALS to develop evidence-based guidance and identify areas for further research.

Methods

We searched eleven electronic databases (Jan 1998 – May 2018) for all types of quantitative and qualitative studies. Supplementary grey literature searches were conducted. Records were screened against eligibility criteria, data were extracted from included studies and risk of bias was assessed. We present findings using a narrative synthesis.

Results

We screened 2430 unique records and included 52 quantitative and 6 qualitative papers. Factors reported to be associated with NIV optimisation included: co-ordinated multidisciplinary care, place of initiation, selection of interfaces, ventilator modes and settings appropriate for the individual patient, and adequate secretion management. The literature indicated that patients with significant bulbar dysfunction can still derive considerable benefit from NIV if their needs are met. Research emphasises that obstructive airway events, mask leak and uncontrolled secretions should be addressed by adjustments to the interface and machine settings, and the concomitant use of cough augmentation.

Conclusion

This review highlights that NIV optimisation requires an individualised approach to respiratory management tailored to the differing needs of each patient. Ultimately this should lead to improved survival and quality of life. This review expands on recommendations in current international guidelines for NIV use in ALS and identifies areas for future research.

Background

In patients with amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND), hypoventilatory respiratory failure is the most common cause of death and respiratory morbidity is related to a poorer quality of life (1). Non-invasive ventilation (NIV) improves survival and quality of life for patients with ALS in respiratory failure by up to 18 months (2, 3). However, the success of NIV is related to its optimisation: the quality (ventilation) and quantity (adherence) of NIV received are prognostic factors in ALS (4).

If ventilation is not optimised the benefits are dramatically reduced: the one-year survival was 75% in ALS patients experiencing good correction of hypoxia on NIV, reducing to 43% in the absence of good correction (4). Therefore, the effectiveness of ventilation needs to be monitored, with adjustments made to address any issues and compensate for further disease progression. Adherence must also be optimised. Patients who could tolerate NIV for four hours per day demonstrated improved survival post-NIV initiation (14.2 months) relative to those who used it for less than four hours per day (7.0 months, $p=0.002$) or those who declined NIV (4.6 months, $p<0.001$) (5).

NIV is a complex intervention (6), the success of which is influenced by the interaction of multiple service, equipment, patient and carer factors. These may include: the service delivery model and process of NIV initiation; the choice of mask interface, ventilator mode and machine settings; and the presence of significant bulbar dysfunction. Guidelines from the National Institute for Health and Care Excellence (NICE) (7), European Federation of Neurological Societies (EFNS) (8) and American Academy of Neurology (AAN) (9) for the management of NIV in ALS reflect the lack of evidence on how best to address these factors and, consequently, practice varies between services (10). The aim of this systematic review was to identify factors associated with optimal NIV initiation and ongoing adherence and ventilation in ALS to develop evidence-based guidance and identify areas for further research.

Methods

Protocol

The review protocol was registered with the PROSPERO database (CRD42018094394) and was conducted in accordance with PRISMA reporting standards (see Appendix 1) (11).

Search strategy

Eleven electronic databases were searched (from Jan 1998 – May 2018, except where stated): MEDLINE via OvidSP, MEDLINE In-Process & Other Non-Indexed Citations & Epub Ahead of Print & MEDLINE ® without Revisions via OvidSP, EMBASE via OvidSP, CINAHL via EBSCO, PsycINFO via OvidSP, Cochrane Database of Systematic Reviews via The Cochrane Library (2005 – May 2018), Database of Abstracts of Reviews of Effects via The Cochrane Library (1998 – April 2015; archive only), Cochrane Central Register of Controlled Trials (CENTRAL) via The Cochrane Library, Health Technology Assessment Database via The Cochrane Library, Science Citation Index via Web of Science and Social Sciences Citation Index via Web of Science.

Supplementary searching techniques included handsearching of included studies' reference lists and grey literature searches using OpenGrey and websites of relevant organisations, including those of the Motor Neurone Disease Association (https://www.mndassociation.org), NICE (https://www.nice.org.uk) and NHS Evidence (https://www.evidence.nhs.uk).

Search terms involved a combination of MeSH subject headings (e.g. Motor Neuron Disease, Noninvasive Ventilation, Artificial Respiration) and free-text terms (e.g. ALS, NIV, respiratory failure), with the search strategy developed and led by an information specialist. Searches were limited to humans and English language. The search strategy for MEDLINE is provided in Appendix 2.

Study selection

Citations retrieved from electronic database searches were uploaded to EndNote (Version 7). Titles and abstracts were independently screened by two reviewers against the eligibility criteria (see Table 1); a third reviewer resolved any uncertainties. The level of agreement between the two reviewers regarding study inclusion was over 95%. Full texts were then obtained.

Table 1. Study eligibility criteria

Criterion	Eligibility criteria
***P**opulation*	Studies in patients with a diagnosis of ALS/MND, or their families and caregivers, or healthcare professionals involved in their care.
***I**ntervention*	Studies involving any form of long-term, domiciliary NIV, defined as ventilatory support administered via a removable mask/mouthpiece.
***C**omparator*	Studies with comparator and non-comparator designs.
***O**utcome*	Studies reporting any outcome related to the optimisation of NIV initiation, monitoring and ongoing care (e.g. oxygen and carbon dioxide saturations, patient adherence and quality of life metrics).
***S**tudy design*	Empirical quantitative* and qualitative studies published in English in the last 20 years.**

ALS, amyotrophic lateral sclerosis; MND, motor neuron disease; NIV, non-invasive ventilation

* A range of quantitative studies were eligible, including randomised controlled trials and other experimental designs; prospective, retrospective and cross-sectional observational studies; and, case studies.

