Research letter

One Evidence Base; Three Stories: Do Opioids Relieve Chronic Breathlessness?

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ABSTRACT

The efficacy of low dose systemic opioids for chronic breathlessness was questioned by the recent Cochrane review by Barnes 2016. We examined the reasons for this conflicting finding and re-evaluated the efficacy of systemic opioids.

Compared with previous meta-analyses, Barnes 2016 reported a smaller effect and lower precision, but did not account for matched data of crossover trials (11/12 included trials) and added a risk-of-bias criterion (sample size). When re-analyzed to account for crossover data, opioids decreased breathlessness (SMD −0.32; −0.18 to −0.47; I^2=44.8%) representing a clinically meaningful reduction of 0.8 points (0–10 numerical rating scale), consistent across meta-analyses.

INTRODUCTION

Chronic breathlessness [1] is common across a range of advanced diseases and associated with major adverse health outcomes.[2] The candidate treatment with best evidence to date is regular, low-dose, non-nebulized (systemic) morphine.[2] The efficacy of low dose systemic opioids was supported by a Cochrane review of Jennings 2001,[3 4] an adequately powered crossover-trial in 2003,[5] and the meta-analysis in people with severe chronic obstructive pulmonary disease (COPD) by Ekström 2015.[6]

A new Cochrane meta-analysis by Barnes 2016,[7] drawing from a similar evidence base, reported a smaller benefit of opioids than the other reviews, and wider 95% confidence intervals (CI) which nearly crossed zero. The risk of bias was rated as 'high' for all studies; previous ratings were mainly 'unclear' or 'low'.[3 4 6] Barnes 2016 rated the quality of evidence for opioids for breathlessness as 'very low'.[7]

We aimed to determine the reasons for the different conclusions and to re-evaluate the efficacy of systemic opioids for chronic breathlessness.

METHODS

Data were extracted from the published meta-analyses by Jennings 2001,[3 4] Ekström 2015,[6] and Barnes 2016 [7] (by ME), and cross-validated (DCC and MJJ) regarding study populations, designs, interventions, and methods, for the whole study population and in participants with COPD, respectively.

Breathlessness measures were analyzed as standardized mean differences (SMD).[8] For cross-over trials, the standard error was estimated using the cross-over information, directly from the published report or calculated from significance test statistics as recommended.[8]

The effect of opioids compared with placebo was analyzed using a random effects model. A detailed description of the statistical methods is given in the online supplement (Appendix 1).

RESULTS

Included studies

All included studies were double-blind, placebo-controlled randomized trials; 13/14 studies were crossover designs (Table 1). Jennings 2001 and Barnes 2016 included patients with any advanced, life-limiting disease, whereas Ekström 2015 restricted the analysis to patients with COPD. Research questions, interventions, comparisons and treatment durations were similar between the three meta-analyses (Table 1).

The study populations overlapped significantly with over half of the studies in Barnes 2016 also included in Jennings 2001 and Ekström 2015 (Table S1 in the online supplement). For two studies omitted by Barnes 2016, the reasons for exclusion were not stated.

Efficacy

In contrast to the other meta-analyses, Barnes 2016 used a fixed effects model which does not account for variations in the true effect between studies, and analyzed all data as if from parallel trials and did not account for matched crossover data (11/12; 92% of included studies).

Opioids were associated with a decrease in breathlessness in both Jennings 2001 and Ekström 2015 (Table 1). In the primary analysis of Ekström 2015, systemic opioids improved

breathlessness in COPD outpatients measured at *steady state* (five studies, 91 participants), SMD −0.33 (95% CI, −0.52 to −0.14).

Barnes 2016 split the analysis by route of administration and type of outcome measure (Table 1). Point estimates of efficacy ranged from SMD −0.27 (oral opioid, post treatment scores) to mean difference 0.20 (subcutaneous opioid, change scores). Precision was markedly lower across all analyses. The estimate for COPD in Barnes 2016 included all types of both systemic and nebulized opioids. Estimates for systemic opioids or efficacy at steady state were not reported.

When Barnes 2016 was re-analyzed using a random effects model accounting for crossover data (Figure 1), opioids decreased breathlessness, SMD −0.32 (95% CI, −0.47 to −0.18; $P < 0.001$; $I^2 = 44.8\%$) compared with placebo, consistent with Jennings 2001 and Ekström 2015. Using the standard deviation from a large study,[5] this effect size corresponds to a reduction of 0.8 points on a 0-10 numerical rating scale (NRS). The finding was consistent when excluding the three studies for which the standard errors were imputed.

Risk of bias and quality of evidence

Conclusions regarding risk of bias were similar between Jennings 2001 and Ekström 2015 with unclear or low risk of bias for most items (Table 1). In contrast, Barnes 2016 categorized all studies as having high risk of bias due to low sample size defined as < 50 participants in each treatment arm. This criterion had no stated rationale and resulted in the quality of evidence for systemic opioids being downgraded from moderate (Ekström 2015) to low or very low in Barnes 2016 (Table 1).

DISCUSSION

The conflicting findings regarding the efficacy of opioids for chronic breathlessness in the recent Cochrane review are likely due to their use of inappropriate methodology. When re-analyzed to account for crossover data, opioids were associated with a statistically and clinically significant reduction in breathlessness,[9] consistent across meta-analyses.[3 4 6]

Analyzing crossover studies as parallel studies can result in selection bias, with spuriously too high or too low effect estimates, as well as reduced precision.[10] Recommended methods to account for crossover data are available [10] and were used by Jennings 2001 and Ekström 2015.[3 4 6] In addition, study selection should align to pre-defined eligibility criteria with reasons for exclusion stated to minimize selection bias.

