Blinded Patient Preference of Morphine Compared to Placebo in the Setting of Chronic Refractory Breathlessness – An Exploratory Study

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Word count

Manuscript	2432
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Abstract:

Context

Patients' preference for morphine therapy has received little attention in the setting of chronic refractory breathlessness. However, this is one important factor in considering longer term therapy.

Objectives

The aim of this secondary analysis is to explore blinded patient preference of morphine compared to placebo for this indication and to define any predictors of preference.

Methods

Data were pooled from three randomized, double-blind, cross-over, placebo-controlled studies of morphine (4 days each) in chronic refractory breathlessness. Blinded patient preferences were chosen at the end of each study. A multivariable regression model was used to establish patient predictors of preference.

Results

Sixty-five participants provided sufficient data (60 males; median age 74 years; heart failure 55%, COPD 45%; median ECOG 2). Forty-three percent of participants preferred morphine (32% placebo and 25% no preference).

Morphine preference and younger age were strongly associated: OR = 0.85 (CI = 0.78, 0.93; $p<0.001$). There was also an inverse association between morphine preference and sedation OR = 0.77 (CI = 0.60, 0.99; $p<0.05$). An inverse association was also seen between nausea and morphine preference in the univariate model only ($p<0.05$). No association was seen between morphine preference and breathlessness intensity, either at baseline or change from baseline.

Conclusion

Participants preferred morphine over placebo for the relief of chronic refractory breathlessness. Morphine offers clinically important improvement but net benefit can be easi-

ly outweighed by side-effects reducing net benefits. Side-effects require aggressive management to allow more patients to realise benefits.

Keywords: patient preference, palliative care, breathlessness, COPD, morphine, randomized controlled trial

Running title: Blinded patient opioid preference in dyspnoea

Introduction:

Persistent breathlessness despite optimal medical therapy and a person's own adaptation (refractory breathlessness), is prevalent in people with advanced disease.[1] Such refractory breathlessness is multifactorial, influenced by physical, psychosocial and spiritual factors.[2]

Studies have demonstrated encouraging results for the safe use of opioids for reducing chronic refractory breathlessness.[3-7] A secondary pooled analysis of three randomized, double-blind, cross-over studies revealed that younger age and higher baseline breathlessness were predictors of greater likelihood of response to opioid therapy whereas functional status and aetiology were not.[8] Further, analysis of this pooled dataset found that a difference of only 9mm on a 0-100mm visual analogue scale (VAS) was sufficient for a participant to prefer one treatment arm over another.

Patient preferences for an intervention are derived from the net benefit - that is, patients' perceived balance of benefits and side-effects. A better understanding of preferences may allow insight to improve individually tailored prescribing for refractory breathlessness. Factors not yet identified could also influence the net clinical effects in patients' perceived response, impacting on choice and ongoing compliance.

The aim of this study was to explore blinded patient preferences for morphine or placebo for chronic refractory breathlessness from data pooled from the only three double-blind, cross-over, randomised controlled trials (RCTs) performed in this setting[4-6] – two adequately powered to detect a minimally clinically important difference (MCID)[4,5,9] and one pilot study.[6]

Methods:

Design: Ninety-three participants with refractory breathlessness, defined as that which persists despite optimum treatment of the underlying condition,[5]were included in these studies. Inclusion criteria in this pooled analysis included completion of the cross-over trial and availability of blinded patient preference for the arm of the study which they felt *provided better benefit for breathlessness*. In the Oxberry *et al* study patients were randomised to morphine, oxycodone or placebo.[4] To optimize comparability in the

analysis, patients whose blinded preference relied on oxycodone were excluded (n=9). Almost all participants had heart failure (HF; n=36) or chronic obstructive pulmonary disease (COPD; n=29). Two patients had other aetiologies (restrictive lung disease (n=1) and cancer (n=1)) and were also excluded leaving 65 participants (Figure 1). Data were already anonymised. Ethics confirmed that permission was not required for analysis of pooled, anonymised data, where appropriate written informed consent had been obtained for each participant.

