Is there Evidence that Non-Invasive Ventilation has an Effect on Anxiety and Dyspnea and thus on Health Related Quality of Life in Patients with COPD?

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ABSTRACT

Objective: Patients with Chronic Obstructive Pulmonary Disease are a growing group. The main symptom is dyspnoea and subsequent disease is long, often marked by anxiety and reduced quality of life. The literature indicates a link between anxiety, dyspnoea and quality of life, and that non-pharmacological actions have an effect on these symptoms.

Non-invasive ventilation NIV is a non-pharmacological intervention given to patients in hospitals as well as in homes when stable.

This article therefore raises the following questions: Is there evidence that NIV has an effect on anxiety and dyspnoea, and thus on Health Related Quality of Life HRQL?

Methods: A systematic review including search strings in PubMed, Cochrane and CINAHL.

Results:

- Moderate evidence indicates that NIV has significant effect on dyspnoea.

- Low evidence indicates that NIV has significant effect on HRQL measured by the difference between the intervention and control groups.

-There is no evidence of the effect of NIV on anxiety.

Significance of results: The conclusion is interesting with regard to the perspective of mainstreaming NIV as a palliative part of future pulmonary rehabilitation because the relief of dyspnoea may provide patients with a better opportunity to actively participate in rehabilitation and thereby increase HRQL.

Keywords: Anxiety, COPD, Dyspnoea, HRQL, Non-invasive ventilation (NIV)

INTRODUCTION

The number of patients living with Chronic Obstructive Pulmonary Disease COPD is growing. The course of the disease is usually drawn out. In Denmark, COPD is diagnosed, treated and prevented through COPD guidelines set out by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1]. According to WHO, more than 3 million persons died from COPD in 2012, which represents 6% of global deaths that year [2].

It is estimated that approximately 320,000 persons in Denmark suffer from COPD [3], hereof 50,000 from severe COPD [4]. The total additional cost of treating COPD in Denmark amounts to about 3,345 billion [3].

The main symptom of COPD is dyspnea, which progresses with the course of the disease. The process is characterized by acute exacerbations in the patients' respiratory condition, in addition to normal day-to-day changes [2,5,6].

Dyspnea is difficult to treat and has an impact not only on patients' respiration, but also on their cognitive and emotional functions, especially with regard to the incidence of anxiety and depression [7-11]. The prevalence of anxiety is up to 10 times higher among patients with COPD than in the general population [11-13]. Dyspnea induces anxiety, and anxiety amplifies dyspnea [8,10,14-16].

Because anxiety has a negative impact on dyspnea, it significantly impacts the patient's physical activity levels, lung function, feeling of tiredness, risk behavior and compliance [17-22]. Similarly, anxiety increases the risk of hospital admissions and thus mortality [5,15]. The risk of dying, is 7% during hospitalization and 25% in the following year when admitted with COPD [4].

In addition to having an indirect effect on the number of admissions, mortality and health care costs, anxiety affects the experience of Health Related Quality of Life (HRQL) of patients with COPD [19,20,23]. Studies show that the mental status of the patients [20,22,23-25] has a greater influence on patients' performance status than, e.g. forced expiratory volume in the first second (FEV1), which is traditionally considered a measure of COPD [20,26].

Thus, to relieve dyspnea and anxiety in patients with COPD makes sense, from an economic as well as a patient-related perspective.

The literature discloses that anxiety is often attempted subdued by drugs, i.e., Benzodiazepines and opioids [9,27-31]. As many as 1/3 of elderly patients with COPD initiate a consumption of benzodiazepines. This rate is increases as the disease progresses and especially during exacerbations [9,27]. The benzodiazepines are known for their negative effects on respiration, including decreased minute ventilation, hypoxia, hypercapnia, decreased strength and endurance of respiration muscles and somnolence [27]. This medication, thus, represents a dilemma in symptom treatment, creating evidence that both "American Thoracic Society" and "European Respiratory Society" in their guidelines for the treatment of patients with COPD recommend avoiding Benzodiazepines [27,32].

A Cochrane review focusing on pulmonary rehabilitation has shown, as a secondary outcome, that non-pharmacological measures have a positive effect on both dyspnea and anxiety [33]. According to a randomized clinical trial, breathing exercises have a significant positive effect on anxiety in patients with COPD [24]. Cognitive therapy has also shown an effect on anxiety [7,34]. Meta-analysis and cross-sectional patient's self-reported surveys have shown that when patients believe that they can effectively intervene on their own symptoms, i.e., feelings of self-efficacy, it impacts the way they experience anxiety [13,35,36]. Therefore one must also look into these non-pharmacological elements when focusing on palliation/relief of anxiety.

On this background, new treatment initiatives have self-efficacy as an outcome of interventions such as cognitive therapy, training in the handling of own illness symptoms, breathing exercises and/or physical exercise [13,34,35,37-39]. If patients with COPD have more opportunities for intervention/control of their symptoms, especially their dyspnea, this could contribute positively to their sense of self-efficacy and thereby relieve anxiety and improve quality of life. An opportunity to give patients a sense of control and self-efficacy in relation to the management of dyspnea and the accompanying anxiety could be Non-Invasive Ventilation (NIV).