** The review was restricted to studies published in the last 20 years to ensure findings are relevant to current practice and given potential changes in prognosis during this timeframe.

Data extraction

Data were extracted from included studies using a pre-piloted extraction form. We collected data on: first author, publication year, study design, sample size, population characteristics, data collection method, outcome measures, intervention characteristics, theoretical underpinning, summary of results and main author conclusions. The form was suitable for all types of quantitative study designs and was modified for qualitative studies. Extraction forms for each study were completed by one reviewer and verified by a second, as is recommended as an accepted minimum (12). Multiple citations from a single study were brought together into a single extraction where possible, to avoid double-counting data.

Risk of bias assessment

We assessed the risk of bias using the established hierarchy of evidence and checklists for each study type, where appropriate. For controlled studies, we considered sources of potential bias as recommended by Cochrane (13). For other quantitative studies, we used the National Institutes of Health checklists (14). For qualitative studies, the Critical Appraisals Skills Programme checklist was used (15). Due to significant between-study heterogeneity, risk of bias was not assessed across the cumulative evidence.

Synthesis

Study heterogeneity precluded the use of a meta-analysis. Quantitative data were synthesised using a narrative synthesis method. Themes reported in qualitative studies were integrated where they related to the quantitative findings. We brought together studies examining similar processes or reporting similar outcomes, identifying where data agreed and where it conflicted, and provide an indication of the volume and quality of the evidence.

Results

Study selection

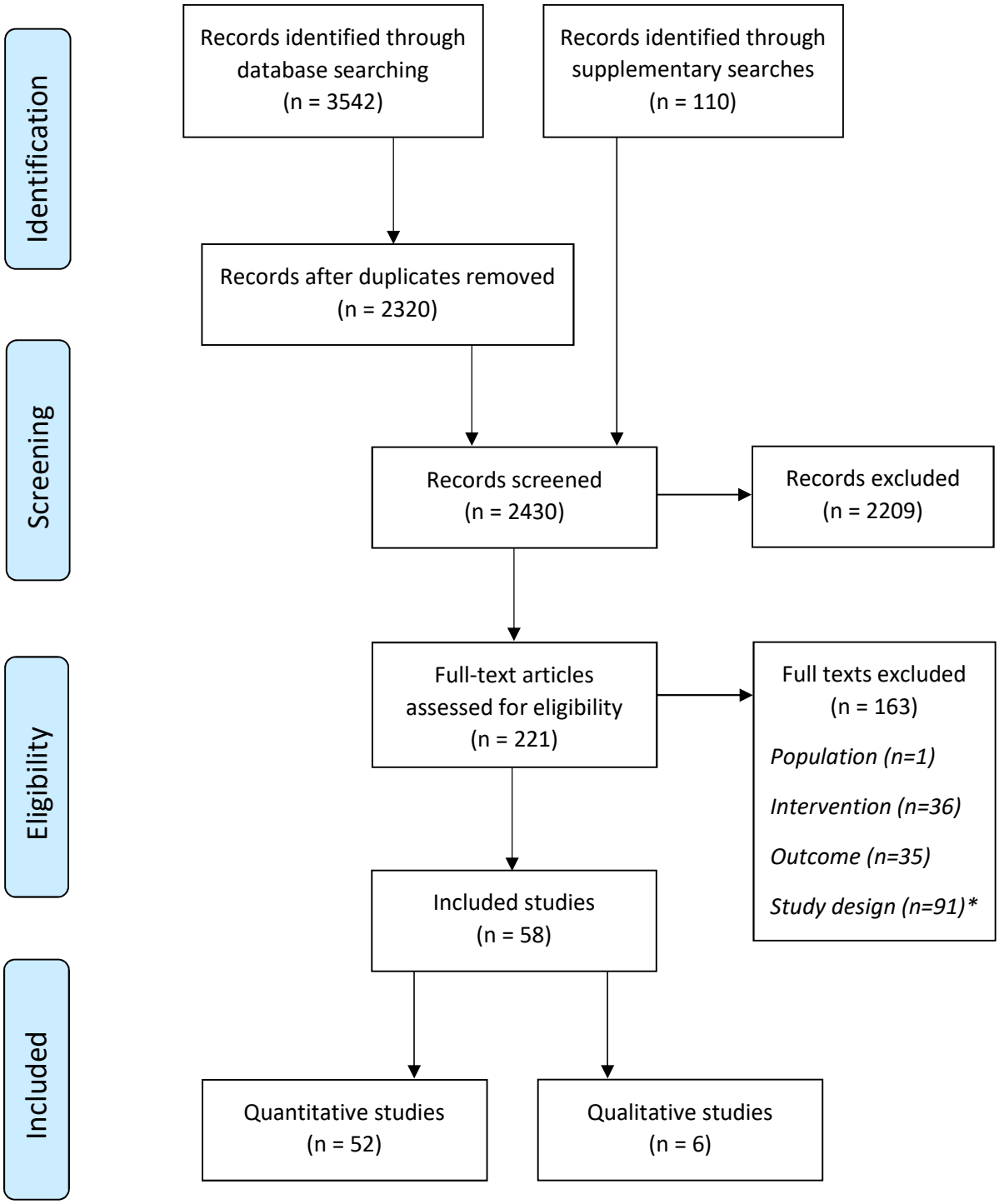
Of 2430 records screened, 221 documents were assessed at full-text level for eligibility, and 58 studies (52 quantitative and 6 qualitative) were included in the review (see Figure 1).