Methods: Measurements of breathlessness before and after 4 days of morphine (20mg/day or 10 mg/day if creatinine > 200 μmol/L (n=2)), and placebo were collected, seeking to define the effect of morphine on refractory breathlessness. The studies' methods are described in detail elsewhere, including the rationale for combining measures of breathlessness intensity and performance status.[4,5,6]

Study participants: Participants had chronic refractory breathlessness. Baseline participant characteristics collected by all included studies were age, gender, disease aetiology, breathlessness intensity and functional status.

Scale measurements: Numerical Rating Scale (NRS) were converted to Visual Analogue Scales (VAS) as patients' reporting have similar distributions[10,11] and thus NRS scores were represented as equivalent 0/100 in the pooled data. For the functional status, New York Heat Association (NYHA) was converted to Karnofsky Performance Scale (KPS)[12] and all measures using KPS were converted to Eastern Cooperative Oncology Group performance scale (ECOG).[13] For toxicity, qualitative outcomes were used due to heterogeneity in the scales used.

Statistical analysis:

Anova or Kruskall-Wallis tests compared differences between groups for covariates that were normally and non-normally distributed respectively. Chi-square tests compared proportions for categorical variables between groups. The primary outcome, morphine preference, is trichotomous: morphine preference; preference for placebo or no preference. Multivariable ordinal logistic regression assessed associations between morphine preference and age, performance status (ECOG), disease aetiology (HF *vs* COPD), baseline breathlessness, improvement in breathlessness, nausea, sedation and constipa-

tion. Improvement in these four symptoms was defined as the change in each attribute over the morphine study period minus the change in each attribute over the placebo period. The proportional odds assumption was examined (using Stata's brant command) and no evidence of model violation was found (p=0.66). Results are presented with 95% confidence intervals and a p-value of less than 0.05 (two-sided) is considered statistically significant. All analyses were performed with Stata 13.1, (StataCorp, Texas, USA).

Results:

Baseline data from each study are presented in Table 1. Changes in breathlessness achieved in each study are described in Table 2. The combined dataset yielded a population with a mean (sd) age of 71.6 (9.8) years of whom 60 were male. (Table 1) Disease aetiology for breathlessness was HF (55%) and COPD (45%). The median ECOG was 2 (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours) and the median (IQR) baseline breathlessness was 48mm (30 to 60) indicating moderately intense breathlessness.

Data from 28 participants were excluded or missing (Figure 1) with 11 participants not completing the cross-over, and missing blinded preference data in 6 participants. A relative predominance of the excluded subjects were females but otherwise clinic and demographic characteristics were similar between the two groups.

Preference: Twenty-eight participants (43.1%) preferred morphine, 21 (32.3%) placebo and 16 (24.6%) had no preference. For the patients who stated preference, median breathlessness improvement is presented in Figure 2.

Predictors of preference: In multivariable analysis, there was a strong association between morphine preference and younger age (OR = 0.85 (CI = 0.78, 0.93; p<0.001); Table 3). There was also an inverse association between morphine preference and sedation (OR = 0.77 (CI = 0.60, 0.99; p<0,05)). An inverse association was seen between nausea and morphine preference in the univariate model only (p<0.05). No association was seen between morphine preference and breathlessness intensity, either at baseline or change from baseline.

Fifty-five percent of the patients with HF preferred morphine compared to 28% of people on COPD although this was not statistically significance (OR = 0.50 (95% CI = 0.07, 3.38); p=0.48). Only one study provided information on sleep quality[5]. None of the patients whose sleep quality improved on morphine showed a preference for this drug and so this was not included in regression modelling.

Analysis was conducted exploring three adverse effects on morphine preference. There was no multivariate association between blinded patient preference and nausea (p=0.25), although in the univariate analysis those experiencing nausea were less likely to prefer morphine (p=0.049). No association between constipation and blinded patient preference was evident (Table 3).