With NIV treatment a machine assists spontaneous breathing, with a positive pressure in both in- and expiration, via a mask over the nose and/or mouth [32]. Traditionally NIV was thought as a therapeutic treatment focusing on treatment of hypoxia and hypercapnia in patients with COPD [1]. NIV treatment takes place both in the acute phase of the disease in the hospital and in stable phase in the patient's own home. Treatment is initiated with a therapeutic aim. COPD patients who receive this treatment often have advanced disease and thus a high degree of dyspnea and increased risk of anxiety.

When NIV is administrated as home-based, the patient determines when to take the mask on and the extent of the therapy. The patient may intervene on himself when he is feeling dyspnea.

If NIV has an impact on how patients with COPD experience dyspnea and anxiety, because the treatment positively contributes to the patient's ability to control symptoms via self-efficacy, then NIV may reduce the consumption of anti-anxiety and respiration suppressive medicine while having a positive effect on the quality of life.

In spite of this thesis, GOLD advocate in their current guidelines that "NIV combined with oxygen therapy may improve survival, but not the quality of life". This statement is furthermore contradicted by the fact that dyspnea and anxiety are parameters in patients' assessment of HRQL [33].

AIM

The aim of this study is to conduct a review of literature, to seek evidence that NIV treatment affects patients with COPD's experience of anxiety and dyspnea and thus has an effect on HRQL.

METHOD

The following search matrix was set up and searched PubMed, CINAHL and Cochrane. By limiting terms PsycINFO were excluded **(Table 1)**.

Table 1. Search matrix.

BLOCK 1 COPD	BLOCK 2 Anxiety	BLOCK 3 Dyspnea	BLOCK 4 NIV	BLOCK 5 HRQL
COPD(text word) OR "pulmonary disease, chronic obstructive" (MeSH)	Anxiety(MeSH)	Dyspnea (MeSH) Breathlessness	Non-invasive ventilation Non-invasive positive pressure ventilation Non-invasive mechanical ventilation Inspiratory positive pressure breathing Mechanical ventilators Ventilation, non-invasive positive pressure Artificial ventilation Ventilation, mechanical Non-invasive home ventilation	Health related quality of life
"All fields" search 1st April 2016 in Pub Med, retrieved the following result: Block 1=65055 Items found	"All fields" search 1st April 2016 in PubMed, retrieved the following result: Block 2=177292 Items found	"All fields" search 1st April 2016 in Pub Med, retrieved the following result: Block 3=44127 Items found	"All fields" search 1st April 2016 in PubMed, retrieved the following result: Block 4=89316 Items found.	All fields" search 1st April 2016 in Pub Med, retrieved the following result: Block 5=51194 Items found.

These blocks, with associated large discoveries were combined as follows:

- #1: Block 1 and block 4=4076 items found.
- #2: #1 and block 2=32 Items found.
- #3: #1 and block 3=342 Items found.
- #4: #1 and block 5=69 Items found.
- #5: #1 and Unit 2 and Unit 3 and Unit 5=2 items found.

No limits in subsequent search strings were used as the result was already limited **(Figure 1)**.

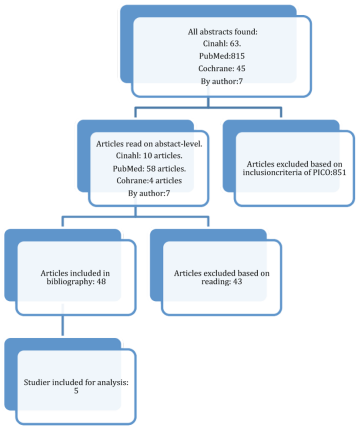

Figure 1. Flowchart of the selection of literature.

Similarly, search strings followed in CINAHL (inclusion criteria; "find specify any of my search items", Danish or English language and full text available), and the Cochrane Library (Inclusion criteria; Cochrane reviews, search the MeSH under the title, abstract and key words). Depending on the search engine's requirements possible inclusion criteria was made as wide as possible and exclusion criteria as narrow as possible, in the desire to make the search wide, to include the maximum number of abstracts/articles. Only PubMed succeeded in finding articles including all five blocks.

The total search resulted in 930 abstracts. 48 was, on the basis of relevance, after reading included in the bibliography of the assignment as a base of the background section and perspective, while 5 were specifically selected to illustrate the question in focus.

RESULTS

Table 2. Assessment of evidence accessed in the following schemes using Cochrane's Grading of recommendations assessment, development and evaluation.