Study characteristics

The included studies involved a range of 1 – 474 participants (mean: 70.69). Five studies used an experimental design: two randomised controlled trials (RCT) (3, 16), two randomised crossover studies (17, 18) and one quasi-randomised controlled trial (19). The remaining quantitative studies were observational: 13 prospective, 16 retrospective, seven cross-sectional and 11 case studies. Six qualitative studies were also included. See Appendix 3 for the characteristics of included studies.

The included RCTs were found to be at a low risk of bias, while the other three experimental designs had a higher risk of bias, due to issues including: unclear random allocation method and reporting bias. The observational studies were all considered to be at higher risk of bias, although some provided more robust evidence than others; for example, seven included studies used a prospective design with sample size greater than 30 and adequate control for confounding variables (20–26). Completed quality assessments for individual studies are available as Appendix 4.

Figure 1. PRISMA flow chart illustrating the study selection process



n, number of studies; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

* The majority of those excluded on study design were conference abstracts (n=80) for which no full text could be obtained.

Service factors that influence NIV optimisation

Service delivery model

Eight studies investigated the effects of a multidisciplinary team approach to ALS care on NIV usage: one prospective (27), one retrospective (28) and six cross-sectional studies (29–34). Evidence was found in all for a positive effect of multidisciplinary care on outcomes related to NIV usage, including access to NIV, patient acceptance and adherence. A prospective Italian study in 37 patients evaluated a complex intervention during the initial adaptation to NIV, involving a patient education session, intensive inpatient monitoring, and follow-up with adjustments made as necessary (27). Adherence above four hours per night was achieved in all 37 patients at discharge after a mean inpatient stay of 12 ±2 days. At one-year, 35 of 37 (95%) patients remained NIV-adherent. A retrospective before-and-after study in 77 participants observed an increase in NIV acceptance following the addition of a respiratory therapist to the ALS clinic (54% to 82%, p=0.007) (28). Adherence above four hours per day also increased (22% to 73%, p=0.027). Both studies failed to adequately control for confounding variables.

In an epidemiological study of 259 patients in Italy, NIV was more frequently initiated within tertiary ALS centres than general neurology clinics from 1995–2004 (37.2% vs. 8.8%, p=0.0001) (29). Seventy-six Italian respiratory centres were surveyed in another study: 90% used a multidisciplinary approach, involving close co-operation between respiratory and neurology physicians, physiotherapists and psychologists (31). High-referring centres more frequently reported good collaboration with neurologists than low-referring centres (45% vs. 23%, p=0.04). Response rates below 50% increase the risk of bias here. A survey of 11 Canadian ALS specialists cited effective co-ordination between respiratory and neurology services and the availability of respiratory specialists as contributors to good NIV adherence (30). A UK audit described the utility of joint respiratory and palliative multidisciplinary clinics for monitoring respiratory function, commencing NIV and discussing end-of-life care in six patients (34).

Place of initiation

Five studies examined the effects of place of NIV initiation: one RCT (16), one prospective before-and-after study (26), two cross-sectional studies (34, 35) and one qualitative study (36). Two studies evaluated a day case (outpatient) model of initiation (16, 26). An Italian RCT compared initiation as a day case (n=25) versus an overnight inpatient (n=25) (16). Similar rates of NIV adherence were observed during initiation (76% vs. 80%, p=0.733) and at three months (68% vs. 76%, p=0.529). Patient and healthcare professional satisfaction, respiratory function changes and symptom control were similar in both groups. An Australian centre compared a multi-day inpatient initiation (n=17) to a day case initiation (n=12) in a prospective before-and-after study (26). 'Suitable patients' were initiated as outpatients, highlighting a possible selection bias. Median waiting time for NIV initiation fell from 30 to 13.5 days (p<0.04), and adverse events (death or acute admission with respiratory failure) declined from four out of 17 (24%) to 0 out of 12 (0%), while daytime arterial CO_2 levels were equivalent. Median post-initiation survival was extended from 278 to 580 days (hazard ratio: 0.41, p=0.04).

An international survey of 186 ALS clinicians found that patients are admitted to hospital for initiation more often in Europe than the USA (16/39 [41.0%] vs. 0/57 [0%], p<0.001) (35). However, a UK audit described successful home initiation in six patients with the support of a specialist respiratory nurse (34). A qualitative study reported patient anxiety regarding hospital admission; this was a major barrier for one patient who eventually accepted a trial of NIV as a day case (36).