Discussion:

This secondary analysis showed that younger age is an important factor in opioid preference for the relief of refractory breathlessness when compared with placebo. Additionally, there is an inverse relationship between the side-effects of sedation and nausea, and morphine preference, which suggests that these side-effects can easily outweigh any benefits obtained.

Younger age: Younger age is correlated with patient preference. One observation in this dataset that may help to explain this difference is that there was a lower frequency of nausea in younger participants (13% under 70 and 26% over 70 years old). A sub-group analysis to determine the predictors of preference amongst younger participants was not conducted since there were insufficient participants to conduct a thorough statistical analysis. Additionally, it is possible that an opioid-related reduction of sympathetic drive may be more effective in younger people which may relate to some dimensions commonly associated with breathlessness. Future studies could explore this sub-group in more detail.

Disease aetiology: The proportion of participants who preferred morphine was notably higher in heart failure than COPD. Extensive work has been conducted on the role of opioids in the relief of breathlessness. Central opioid receptor pathways seem to be aetiology independent,[14] much discussion is still ongoing regarding the role of different

aetiology-specific peripheral pathways for breathlessness.[15] Future work should address this issue in more detail.

Baseline breathlessness intensity and clinical response: On an individual level, it would appear that higher clinical response rates may lead to higher morphine preference rates.[4,6] In this set of data, baseline breathlessness intensity did not correlate with blinded patient preference. This finding was unexpected since previous work has shown that higher values of baseline breathlessness were predictors of response to opioid therapy.[8] Nevertheless, morphine reduces but does not eliminate breathlessness and the presence of undesirable side effects seems to have a clear impact on patients' choice, outweighing any clinical benefit obtained.

Other measures such as the affective component of breathlessness (the unpleasantness of breathlessness) may help to explain why more people, while still blinded, chose morphine than the other options. None of these studies included an affective measure.

Functional status: No correlation was found between baseline functional status and blinded patients' preference. The studies did not measure physical functioning, either for activities of daily living or physical activity, during or at the end of participation. Patients may continue to exert themselves to the same level of breathlessness so that they may feel that their breathlessness has not changed while on morphine although they are more active. Intensity of breathlessness may ultimately improve but only over time as skeletal muscles and sympathetic activity respond to improved conditioning.[16,17] Therefore, it is likely that these studies have not captured all the patient-relevant benefits.

Alternatively, a lower functional status can predispose patients to a higher degree of immobility which could be thought to reduce breathlessness and exacerbate other adverse symptoms such as constipation.

Adverse Effects: There were inverse relationships between blinded morphine preference and separately sedation and nausea. Constipation did not seem to play a significant role in morphine preference. On the whole, patients' preference for morphine seems to be

hindered by the occurrence of side effects, at times possibly overshadowing any direct effect on the relief of breathlessness.

Previous studies have analysed patient preference in several fields of medicine with conclusive evidence that medication efficacy and even symptom control are sometimes secondary when compared to medication induced side effects.[19,20] Some studies also reached the conclusion that lack of sedation or nausea is particularly important when preferring or adhering to one therapy over another.[20-22] In the setting of pain control, the importance of side effects has also been noted.[23,24,25]

The minimally clinically important difference (MCID) in chronic breathlessness is smaller when compared to acute breathlessness with the implication that any harms, toxicities or side-effects may have greater impact on patient preference in chronic breathlessness.[9,26] This highlights that side effects should be carefully addressed and aggressively handled which ultimately might improve the rates of a perceived net clinical benefit, best expressed by patients' blinded preference and, ultimately, long term compliance with medications.

These data included three short term studies with a cross over design. As it is known, unwanted side effects are most strongly noted in the first days of morphine treatment and often preventive medication is required. In these studies, drugs like anti-emetics or laxatives were not regularly used. As such, the first four days of therapy may not be representative of longer term therapy.

Quality of sleep: Previous studies have shown improvement in quality of sleep in other clinical contexts, at the appropriate morphine dosages.[27] None of these studies however focused on morphine preference. Only one of the initial studies analysed herein included data on sleep quality,[5] but participants in this study who reported decreased breathlessness whilst taking morphine were also likely to report improved sleep quality with morphine ($p=0.039$). Despite an improvement in sleep quality in the morphine arm, this was not a factor in determining morphine preference.