Title	"Two year home-based nocturnal non-invasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients; A randomized controlled trail".	"One year non-invasive ventilation in chronic hypercapnic COPD: Effect on quality of life".	"Non-invasive ventilation in pulmonary rehabilitation of COPD patients".	"The Italian multicenter study on non-invasive ventilation in chronic obstructive pulmonary disease patients".	"Non-invasive positive pressure ventilation in subjects with stable COPD: A Randomized trail.
Author	Duiverman et al. [40]	Tsolaki et al. [41]	Khnlein et al. [42]	Clini et al. [43]	Bhatt et al. [44]
Year	2011	2008	2009	2002	2013
Country	Netherlands	Greece	Germany	Italy/France	Iowa/ USA
Design	Prospective not blinded RCT with Parallel gr.	Prospective not blinded, parallel cohort study. Not randomized	Prospective observational cohort study with retrospective control group/1 year prospective og 1 year retrospective. Not randomized!	French/Italian multicenter based prospective RCT	RCT
Oxford-Evidence level	Oxford evidence 1c	Oxford evidence 2b	Oxford evidence 2b	Oxford evidence 1b	Oxford evidence 1b
Time	2 years	1 year	1 year	2 years	6 months
Follow-up	Follow-up: 3, 6, 12 og 18 months.	Follow-up: 1, 3, 6, 9 og 12 months.	Follow-up: 29 days.	Follow-up: 1 month and every 3 months thereafter up to 2 years.	Follow-up: 6 weeks, 3 og 6 months.
Population	N=56 Intervention: N=24 Mean age (SD); 63 (10) Control group: N=32 Mean age (SD); 61 (8) Inclusion criteria: Patients with COPD (GOLD 3,4).	N=47 Intervention: N=27 Mean age (SD)= 65,2 (8,9) Control group: N=22 Mean age (SD)=68,9 (5,6) Inclusion criteria: Patient's with COPD (severe, very severe according to ATS/ERS guidelines), age<=75, pack years >20.	N=40 Intervention: N=40 mean age (SD):57,9 (9,1) Control group: N=40 Mean age (SD): 56,8(8) Inclusion criteria: Patient's with COPD (GOLD 4) stable phase.	N=90 Intervention: N=43 Mean age (SD):64(7) Control group: N=47 Mean age (SD): 66(14) Inclusion criteria: Patients with advanced COPD treated with Long-Term Oxygen Therapy LTOT min 6 mo.	N=30 Intervention: N=15 Age Median (interquartile range) 70 (66-73) Control group: Age median (interquartile range) 68 (65-78) Inclusion criteria: Stable phase COPD (no exacerbation in 4 weeks before inclusion) $PaCO_2$<52 mm Hg. Fev1<50% of expected. Fev1/FVC<0.70. Min. 10 pack years.
Aim	The purpose was to investigate the effect of nocturnal NIV+pulmonary rehabilitation, compared with pulmonary rehabilitation alone.	The objective was to evaluate the effects of nocturnal NIV in HRQL compared with standard therapy and to find the determinants of HRQL.	The purpose was to test the feasibility and efficacy of NIV in addition to pulmonary rehabilitation.	The purpose was to test the effect of NIV in addition to the Long-Term Oxygen Therapy Ltot, compared to Ltot alone.	The purpose was to investigate the effect of NIV in HRQL and dyspnea in patients with COPD who were normocapnic.
Intervention	Intervention: Nocturnal NIV my 5 h/night treatment titrated after A-gas and saturation, given the moment in their own homes who received standard medical treatment	Interventions: Nocturnal NIV my 5 h/night, titrated by the A gas and the use of auxiliary muscles, given to patients in standard medical treatment in their own homes.	Intervention: Nocturnal NIV treat min 5 h/night, titrated after A-gas. Given to the moment in their own homes, which followed standard	Interventions: Ltot+Nocturnal NIV my 5 h/night, titrated by the A gas and saturation>90 and standard medical treatment.	Interventions: Ltot+Nocturnal NIV my 5 h/night, titrated by the A gas and saturation>90 Control group: Standard medical treatment.

	and participated in a pulmonary rehabilitation program. Control group: Patients who received standard medical treatment and participated in a pulmonary rehabilitation program.	Control group: Had chosen to refrain from offering NIV treatment, but received standard medical treatment.	medical treatment and participated in a hospital-based pulmonary rehabilitation program. Control Group: Standard medical treatment and hospital-based pulmonary rehabilitation program.	Control group: Ltot+standard medical treatment.	
Endpoints	Primary outcome: HRQOL measured by: Chronic Respiratory Questionnaire CRQ. Mauqeri Respiratory Failure Questionnaire MRF (28). Severe Respiratory Insufficiency Questionaries' SRI. Secondary outcomes: Hospitals Anxiety and Depression Scale HADS. Medical Research Council MRC dyspnea scale.	Primary outcome: HRQOL assessed in: SF36 Health survey (Greek validated Questionnaire validated for COPD patients) SF 36 can be divided in to 2 subscales: Physical Component Summery PCS. Mental Component Summery MCS. Secondary outcome: Medical Research Council MRC dyspnea scale.	PrPrimary outcome: HRQOL assessed in SF-36.	Primary outcome: 3 equilateral questionnaires of HRQOL: St.George's Respiratory Failure Questionnaire. SGRQ. Maugeri Foundation Respiratory Questionnaire MRF-28. Dyspnea measured by MRC.	Primary outcome: Dyspnea measured by TDI. HRQL measured by CRQ. Secondary outcome: Changes in Negative inspiratory force NIF, PaO_2, Fev, 6MWD.
Results	Primary outcome: • CRQ • MRF (28) P=0.005 • SRI Secondary outcome: • HADS P=0.05 • MRC P=0.05	Primary outcome: • PSC: P<0.0001 • MCS: P=0.009 Secondary outcome: • MRC: P=0.029	Primary outcome: SF-36 PCS: effect size intervention: 0,00 SF-36 MCS: effect size intervention: 0.73 • Role-function physical: 0.61 • Vitality: 0.83 • Social function: 1.16 • Mental health: 0.57 • Mental Component Summery Score: 0.73 Control group had improved by: • Vitality: 0.67	Primary outcome: • MRF-28 p=0.041 • SGRQ p=0.554	Primary outcome: TDI P=0.03 CRQ-global: No change. CRQ-Mastery P=0.04

Assessment of evidence accessed in the following schemes using Cochrane's Grading of recommendations Assessment, Development and Evaluation GRADE [45,46] GRADE system differentiates itself by relating to the risk of bias by outcome across studies [46] **(Table 2)**. In each case it is color-coded; if the criterion is met (green), it is unclear whether it is satisfied (yellow), or if it is not met (red). From these color codes, the risk of bias of each outcome assessed to be high, insecure or low and thus form the basis for assessing the risk of bias has an effect on the evidence on 3 different levels: "Not serious" (no change in evidence category), "serious" (downgrade by one level), "very serious" (downgraded by two levels) [38]. Evidence category classified into four levels: high (++++), moderate (+++), low (++) or very low (+) [38].