Equipment factors that influence NIV optimisation

Interface

Sixteen studies examined the effect of the interface on NIV optimisation: one RCT (3), one randomised crossover trial (18), three prospective cohorts (22, 37, 38), four retrospective cohorts (4, 39–41), one cross-sectional survey (30), four case reports (42–45) and two qualitative studies (46, 47). Interface intolerance was associated with poor adherence in two prospective studies (22, 37), one cross-sectional (30) and one case report (44). Commonly reported problems in two qualitative studies included reluctance to use the mask in company, interference with eating and communication, pressure sores, dry mouth, mask leak and claustrophobia, which may contribute to poor adherence (46, 47). Six studies identified interface-related causes for ineffective ventilation: mask leak in four studies (4, 18, 38, 41) and obstructive sleep apnoea (OSA) in two (39, 42). A retrospective analysis identified mask leak as a leading source of persistent nocturnal desaturations in 53% of cases in 82 patients studied (4). Optimisation of mask fitting successfully minimised leak in this study and a case report (4, 45). In a retrospective cohort, NIV-associated OSA was present in 19 of 93 (20.4%) patients using oronasal masks (39). A case report also described OSA induced by an oronasal mask (42). Both studies reported changing to a nasal mask with a chin strap to eliminate obstructive events. One higher-quality RCT (3), one retrospective cohort (40) and a case report (43) highlighted the value of daytime mouthpiece ventilation, which facilitates adjuvant cough augmentation to expectorate secretions, although this requires adequate bulbar function (3, 40, 43).

Ventilator type, mode and settings

Eighteen studies assessed the effect of ventilator type, mode or settings on NIV optimisation: one randomised crossover trial (17), two prospective (37, 38), six retrospective (2, 4, 39, 41, 48, 49), six case reports (42, 45, 50–53) and three qualitative studies (46, 54, 55). A retrospective multicentre cohort with adequate control for confounding variables reported effective ventilation at one-month in 45 of 62 (72.6%) patients using volume-preset (Vol-NIV) systems compared with 40 of 82 (48.8%) patients using pressure-preset (Pres-NIV) systems ($p<0.001$) (2). However, there were no survival differences between the two groups ($p=0.533$). In a retrospective study of 271 patients, average volume-assured pressure support (AVAPS) ventilation produced greater average tidal volumes than Pres-NIV (390 vs. 356mL, $p=0.007$) with similar usage (6.5 vs. 6.6h/day, $p=0.703$) (49). These findings are limited by the possibility of selection bias and the use of surrogate outcomes for ventilation (lung volumes) rather than alveolar gases. Three studies reported the effects of switching from Pres-NIV to Vol-NIV or vice-versa. Switching from Pres-NIV to Vol-NIV resolved OSA in one patient in a large retrospective study (48) and improved ventilation in another case (44). A case series described a switch from Vol-NIV to Pres-NIV (in the case of increased leak) and vice-versa (in the case of increased secretions), which corrected hypoxia and hypercapnia, and improved symptoms, respectively (51).

The need to make decisions on a case-by-case basis was also demonstrated in a randomised crossover trial of spontaneous (S) and spontaneous/timed (ST) NIV modes in 13 patients (17). The ST mode provided more effective ventilation overall in terms of mean overnight oxygen saturations (87% vs. 83%, $p<0.05$) and time spent with an overnight transcutaneous CO_2 >55 mmHg (0% vs. 20%, $p<0.05$); however, four patients (who could not be predicted from baseline characteristics) displayed better ventilation outcomes on the S mode. Survival effects were not assessed, while the risk of bias was considered high due to the small sample size and non-

reporting of randomisation processes. Two prospective studies from the same centre described intolerance of the ST mode in seven out of 35 (20%) patients (five with bulbar involvement) (37) and six out of 22 (27%) patients (four with bulbar involvement) (38), respectively, which improved upon switching to the S mode in all cases.

Low-quality evidence from three case reports suggested poor NIV adherence due to air-swallowing (53), excessively high airway pressures on Pres-NIV machines (50) and target tidal volumes on Vol-NIV systems (45). In the latter case, adherence improved when target tidal volumes were reduced from 8ml/kg to 6ml/kg. Three qualitative studies linked discomfort associated with air pressure to reduced adherence (46, 54, 55). Conversely, insufficient ventilation settings were associated with poor ventilation in 34.7% patients in one retrospective study (41). Three studies reported the benefit of increasing ventilator support to improve ventilation, by increasing inspiratory positive airway pressure (IPAP) in a retrospective cohort (4) and case report (45) and increasing target tidal volumes in another case report (51). Increasing expiratory positive airway pressure (EPAP) helped to eliminate OSA in three retrospective studies (4, 39, 48). Other successful measures found to improve ventilation are reported in Table 2. A flow chart summary can be found in Appendix 5.