Strengths of the study: To our knowledge, this was the first study evaluating blinded patient preference for morphine in the setting of chronic refractory breathlessness, alt-

hough previous analysis of this pooled dataset has investigated the clinical improvement in breathlessness intensity required for patients to choose one treatment arm over another irrespective of final choice.[9] This parameter has been largely under-evaluated while there is evidence to show that patient preference and lack of adverse effects is often associated with compliance[22,28,29] and, possibly, clinical outcomes.

Limitations: This was a *post-hoc* (secondary) analysis conducted on three studies. Two of these studies were adequately powered and one was a pilot. This was an exploratory, hypothesis generating study. The main aim thus was to provide a basis for future research.

The study conducted by Oxberry *et al* had three arms (morphine, oxycodone and placebo). The patients that preferred oxycodone were excluded from the analysis. Apart from making the data more comparable, as previously stated, there is significant controversy on the role different opioids play in the relief of breathlessness.[30] Further adequately powered studies are necessary to shed light into this topic.

Measuring breathlessness constitutes a challenge. The most commonly used measurement scales in both clinical practice and research rely solely on uni-dimensional measurement of breathlessness intensity. Given the multi-dimensional nature of this symptom, it is easy to miss important benefits obtained with morphine treatment. In addition, a similar issue applies to unidimensional measurements of other symptoms such as nausea and sedation, such as the measurement used in these studies. This unidimensional assessment of side-effects might also miss important features that may significantly influence patients' preference.

Furthermore, in order to analyse breathlessness scores, functional status and adverse effects, it was necessary to achieve common outcome measures, converting different scales. This could have had an impact in the obtained results.

Sample: The studies analysed contained a predominance of male subjects. The relative proportion of female subjects who did not complete the cross-over was higher than their male counterparts. The opioid trial period was of 4 days and it could be that were adverse events such as nausea and sedation treated more aggressively as opioids were ini-

tiated, there could have been more completions, especially as these symptoms often completely resolve soon after opioids are initiated. Longer term data are needed to answer this question. In terms of aetiology, the analysis is limited to participants with COPD and heart failure.

Clinical implications: This study analysed blinded participants' preferences rather than the stated primary outcome. In fact, there was no significant direct association between change in breathlessness intensity and blinded morphine preference. This highlights the need to consider patients' perceived net benefit when initiating a therapy including whether level of function improves. The occurrence of side-effects should be actively monitored and aggressively treated. Routine enquiry about other important patient-relevant outcomes such as perceived breathlessness unpleasantness and exercise tolerance may help assess whether opioids have provided net clinical benefit.

Unanswered questions and future directions: Adequately powered randomized, double blind studies should be performed to address the issues concerning predictors of preference. Also, predictors of side effects and the ways to prevent them should be addressed, since they seem to be a key factor in influencing blinded patients' preference. This work also outlines the need to include other measures of breathlessness, such as the affective component associated and an objective measure of physical activity and function. This could explain the apparent lack of correlation between morphine preference and clinical response. Given the age related asymmetries of clinical response and preference for opioid therapies, sub-group analysis of younger and older patients should be considered in future studies.

These data included three short term studies. Longer term studies using morphine may help to determine if side effects have the same impact on patients' preference.

Conclusions

In this study, participants preferred morphine over placebo for the relief of chronic refractory breathlessness. Morphine offers clinically important improvement but net benefit is easily outweighed by side-effects reducing overall preference. Side-effects require

aggressive management to allow more patients to realise benefits. Single, unidimensional measures of breathlessness may miss key benefits of therapy

Conflict of interests:

DCC has received inventor payments and worked as a consultant to Mayne Pharma; received an unrestricted research grant from Mundipharma; been an unpaid member of an advisory board for Helsinn Pharmaceuticals. MJ has worked as a consultant to Mayne Pharma. APP has research funding from the National Institute of Nursing Research, National Cancer Institute, Agency for Healthcare Research and Quality, DARA, Glaxo Smith Kline, Celgene, Helsinn, Dendreon, Kanglaite, Bristol Myers Squibb and Pfizer; these funds are all distributed to Duke University Medical Center to support research including salary support for APP. Pending industry funded projects include: Galena and Insys. She has had consulting agreements with or received honoraria from (>$5,000 annually) Bristol Myers Squibb and ACORN Research. Dr. Abernethy has corporate leadership responsibility in athenahealth (health information technology [IT] company; Director), Advoset (an education company; Owner), and Orange Leaf Associates LLC (an IT development company; Owner). All other authors declare they have no conflict of interest.

Acknowledgements

The authors wish to thank Ms Debbie Marriott for her ready assistance and for her expertise in manuscript formatting and submission.

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Table 1 – Characteristics of the 65 participants who provided data on opioid or placebo preferencechoice for chronic refractory breathlessness.

Variables	Johnson et al.	Abernethy et al.	Oxberry et al.	P-value for difference
	n=10	n=29	n=26	
Age (years), median (IQ 25-75)	**66.2 (11.6)**	**75.8 (5.1)**	**69.1 (11.4)**	**0.005**
Male gender, n(%)	10 (100)	26 (89.6)	24 (92.3)	0.84
HF disease†, n (%)	**10 (100)**	**0 (0)**	**26 (100)**	**<0.001**
Intensity of baseline breathlessness, median (IQ 25-75)	**46.5 (14.3-58.0)**	**46.0 (30.0-60.0)**	**50.0 (30.0-60.0)**	**<0.001**
ECOG , n(%)				**0.002**
ECOG 1	0 (0)	9 (31.0)	5 (19.2)	
ECOG 2	10 (100)	13 (44.8)	21 (80.8)	
ECOG 3 and 4	0 (0)	7 (24.1)	0 (0)	

† HD vs. COPD

Table 2 – Improvement in chronic refractory breathlessness and blinded patients preference for morphine.

	Baseline breathlessness	**Absolute breathlessness improvement**	**Pts that preferred Morphine (%)**
Study	Median (IQ range)	Median (IQ range)	
Johnson *et al* (N=10)	46.5 (14.25 to 58)	18 (2.75 to 38.25)	6 (60%)
Abernethy *et al* (N=29)	46 (30 to 60)	0 (-12 to 17)	8 (27.6%)
Oxberry *et al* (Morphine arm) (N=26)	50 (30 to 60)	10 (0 to 12.5)	14 (53.8%)
Combined	48 (30 to 60)	9 (-1.5 to 20)	28 (43.1%)

Table 3: Associations between morphine preference and variables from pooled data of three randomised, double-blind, placebo controlled cross over studies of morphine for refractory breathlessness.

	Univariable□	Multivariable‡
Breathlessness	→ (95% CI)	→ (95% CI)
Gender	2.07 (0.34, 12.54)	2.95 0.30, 28.85)
Age	**0.88 (0.81, 0.94)*** **	**0.85 0.78, 0.93)*** **
Aetiology of breathlessness	0.55 (0.22, 1.36)	0.46 (0.07, 3.18)
Improvement in breathlessness of day 4 over	0.99 (0.98, 1.01)	1.00 (0.98, 1.02)
Baseline breathlessness	1.00 (0.98, 1.01)	1.00 (0.97, 1.03)
Nausea	**0.82 (0.68, 1.00)***	0.84 (0.97, 1.03)
Sedation	0.92 (0.76, 1.11)	**0.77 (0.60, 0.99)***
Constipation	1.58 (0.62, 4.04)	1.61 (0.42, 9.16)
Eastern Cooperative Oncology Group performance scale		
2	0.49 (0.19, 1.32)	0.24 (0.04,1.43)
3	0.77 (0.17, 3.50)	1.00 (0.11, 9.13)

p<0.05 *, p < 0.01**, p<0.001***

Fig 1 – Diagram concerning the selection of patients for this study.