GRADE is designed to reflect the two author's individual assessment. The following figures reflect only a single author's assessment **(Figures 2-5)**:

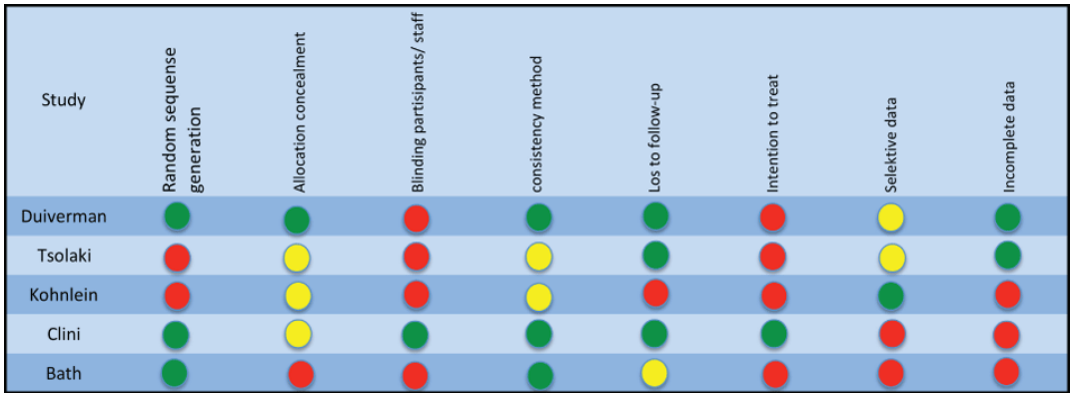

Figure 2. Cochrane GRADE risk of bias.

On this basis, assessed the level of evidence for the studies as follows [40-44]:

Duiverman=high, Tsolaki=low, Kohnlein=low, Clini=high and Bhatt=moderate.

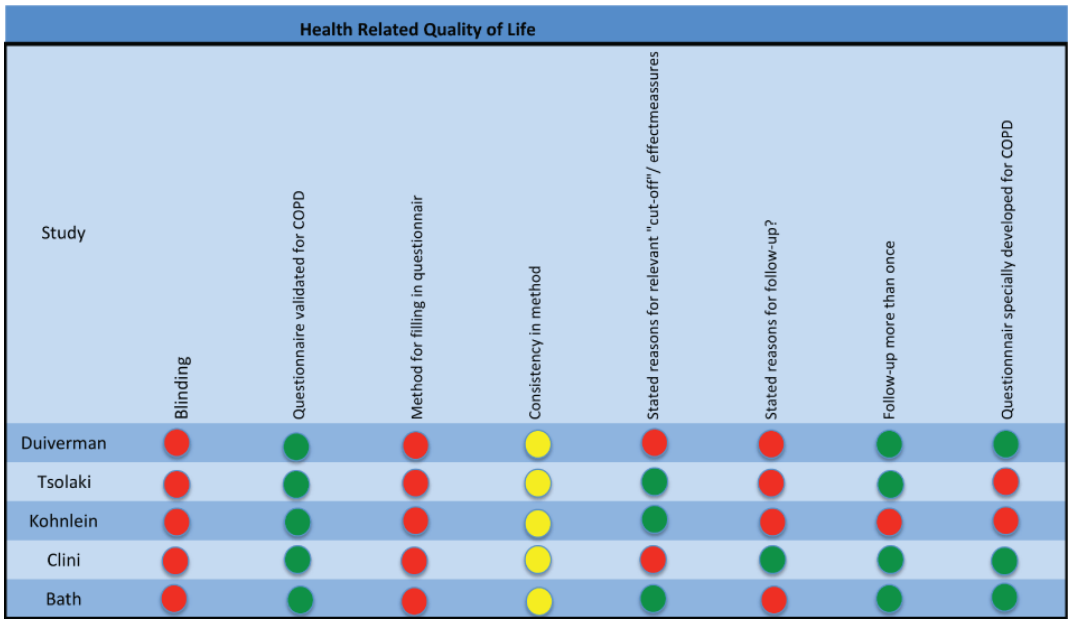

Figure 3. Cochrane GRADE risk of bias table" tailored to bias the outcome HRQL.

Note: Blinding: the patient, researcher or analyst? Validation: is the table approved for the included patient group? Method and consistency of this: is it described if the scheme is completed by the patient or health care worker, which info is given before filling it out, the circumstances under which it is completed and has consistency been ensured? Relevant Cut-off/endpoints: Are there any relevant measure of clinical importance of measuring units? Follow-up: is reasons stated for follow-up/possible considerations with respect to impact on the outcome. Is there any reference to the GOLD standard? Follow-up for more than 1 time: tested more than once, and the possibility that a single measurement can stand alone/regard to the evidence based on the test-retest of the table. Schedule specifically developed for COPD: Are schedules a generic form and then validated or are they specifically designed for patients with COPD?