Table 2. Troubleshooting: NIV problems and solutions

Problem	Solution	Level of evidence
Obstructive airway events	Increase EPAP	Three retrospective studies (4, 39, 48)
	Switch to an auto-titrating mode of NIV	Two retrospective studies (39, 48)
	Switch from an oronasal mask to a nasal mask with a chin strap	One retrospective study (39) and one case report (42)
	Reduce inspiratory time and reduce IPAP	One case report (42)
	Switch from Pres-NIV to Vol-NIV	One retrospective study (48)
Mask leak	Optimise mask fitting	One retrospective study (4) and one case report (45)
	Switch from Vol-NIV to Pres-NIV	One case report (51)
Hypoventilation	Increase IPAP (Pres-NIV machines)	One retrospective study (4) and one case report (45)
	Increase target tidal volumes (Vol-NIV machines)	One case report (51)
	Switch from Pres-NIV to Vol-NIV	One case report (44)

Auto-triggering patient-ventilator asynchrony	Trial an increase in minimum inspiratory time*	One case report (52)
Excess respiratory secretions	Use adjuvant cough-assist devices	Three retrospective studies (56–58) and two case reports (43, 44)
	Switch from Pres-NIV to Vol-NIV	One case report (51)
Excess oropharyngeal secretions	Subcutaneous glycopyrrolate infusion	One case report (59)

EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; Pres-NIV, pressure-preset non-invasive ventilation; Vol-NIV, volume-preset non-invasive ventilation

* Only after first ensuring that the mask and tubing are free from condensation, that unintentional leak is minimised, and that appropriate trigger and cycle sensitivities are set. Minimum inspiratory times may not be adaptable on some ventilators.

Adjuvant therapies

Seven studies described the use of adjuvant interventions: two prospective (27, 60), two retrospective (48, 61) and three case studies (44, 50, 62). Music-assisted relaxation was beneficial in supporting NIV transition within the first week in a prospective feasibility study of 15 patients (60); however, risk of bias was deemed high due to methodological flaws in participant selection, outcome measurement and statistical analysis. Successful use of a portable hand-held ventilator (Philips 'Vitabreath') in three patients was reported in a case series, although the authors indicated that patients may struggle with the pressure differences compared to their usual ventilators (62). Two studies examined the use of mandibular advancement devices in treating OSA and improving NIV adherence: one case report described its successful use (50) while a retrospective study found no benefit (48).

Secretion management

Nine studies examined the impact of controlling secretions on NIV optimisation: two prospective (24, 27), three retrospective (56–58), three case reports (43, 44, 59) and one qualitative study (46). An association between excess oropharyngeal or airway secretions and poor adherence was found in two prospective studies (24, 27) and one case report (59). One prospective study found that an absence of airway secretions was predictive of good adherence (odds ratio: 11.5 [1.3–98.4]), while the case report described an improvement in NIV usage (from <1h to 6–8h/night) following treatment with a subcutaneous glycopyrrolate infusion (59).

Five studies highlighted the role of cough augmentation in the active management of secretions: three retrospective studies (56–58) and two case reports (43, 44). A retrospective analysis of 474 patients found a significant improvement in survival between NIV users who also used daily cough-assist compared to those using NIV alone (median: 25.73 months vs. 15.00 months, $p<0.001$) (58). Combined use of NIV and cough-assist was successful in avoiding tracheostomy in

two retrospective studies of 101 patients each (56, 57) and resolving 43 out of 78 (55%) desaturation episodes (57).

Efficacy monitoring

Monitoring ventilation

Two retrospective studies reported that effective ventilation predicted survival (4, 48), while another retrospective study did not find the effectiveness of NIV to be a prognostic factor (2). In one study, only 40 of 82 (49%) patients were effectively ventilated at one-month (4). Importantly, one-year survival was 75% in those effectively ventilated at one-month, declining to 43% in those ineffectively ventilated (p=0.002). Remedial measures at one- and three-months corrected ventilation by month six in 12 (43%) patients and one-year mortality in this subgroup was similar to those effectively ventilated at one-month (four deaths vs. three, p=0.13). In 16 (57%) patients NIV was still inadequate at month six despite corrective measures. One-year mortality in this subgroup was significantly higher than in those effectively ventilated at one-month (seven deaths vs. three, p=0.002). Another study found ineffective ventilation in 73 of 179 (41%) patients at one-month, due to OSA in 49 cases (67%) (48). Individuals adequately ventilated at one-month, and those for whom OSA was successfully eliminated within the first month, experienced greater median survival (26 [13–45] months and 29 [20–53] months, respectively) than those who were inadequately ventilated at one-month due to uncorrected obstructive events (14 [7–27] months, p<0.05) or other causes (12 [6–23] months, p<0.05).

Two retrospective studies investigated the need for longitudinal adaptations to machine settings with disease progression (2, 61). Twenty-eight out of 36 (78%) patients required at least one upward change in pressure settings (61). In a two-centre comparison, ventilator setting changes were required more frequently in 82 patients using pressure-preset (Pres-NIV) than 62 using volume-preset (Vol-NIV) machines: 51% vs. 14% (p<0.001) (2). Of those ineffectively ventilated in the first month, effective ventilation was achieved after the first modification in 79% of the Vol-NIV group and 31% of the Pres-NIV group (p<0.001).

Monitoring adherence

Survival correlated with hours of NIV use in three papers: one prospective cohort (21) and two retrospective cohorts (5, 58). Seventeen studies reported NIV adherence rates: nine prospective (20–24, 27, 37, 38, 63), seven retrospective (2, 4, 28, 48, 49, 61, 64) and one cross-sectional study (29). The proportion of patients achieving at least four hours of use per day ranged from 46–100%.

Telemonitoring

The costs of a home telemonitoring system were analysed in a quasi-randomised controlled trial of 39 patients, observing a 55% reduction in average total costs in patients with the telemonitoring system (€8908.6 ± 6552.7) versus those on standard care (€19664.9 ± 5256.5) due to reduced healthcare utilisation (19). However, this reduction did not reach statistical significance (p=0.058). The impact of the telemonitoring system on NIV efficacy or survival was not assessed. This trial was judged to be at high risk of bias due to a non-random allocation method and potential reporting bias.