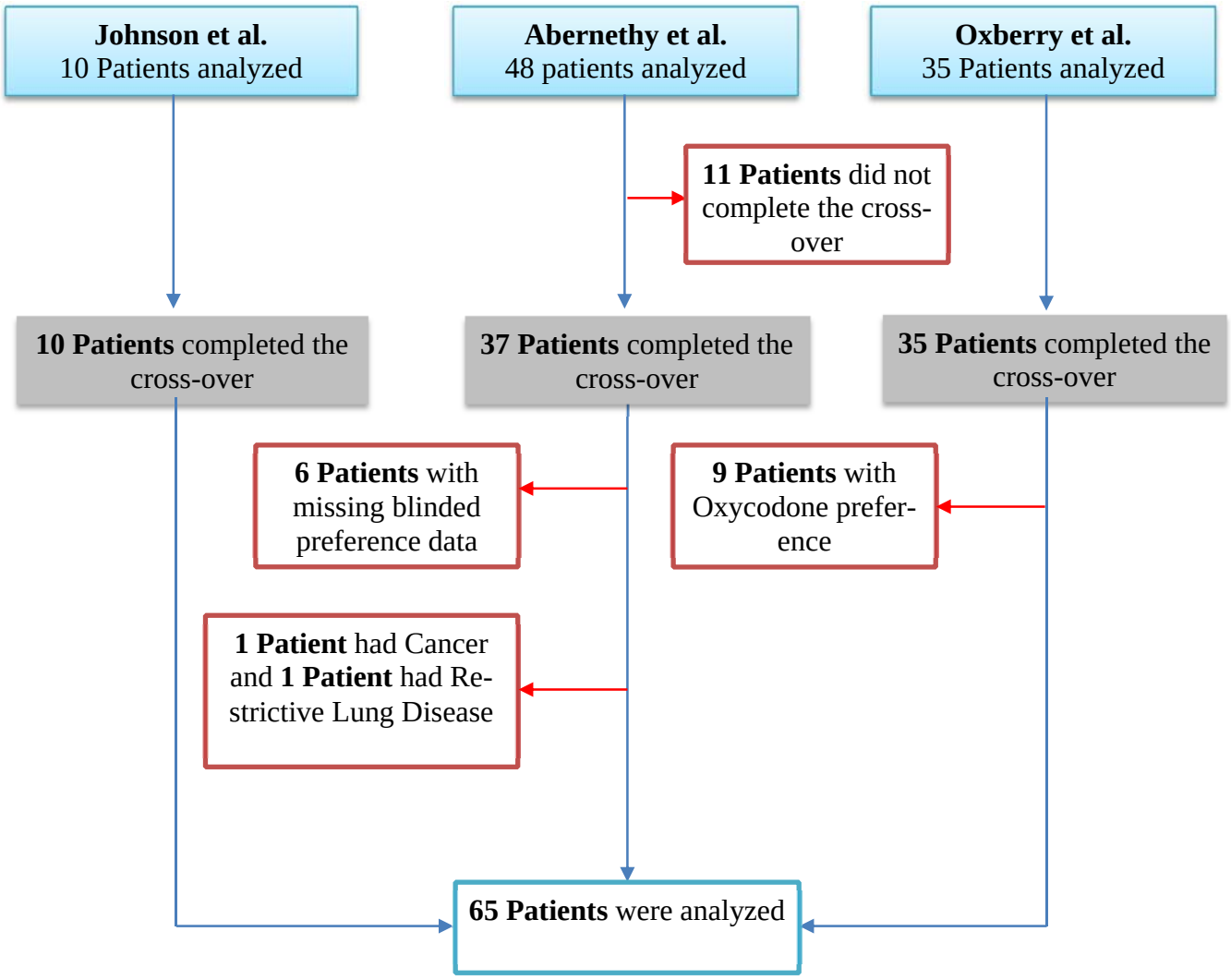

Fig 2 - Variation in median breathlessness intensity (baseline and conclusion) with placebo and morphine.