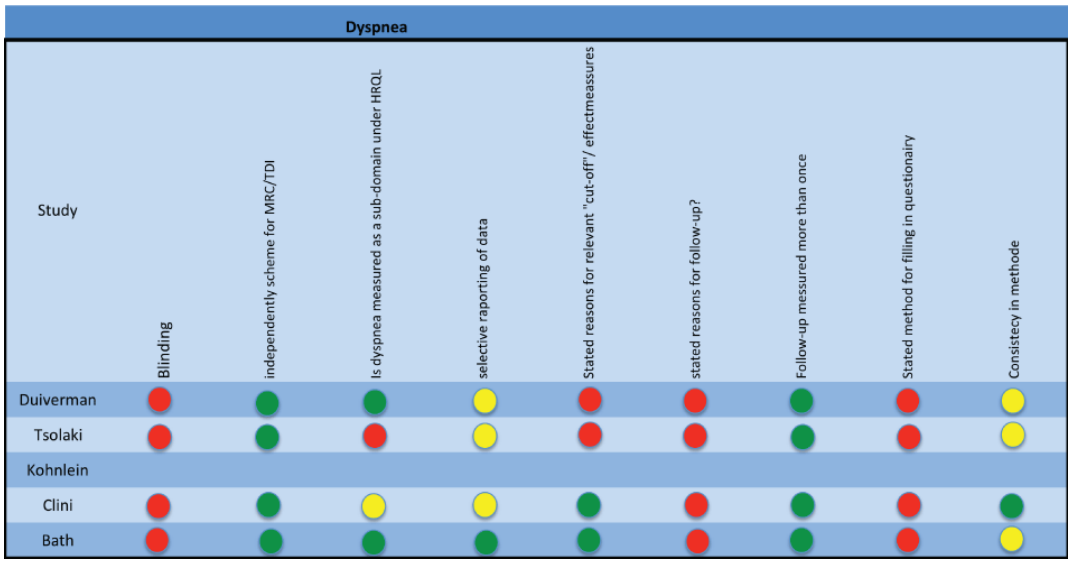

Figure 4. Cochrane GRADE risk of bias table" tailored to bias the outcome dyspnea.

Note: Blinding, appropriate cut-off, reasons for follow-up, follow-up more than once, methodology and consistency for completion of Form: (see note to HRQL above)! Independently scheme: A scheme that only accesses a single parameter, the more sensitively the outcome. Indicated dyspnea as sub-domain under the HRQL: When parameter is included as sub-domain sensibility on outcome may be reduced. Selective reporting of data: The Kept changes in sub-domains as independent expression of relevant outcome (Ex. Dyspnea or anxiety) and does author relate to whether it correlates with independent scale?

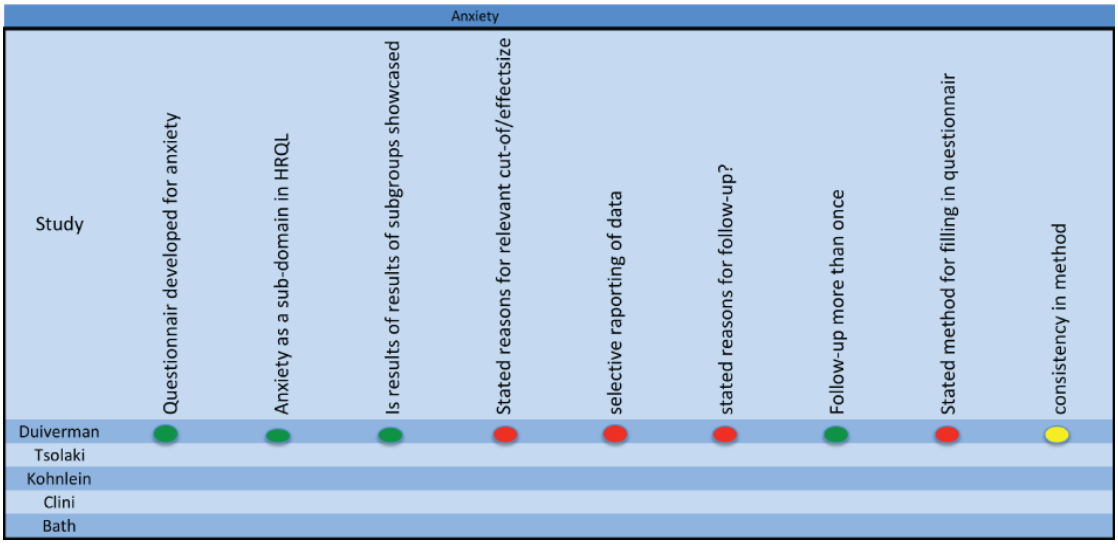

Figure 5. Cochrane GRADE risk of bias table" tailored to bias the outcome anxiety.

Note: See above schemes!

Based on the above analysis assessed following evidence levels of outcome:

HRQL=low, Dyspnea=moderate and anxiety=very low.

RESULTS

The review is focused on the scales, which describes the anxiety, dyspnea and HRQL. Results in the following text are expressed as mean +/- SD 95% CI, unless otherwise indicated

Dulverman et al. [40]

The main objective is to verify the results from a small study at three month follow-up. The aim of the study is to examine whether nocturnal NIV plus Pulmonary Rehabilitation PR, compared with PR alone, improving both primary and

secondary outcome [40]. The primary outcome is HRQL, measured at three different validated questionnaires: Chronic Respiratory questionnaire (CRQ), Maugerie Respiratory Failure questionnaire (MRF-28) and Severe Respiratory Insufficiency Questionnaire (SRI). Secondary outcomes include anxiety/depression measured at the Hospital Anxiety and Depression Scale (HADS) and Dyspnea measured at the Medical Research Council scale (MRC scale).