Patient and carer factors that influence NIV optimisation

Bulbar dysfunction

Twenty-three studies investigated the effects of bulbar impairment on NIV optimisation: two RCTs (3, 16), ten prospective cohorts (20–25, 37, 38, 63, 65), six retrospective cohorts (40, 56–58, 64, 66), two cross-sectional studies (29, 30) and three case reports (43, 44, 67). Nineteen studies found an association between bulbar impairment and poorer adherence or ventilation, while four studies (including one RCT) identified no such association. In this RCT, bulbar-onset disease predicted greater NIV adherence (16); however, another RCT reported an average use per day of 9.3 hours in the more preserved bulbar function subgroup versus 3.8 hours in those with poor bulbar function (3). In two prospective studies of 71 and 73 participants with adequate control for confounding variables, those with more severe bulbar impairment had an increased risk of poor adherence: six-fold in one (odds ratio: 6.09 [1.18, 31.52]) (21) and eight-fold in another (odds ratio: 8.5 [1.6, 46.2]) (24). In the latter trial, bulbar-predominant patients were reported to need more intensive and prolonged monitoring at NIV onset to maximise adherence (24). In spite of this, one prospective cohort reported one-year adherence above four hours per day in 35 out of 37 (95%) patients who had undergone an intensive education and adaptation programme at initiation despite nine presenting severe bulbar involvement at initiation and 23 mild-moderate impairment (27).

Eighteen studies investigated survival or quality of life outcomes in patients with bulbar dysfunction using NIV. Fourteen studies found that bulbar patients derived some benefit from NIV: two RCTs (3, 16), six prospective (20, 21, 27, 37, 38, 65), five retrospective (5, 41, 58, 64, 68) and one cross-sectional study (29). Four studies reported no benefit: three retrospective (40, 56, 57) and one case study (67). Generally, the gains derived in bulbar patients were reduced compared with non-bulbar patients, as reflected in an RCT where a subgroup with poorer bulbar function experienced no survival gain despite some quality of life benefits (3). However, the trial was not powered for this subgroup analysis. Perhaps surprisingly, one retrospective study observed a median survival benefit from NIV of 13 months in all 219 patients, increasing to 19 months in 58 with bulbar-onset disease (68).

Patient and carer perceptions

The effect of patient and carer perceptions on the optimisation of NIV was examined in four qualitative studies, involving between five and 37 participants (46, 47, 54, 69). Adaptation to NIV takes time for many patients, beginning with familiarisation with the equipment (69). Some patients highlighted the importance of an initial trial period to gauge the positive effects of NIV (69). Determination and perseverance were required to optimise adherence, while accessible in-person or telephone support might be beneficial in overcoming early obstacles (46). Carers reported a lack of confidence in adjusting the machine (46), which lessened with increased familiarity (47). Sleep disturbance may occur in patients and carers due to the machine noise and having to make adjustments to the system (46, 54). A positive coping style and perceived need to engage with the treatment was related to better adherence, while feelings of hopelessness were associated with poor adherence (54). Hopelessness was observed to be modifiable and improvements positively influenced patients' attitudes to NIV.

Discussion

This review has highlighted the importance of optimising both adherence and ventilation to gain the full benefit from NIV for patients with ALS. Patients must receive effective routine services, which should also be highly adaptable and co-ordinated to support the most complex patients who require the greatest clinical input. We recommend that services should adopt a co-ordinated, multidisciplinary approach aligned with current guidelines (7–9), but go further to recommend the need for specific professionals (including respiratory specialists) to be involved early and throughout the disease course to optimise adherence and ventilation. This will allow barriers to successful NIV use to be addressed prior to NIV initiation. The key benefits of this set-up in optimising NIV use may be one explanation for why multidisciplinary care is associated with improved survival compared to non-specialist services (32, 70–73).

Current guidelines make no reference to place of initiation, leading to practice variation (7–9). Outpatient or domiciliary initiation may promote acclimatisation, minimise patient anxiety and reduce delays in commencing NIV. In patients with chronic respiratory failure, outpatient (74) and domiciliary initiation (75) have been comparable to inpatient models in terms of adherence and ventilation and more cost-effective. The American Academy for Sleep Medicine also suggest that inpatient initiation can be difficult to justify both medically and financially (76). The Medical Research Council advise that complex interventions such as NIV work best if tailored and evaluated according to local circumstances rather than being completely standardised (6). Therefore, we recommend that outpatient (and perhaps home) initiation should be considered as an effective alternative to inpatient initiation; however, there should be means for more complex patients (e.g. those with significant bulbar impairment) to receive greater attention, which could involve an inpatient stay and more intensive monitoring to optimise efficacy.

We have highlighted the importance of the mask interface in NIV success and recommend that interface selection and fitting should be optimised to minimise leak and maximise comfort. This might involve offering a variety of interfaces and providing alternatives as necessary. Particular interfaces will have key benefits in certain scenarios; for instance, switching from an oronasal mask to a nasal mask with a chin strap to address obstructive events and the use of a mouthpiece in patients with adequate bulbar function to allow for daytime use and adjuvant cough augmentation. A recent review highlighted the broad range of airway clearance techniques available, which may be adapted according to individual patient requirements (77). Secretion management via cough augmentation and various pharmacological methods should be optimised alongside NIV.