The study finds that HRQL measured on the CRQ did not change significantly in the intervention group compared to the control group (-1.3 points (95% CI -9.7 two 7.4)). At the same time it was demonstrated that NIV significantly influences HRQL when measured on the MRF-28 scale. The significance of the intervention group compared to the control group (-13.4% (95% CI -22.7 to -4.2; P=0.005). SRI's physical domain improved in the intervention group compared with the control group (10.7% (95% CI 3.8 to 17.6; P=0.003).

The intervention group compared with the control group was significantly improved in both the HADS (-3.8 (95% CI -7.4 to -0.4; p<0.05) as well as MRC (0.4 (95% CI -0.8 to -0.0; p<0.05).

The study shows evidence that NIV as an intervention has a positive significant effect on anxiety/depression measured by HADS and dyspnea measured on the MRC. The study presented conflicting results on the evidence for NIV's positive effect on HRQL, but the authors do not relate to this differentiation. However Duiverman et al. concludes that NIV+PR compared to PR only, has a positive effect on HRQL [40]. Duiverman et al. [40] also describes in his discussion section anxiety/depression score and dyspnea score as determining factors of HRQL. The study does not address anxiety as sub-domain in the SRI.

According to Duiverman et al. [40], there is evidence for the positive effect of NIV on; HRQL and dyspnea. Anxiety is described as sub-domain in HADS and SRI and the study presents no data of sub-domains. This study does not provide the basis of evidence to make a conclusion on the effect of NIV on anxiety.

The weaknesses of this study are the sample size and the fact that to achieve a strength of 80% the population in both groups should have been a minimum of n=40, where it is currently n=32 in the PR group and n=24 in the NIV+PR group. At baseline, there are also significant differences in the two groups according to the number of smokers; 5 of the NIV+PR and 11 in the PR, which is more than double from one group to another.

Another weakness is that the study doesn't argue the choice of scales for the primary outcome. The result section does not show evidence for interpretation/presentation of these scales. For example, the results from SRI are not included in abstract and the study presented nor full data on this chart in the article. The authors do not clarify their choice of scales. They only mention retrospectively in the discussion, that their choice of the method to illuminate HRQL could have been different. Their considerations in relation to the current selection and future alternatives could have contributed insight.

Tsolaki et al. [41]

The main purpose of this study was to investigate the effect of nocturnal NIV in HRQL and to find prospective determinants of HRQL.

The study showed evidence that NIV had significant impact on the HRQL measured at the SF-36, with 8 sub-groups, which could be divided into two sub-domains, respectively Physical Component Summery PCS (31 +/- 4 to 38 +/- 8; P<0,0001) and Mental Component Summary (MCS 28 +/- 7 to 40 +/- 10; p=0.009).

The study also showed evidence that NIV has a positive effect on the measured dyspnea in MRC (3.9 +/- 0.5 to 3.5 +/- 0.7; p=0.029). Furthermore, the study coupler dyspnea measured in MRC and HRQL measured in SF-36. The study displayed evidence that dyspnea is an independent determinant for the PCS and MCS via lines regression analysis. Tsolaki et al. showed that the number of hours in NIV/day was the only independent factor influencing the dyspnea measured in MRC! [41].

This study presents evidence that the number of hours a patient is in the NIV have positive effect on dyspnea measured in MRC and that dyspnea is a determining independent factor of HRQL measured by the SF-36 questionnaire. This study shows evidence that NIV has a positive effect on HRQL and dyspnea. This study does not address anxiety as an independent factor.

The shortcomings of this study are that it is not randomized. All patients were offered NIV, and those who did not want NIV became the control group. This could create patient bias in relation to motivation. The author relates to it, but attributes no great displacement to it due to a high degree of compliance in the control group. In addition, patients were excluded from the study for a month if they had exacerbations during the trial, creating a risk of bias due to positive displacement of the results.

Khnlein et al. [42]

The aim of this study was to test the feasibility of NIV as a tool in Pulmonary Rehabilitation PR. The intervention group and the control group were comparable at baseline and were particular compared by HRQL measured by the SF-36 questionnaire. Effect size (ES) of clinically meaningful changes in terms of SF-36 scores for pulmonary patients, via statistical tests divided into (0.20) small, (0.5) and moderate (0.8) great.

The study found that the intervention group had improved as follows:

- Role-function physical: 0.61
- Vitality: 0.83
- Social function: 1.16
- Mental health: 0.57
- Mental Component Summary Score: 0.73
- The control group had improved as follows:
- Vitality: 0.67

This study shows evidence that NIV has an effect on HRQL, indicated by effect size, but it does not address the effect of NIV on anxiety or dyspnea.

The shortcomings of this study are that it is not randomized, not blinded, as well as the fact that the control group was historically/retrospective and that hereby the cohorts were not parallel. The study does not address that both control and intervention groups increase on vitality.

Clini et al. [43]

The aim of the study was to test the effect of nocturnal NIV+Long-term Oxygen Therapy Ltot, compared to Ltot alone. The endpoints are the severity of hypercapnia, consumption of health resources and HRQL. Dyspnea was measured on the Medical Research Council MRC score, while HRQL was measured on the St George's Respiratory Questionnaire SGRQ and Maugeri Foundation Respiratory Failure Questionnaire MRF-28 [43].

Multicenter study shows 24 months that NIV has an effect on dyspnea measured on the MRC scale with p=0.013 as evidence of significant difference between the intervention group compared with the control group (0.600 (95% CI 0.15 to 1.05). It also demonstrates that NIV has an effect on HRQL measured via MRF-28 (7.1 (95% CI 0.13 to 4.07; p=0.041)) also constitute evidence of significant difference between the intervention group and the control group. There appears no effect of NIV in HRQL measured by SGRQ, the difference between the intervention group and the control group, p=0.554.

So contradictory results, depending on the scale, compared to evidence of efficacy of NIV in HRQL in this study. The study shows evidence for NIV's significant effect on dyspnea measured on the MRC, but does not address anxiety as an independent parameter.

The weakness of this study is that it does not in the results indicate effect size and confidence interval for SGRQ. The choice of scale to HRQL is not stated and the discussion emphasized the lack of correspondence between the results, but the author does not speculate in reasons of this lack, he only states that in the future there is a need for more specific instruments.

Bhatt et al. [44]

This prospective RCT aims to test whether NIV can improve quality of life and reduce dyspnea in patients with severe COPD, which is stable (no exacerbations for 4 weeks prior to enrollment) and relatively normocapnic ($PaCO_2$<52 mm Hg equivalent to 6.9 kPa). Population N=30 were randomly assigned to either an intervention arm who received NIV (15.5 cm H20) in their own homes a 6 h/night for 6 months or a control arm with standard treatment [44]. Primary outcome is HRQL accessed through the Chronic Respiratory Disease questionnaire (CRQ) and dyspnea measured on Transitional dyspnea Index (TDI). Follow-up at 6 weeks, 3 months and 6 months. The study indicates P<0.05 considered statistically significant [44].

The study finds that dyspnea measured on TDI is significantly reduced in the intervention group versus control at 6 weeks (P<0.001) and 3 months (P<0.005), while at 6 months of follow-up there is only significant difference (P=0.03) between the intervention and control groups in TDI-task domain as one of five sub-domains [44]. In all three measurements the difference in TDI between intervention arm and control is more than one device, which Bhatt indicates as the minimal clinically important difference.

Quality of life in terms of CRQ at the 6 months of follow-up show a significant difference between the change in the NIV-arm (0.6) versus the change in the control arm (-0.1), corresponding to P=0.04 in the domain "Mastery", which is one of 4

sub-domains [44]. This change in the intervention group is only just on the border to have a clinically relevant effect since Bhatt indicates that minimal clinical difference measured in CRQ defined as a change in score equal to 0.5 units. Bhatt et al. [44] however, shows through Spearman's analysis that there is a very strong and significant correlation between the number of hours in the NIV and CRQ Mastery domain r=-0.83, P<0.001 [44].

The study shows hereby evidence that NIV has clinically relevant and statistically significant effect on dyspnea measured on TDI. The study shows evidence of statistically significant effect of NIV on quality of life in terms of CRQ-mastery domain at six-month follow-up, but cannot show a clinically relevant effect on some of the CRQ's four sub-domains. The study does not address anxiety.

A weakness of this study is that patients in average were treated by NIV in 3.1 h/night, despite the fact that the intervention was designed to 6 h/night. The limited number of hours in treatment reduces the ability to show an effect of the intervention; thus, lack of an effect on global CRQ. Another weakness is that the study does not address possible explanations for the poor effect of the intervention in terms of global CRQ versus significant and clinically relevant efficacy as measured by TDI. Bhatt complains that he does not believe that a control arm consisting of only men is important for tolerance of NIV, but he does not address how this bias could affect HRQL.

DISCUSSION

Four out of five studies showing significant efficacy of NIV in dyspnea measured on the MRC and TDI. Based on the GRADE evidence the level of dyspnea as outcome across the studies is assessed to be moderate; one of its strengths is that dyspnea is assessed in both independent scale and as a sub-domain under the HRQL. All the authors of the respective studies link dyspnea and HRQL in their discussion.

One study relates to anxiety, but this only as a sub-domain under HADS and SRI, not as an independent parameter. Anxiety forms sub-domains of the scales in HRQL, but none of the studies relate to it nor do they present results that can serve as evidence of efficacy of NIV in these. Grade asses the level of evidence for anxiety as an outcome across the studies as being low.

The clinical studies discussed in this task are inconsistent in their findings on HRQL. The reasons are not specified, but one can speculate that the NIV as a treatment of COPD is an intervention in development. Back in the 1990s NIV were exclusively offered as intensive treatment in patients with COPD and as of later it is beginning to be used in the medical wards (about 2000). Over the last 5-10 years NIV has begun to move in as a treatment in patients' own homes; and only through the last 5-6 years NIV has begun to be a mainstream adjunct to pulmonary rehabilitation. Outcomes for intervention have shifted the focus from endpoints as, e.g. A-gas to HRQL. Furthermore, HRQL a higher degree of complexity due to subscales, which can make it difficult to show an effect on the basis of the entire scale. Duiverman et al. [40] have used three different scales to document the effect of NIV in HRQL, Clini et al. [43] have used two different scales, while Tsolaki et al. [41] has put the focus of his study to find the determining factors for HRQL.