It remains unclear which initial ventilator types, modes and settings are optimal but what is very clear is that setting adjustments are often required to achieve success. Ventilator choice may be restricted within certain health services, while the potentially damaging effects of using a spontaneous mode in patients with progressive respiratory muscle weakness must be considered (76). Effective ventilation is likely to confer a survival advantage, so we recommend this should be a goal in the first few months post-initiation whilst maintaining the balance between effective adherence, ventilation and comfort. To achieve this, and in contrast with published guidance, which suggests reviewing patients every two to three months (7–9), we recommend reviewing patients in the first few days and weeks to screen for and identify causes of poor efficacy and adjust NIV settings accordingly as adjustments appear to prolong survival (4, 48). Particular attention should be paid to patients at higher risk of difficulties. Clinicians should be vigilant in their assessment of the optimal interface and NIV settings over time, as they will likely need

altering due to evolving bulbar dysfunction and gradual weakening of the respiratory muscles. The most appropriate tests to monitor ventilation remain unclear. A working group of ten European ventilation specialists recommended that more complex tests (e.g. polysomnography) could have utility in titrating parameters, troubleshooting for problems and monitoring efficacy in more complex patients, but simple oximetry and ventilator-recorded data may suffice in most cases (78); this would free up resources to focus on those with the most barriers to success. An RCT in patients using positive airway pressure for OSA found that use of a telemonitoring system that allowed clinicians to identify problems and make adjustments to the settings remotely significantly improved adherence versus those using standard care (79). A 2016 systematic review recommended that further evidence is needed to demonstrate the value of telemonitoring in ALS (80).

Currently there is a reluctance among some clinicians to offer NIV to patients with significant bulbar impairment (10) and current guidelines suggest that these patients should only receive a trial of NIV if they are likely to benefit from an improvement in sleep-related symptoms (7), or should instead be offered tracheostomy-assisted ventilation or palliative care (8). Whilst patients with bulbar dysfunction face greater barriers to NIV success, the evidence suggests that they may gain both symptom and survival benefit that could be at least equal to that of non-bulbar patients. This benefit depends on strategies to promote effective use; for example, attention to secretion management, interface optimisation, adequate initial acclimatisation and ongoing active management with vigilant monitoring and adjustments made as necessary. These complex patients derive the greatest benefit from a multidisciplinary approach (71).

Qualitative studies highlighted the need to identify and address the barriers to acceptance and adaptation of the patient and carer to life with NIV. However, there is a lack of evidence on interventions to support patients and carers. An ongoing RCT in patients with chronic obstructive pulmonary disease is evaluating the effects of counselling, relaxation, mindfulness-based exercises and neuropsychological rehabilitation on NIV acceptance and adherence (81). One included study suggested that an educational programme can have a significant impact on adherence (27), while another proposed offering psychological interventions where adherence is suboptimal (55).

Strengths and limitations of this review

This is a systematic examination of the evidence exploring the optimisation of NIV use in ALS. Due to the breadth of the review, reporting has been unable to examine each paper in depth. Studies identified were largely observational with a paucity of randomised controlled trials. Therefore, any conclusions drawn from this review must be interpreted in light of the limited high-quality evidence available. Furthermore, any evidence must be considered in the context of individual patient and service needs. RCT evidence is likely to remain rare in this patient group due to ethical issues and clinical heterogeneity. Nonetheless, the review findings may be used to inform the development of guidelines for optimising the ALS patient care pathway and highlight areas that warrant further research (see Table 3).

Conclusion

There is a substantial body of evidence related to the optimal care of ALS patients on NIV, considering service, equipment, patient and carer factors. Factors optimising care for all patients include: effectively co-ordinated multidisciplinary care; careful selection of interfaces, ventilator modes and settings appropriate for the individual patient; adequate secretion control; and

vigilant monitoring and adjustment of settings. Attention to the factors identified will enable the delivery of evidence-based NIV therapy, which should ultimately improve patients' survival and quality of life.

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Table 3. Evidence-based recommendations

Optimising factor	Recommendations for practice	Level of evidence	Recommendations for research
Multidisciplinary care	The use of multidisciplinary clinics leads to greater NIV uptake.	Eight studies: - One prospective cohort (27) - One retrospective before-and-after study (28) - Three cross-sectional surveys (30, 31, 33) - Two epidemiological studies (29, 32) - One audit (34)	To further characterise the impact of multidisciplinary care and the role of respiratory and speech therapy specialists in certain patients (e.g. those with severe bulbar impairment).
	The involvement of respiratory specialists promotes good adherence.	Three studies: - One retrospective before-and-after study (28) - One cross-sectional survey (30) - One audit (34)	
	Effective co-ordination between neurology and respiratory services leads to good usage.	Two cross-sectional surveys (30, 31)	
Place of initiation	Outpatient initiation of NIV is likely to be an effective, cost-effective and acceptable alternative to inpatient initiation.	Two studies: - One RCT (16) - One prospective before-and-after study (26)	To strengthen the evidence for the comparative efficacy of domiciliary versus hospital inpatient and outpatient initiation, and explore patient preference.
	Initiation at home may be an effective way for patients to acclimatise to the ventilator and interface.	One audit (34)	To assess the feasibility of managing the complexities of NIV initiation in a single outpatient session.
	More complex patients (e.g. those with severe bulbar impairment) might require greater attention, which could involve an inpatient stay and more intensive monitoring in the initial phases to optimise efficacy.	Expert opinion.*	