In total HRQL is measured 8 times in 5 studios in 5 different scales. When the effect of NIV measured on the SF-36, there is evidence for positive effects of NIV measured by the difference between the intervention group and the control group.

When the effect of NIV is measured by MRF-28 studies presents evidence of significant positive effect of NIV, measured by the difference between the intervention group and the control group.

When the effect of the NIV measured respectively CRQ and SGRQ studies cannot show evidence that NIV has an effect on HRQL, which is remarkable since both of these schemes are validated for COPD. Bhatt managed, however, to show statistically significant effect of NIV, but this only on a part-domain "Mastery" under CRQ [44].

When the effect of the NIV is measured on the SRI, the only evidence for a positive effect is on the physical sub-domain, not on the full scale.

Four results in eight produced by two scales (SF-36 MRF-28) shows clear evidence of significant effect of NIV in HRQL between intervention and control group. Both Duiverman et al. [40] and Clini et al. [43] complains that respectively CRQ's and SGRQ's lack of specification with respect to the effectiveness and the patient population may be biased by the lack of correspondence between the results of these and those produced via MRF-28 and SRI. Method for filling in the form, consistency of this, the number of follow-up measurements and possible relevant reasons for these as well as whether the form is generic and subsequently validated for COPD or specially developed, are all factors that affect the bias in relation to HRQL as an outcome. GRADE illustrates the level of evidence on the basis of these as being low. All studies [40-44] conclude, despite conflicting results that the NIV has an effect on HRQOL.

Furthermore, the basis of evidence behind the conclusion of the focused questions is vague, since two out of five studies is characterized as Oxford evidence level 2b, since they are not randomized [41,42] Lack of randomization may be

a significant selection bias in relation to systematic distortion of data [47,48] the studies are included, as they illustrate the focused questions. If they are excluded, the conclusion will be unaffected.

CONCLUSION

- There is moderate evidence that NIV has significant effect on dyspnea [40,41,43,44]
- There is low evidence that NIV has significant effect on HRQOL measured by the difference between the intervention and control groups [40-44].
- Only Duiverman et al. [40] is related to anxiety. Anxiety is described as sub-domain in the HADS and SRI, but the study puts forward no evidence that NIV has an effect on anxiety as an independent concept.
- Thus there is no evidence of NIV's effect on anxiety.

PERSPECTIVE

It amazes and provides evidence for further studies that literature so clearly linking anxiety and dyspnea in patients with COPD, while clinical trials of NIV as intervention in the same group of patients only shows significant effect on dyspnea, but no evidence of effect on anxiety.

Tsolaki et al. [41] explains that dyspnea is an independent determinant for HRQL. Both Tsolaki et al. [41] and Bhatt et al.'s [44] report on the number of hours in NIV per. day was the only independent factor influencing dyspnea measured in MRC.

It might be interesting to elucidate the anxiety in a similar way as the literature provides evidence for the link between anxiety and dyspnea, as well as between anxiety and HRQL [22].

Quantitative tests that only measure anxiety in patients with COPD, has not been seen in studies included in this task bibliography. It would be interesting for future studies to put the focus here.

Another angle of anxiety is given by Strang et al. [49], through her qualitative study. Applications are made to divide anxiety in COPD patients into degrees, which is interesting when speculating in how to detect and measure anxiety in future research. It is clear that wide records of anxiety are unattractive, if in fact only elements of fear that is clinically relevant to the intervention, we want to try.

Strang et al. [49] indicates that anxiety can be divided into two main groups: Life Anxiety and fear of death: Life anxiety, fear of opportunities, fear of life changes, fear of unpredictability.

Death anxiety; fear of suffering/feeling of suffocation, fear of what happens before death, fear of separation, fear of isolation [49]. Patients with COPD experience, according strange, mainly fear of death associated dyspnea. One can speculate that future research should have the fear of death as primary outcome of the interventions we want to test against anxiety, as it is dyspnea we have evidence that could reduce the NIV [40-44].

One can further consider whether NIV could address fear of life through self-efficacy. If we through future studies may show that self-efficacy has a positive effect on the fear of life and that NIV can contribute positively to self-efficacy, thus a new way to intervene on HRQL in patients with COPD will be given. These speculations are supported by a feasibility study including patients with heart failure and diabetes by Ciccone et al. [50]. “Project Leonardo” elucidates that patient-skill-building through treatments path’s that allows doctors to provide instrumental interventions in a proactive approach lessening the gap between recommendations of clinical guidelines and the care patients might receive at home, may improve patient confidents to deal with “disease-related problems” and there by increase self-efficacy and positively impact HRQL [50].

It has been such that in the treatment of patients with COPD palliation has not been implicit, as the tradition has been in areas such as cancer [49]. The reason for that is supposedly in the reversible exacerbations and thus unpredictability of the forecast [49].

The conclusion is interesting with this perspective to mainstream NIV as a possible palliative part of future pulmonary rehabilitation because the relief of anxiety and dyspnea, via self-efficacy, will give patients a better opportunity to actively participate in rehabilitation programs and thus increase the quality of life.

The focus of the intervention hereby becomes the determining factor of HRQL in order to be able to increase the effect of the same. New studies with the aim of developing questionnaires to illuminate HRQL in patients with COPD, focusing on the sensitivity with respect to the psychological domain and including anxiety might therefore be relevant.

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