Interface	Interface selection and fitting should be aimed at optimising adherence by maximising comfort to prevent interface-related intolerance.	Six studies: - Two prospective cohorts (22, 37) - One cross-sectional survey (30) - One case report (44) - Two qualitative studies (46, 47)	To explore the effect of different interfaces on patient adherence and the effectiveness of ventilation. To investigate the optimal interface for patients with bulbar and/or facial muscle weakness.
	Interface selection and fitting should also be aimed at optimising ventilation with a particular focus on minimising unintentional air leak.	Four studies: - One randomised crossover trial (18) - One prospective cohort (38) - Two retrospective cohorts (4, 39)	
	Particular interfaces should be available to trial in certain scenarios, for example: - A mouthpiece for patients with adequate bulbar function to allow for convenient daytime ventilation and adjuvant cough augmentation.	Three studies: - One RCT (3) - One retrospective cohort (40) - One case report (43)	
	- Switching from an oronasal mask to a nasal mask with a chin strap in the presence of obstructive events on NIV.	Two studies: - One retrospective (39) - One case report (42)	
Machine type, mode and settings	The choice of NIV machine, mode and settings should be adjusted according to the clinical scenario; if an individual patient demonstrates poor ventilation or adherence not related to the interface, consider changing:		To compare the efficacy of the different NIV machine types (pressure, volume, AVAPS) and modes (spontaneous, timed, ST).
	- Machine settings (see Table 2)	Six studies: - Three retrospective studies (4, 39, 48) - Three case reports (45, 51, 52)	To explore the potential utility of continuous positive airway pressure (CPAP) therapy in ALS patients with coexisting OSA.
	- Machine mode	Three studies: - One randomised crossover trial (17) - Two prospective cohorts (37, 38)	To further validate the accuracy of data provided by ventilator software (e.g. tidal volumes, leak).

	- Machine type.	Three studies: - One retrospective (48) - Two case reports (44, 51)	
Secretion management	Cough-assist machines for airway secretion clearance should be combined with NIV to maximise survival and quality of life benefits.	Five studies: - Three retrospective cohorts (56–58) - Two case reports (43, 44)	To compare the effectiveness and cost-effectiveness of the various manual and mechanical airway clearance techniques that may be used in ALS.
	Ensure optimal oropharyngeal secretion control prior to and during NIV use to promote effective ventilation and good adherence, through the use of various pharmacological and non-pharmacological methods.	Four studies: - Two prospective cohorts (21, 24) - One case report (59) - One qualitative study (46)	
Monitoring	Close monitoring of all patients in the first few days and weeks post-initiation.	Expert opinion.	To explore a large scale, multidisciplinary initiation programme involving education, adaptive measures and monitoring.
	Additional provision for those at higher risk of difficulties (e.g. patients with severe bulbar impairment).	Expert opinion.	To explore the most clinically- and cost-effective methods for monitoring the effectiveness of NIV.
	Monitoring to identify poor adherence and ineffective ventilation and the implementation of corrective measures that could extend survival.	Two retrospective studies (4, 48)	To explore the best methods for monitoring patients who are deteriorating on NIV.
	Vigilant assessment of the optimal interface and NIV settings over time in the context of evolving bulbar dysfunction and gradual weakening of the respiratory muscles.	Two retrospective studies (2, 61)	To further investigate the potential utility of telemonitoring of NIV in ALS and resolve the issues with current systems (e.g. system specification, pre-determined alerts and the delivery of a patient-specific action plan)
Patient and carer perceptions	Attention should be paid to psychosocial aspects of care for all patients initiating NIV and their caregivers.	Expert opinion.	To explore the effects of different psychological interventions on NIV acceptance and adherence in ALS.

	Psychological interventions may be helpful where adherence is suboptimal.	One qualitative study (55)	
Bulbar impairment	Patients with significant bulbar dysfunction can still derive significant benefit from NIV if their needs are met.	14 studies: - Two RCTs (3, 16) - Six prospective cohorts (20, 21, 27, 37, 38, 65) - Five retrospective cohorts (5, 41, 58, 64, 68) - One cross-sectional study (29)	To further examine the effect of these recommended measures on the efficacy of NIV in patients with significant bulbar dysfunction.
	Measures that should be taken to promote effective NIV use in these patients include: - Multidisciplinary care - Effective secretion management - Optimisation of interface selection and fitting - Initial adaptation, which might involve more intensive inpatient initiation procedures than for those with better bulbar function - Vigilant monitoring and troubleshooting - Proactive management, including attention to the appropriate interface and machine settings over time	Expert opinion.	

ALS, amyotrophic lateral sclerosis; AVAPS, average volume-assured pressure support; NIV, non-invasive ventilation; OSA, obstructive sleep apnoea; RCT, randomised controlled trial; ST, spontaneous-timed (mode)

* Expert opinion: Conclusions drawn by the review authors in their interpretation of the evidence. Some of these conclusions are reflected in the discussion sections of included studies.

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