While any judgement of risk of bias is subjective, the bias criterion related to study size introduced by Barnes 2016, which resulted in all studies being rates as high risk of bias, is questionable. It is the *power* of the study which could lead to bias, and not the sample size *per se* which is based on the power calculation. Adequate power can be provided by trials with total sample sizes below 50,[5] especially in crossover trials where the participant acts as their own control thus increasing power.

We suggest that the analysis by Barnes 2016 and the relevant guidelines for analysis and review of the Cochrane Collaboration are updated to accommodate these issues.

CONCLUSION

Moderate level evidence to date supports that regular, low dose morphine is the first line pharmacological treatment for the relief of chronic breathlessness in severe illness.

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Conflicts of interest: DCC has received intellectual property payments and advisory board payments. MJJ has been a clinical consultant for Mayne Pharma. Authors of this paper have longstanding interest in the research of breathlessness and have published several opioid-related trials and meta-analyses (including ME and DCC [6]). MJJ was an external clinical academic (not statistical) peer reviewer for the original Barnes protocol submitted to Cochrane. The authors declare no further conflicts of interest.

Author contributions: Concept and design: ME, DCC, JMB, MJJ, JAH; first draft: ME, SB; statistical analysis: JMB; interpretation, revision and acceptance of the final version to be published: ME, SB, DCC, JMB, JAH, MJJ.

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TABLES

Table 1. Characteristics of meta-analyses of systemic opioids for breathlessness

Characteristic of meta-analysis	**Jennings 2001[3]**	**Ekström 2015[6]**	**Barnes 2016[7]**
Design of included studies (n)	Double-blind RCTs	Double-blind RCTs	Double-blind RCTs
N studies	9 (all crossover trials)	8 (all crossover trials)	12 (1 parallel and 11 crossover trials)
N trial participants	102	118	198
Population (n trial participants)	COPD (n=80); chronic heart failure (n=12); cancer (n=10);	COPD (n=113); other (n=5)	COPD (n=107); CHF (n=47); Cancer (n=41); other (n=3)
Intervention	Oral or parenteral opioid	Oral or parenteral opioid	Oral or parenteral opioid
Comparison	Placebo	Placebo	Placebo or any other pharmacological or non-pharmacological interventions that were directly compared with the opioid treatment (only 2 trials used non-placebo comparator)

Duration of treatment (n studies)	Single or few doses (N=5); longer treatment of one to six weeks (n=4)	Single dose or one day (n=3); four days to six weeks (n=5)	Single dose or 1-2 days (n=7); four days to six weeks (n=5)
Statistical method for pooling	Random effect models. Change on different scales compared as SMDs	Random effect models. Change on different scales compared as SMDs	Fixed effect models. Changes compared as MD when on the same scale and SMD when on separate scales, and separately for change from baseline and post scores. Random effect model was used in a sensitivity analysis.
Accounted for cross-over designs	Yes	Yes	No (analyzed data as from parallel trials)
Findings for whole study population			

Pooled effect of opioids (95% CI; I^2; n trial participants)*	SMD -0.40 (−0.63 to −0.17; I^2=42.3% ; n=102)	SMD −0.34 (−0.58 to −0.10; I^2=0%; n=118)	Oral opioid, change from baseline: SMD 0.07 (−0.30 to 0.44; I^2= 65%; n=116) Oral opioid, post scores: SMD −0.27 (−0.56 to 0.02; I^2= 0%; n=190) Sc. opioid, change from baseline: MD 0.20 (−2.50 to 2.90; n=20)
Stated quality of evidence	Not stated	Moderate (GRADE)	Not stated for systemic opioids For opioids overall: very low for change from baseline and low for post scores (GRADE)**
Findings in COPD participants			
Pooled effect of opioids (95% CI; I^2; n trial participants)*	SMD −0.26 (−0.44 to 0.08; I^2=23.6%; n=80)**	SMD −0.34 (−0.58 to −0.10; I^2=0%; n=118)	Change from baseline: SMD −0.49 (−1.08 to 0.10; I^2= 0%; n=46)** Post scores: SMD −0.21 (−0.45 to 0.04; I^2= 0%; n=262)**

Stated quality of evidence (criteria)	Not stated	Moderate (GRADE)	Not stated
Risk of bias assessment	Using Jadad score of methods of randomization and blinded. Most items were rated as unclear	Using the Cochrane risk of bias tool. Ratings were low or unclear for all items; no item was rated as high	Using the Cochrane risk of bias tool as well as an additional item based on study size: ≥ 200 (low risk), 50−199 (unclear risk) and < 50 (high risk) participants in each treatment arm. All items in the Cochrane risk of bias tool were rated as low or unclear except three items rated as high: performance bias (n=1), detection bias (n=1) and other bias (n=1).** Risk of study size bias was rated as high risk for all studies.

Characteristics are for trials included in each published meta-analysis.[3 6 7]

* Negative estimate indicates reduction in breathlessness by opioids compared with placebo.

** Included both trials of systemic and nebulized opioids which were not reported separately.

Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; I^2 = proportion of the total variance in effect estimates that are between studies; MD = mean difference; RCT = randomized controlled trial; Sc = subcutaneous; SMD = standardized mean difference.

FIGURE LEGENDS

Figure 1. The meta-analysis of Barnes et al.[7] re-analyzed using random effects model and accounting for matched data of cross-over trials. In the pooled analysis compared to placebo, systemic opioids reduced breathlessness by a mean 0.32 (95% CI, 0.18 to 0.47; $P < 0.001$) standard deviations.

Standardized mean difference

Data set

Abernethy 2003	-0.40 (-0.67 to -0.14)
Bruera 1993	-0.79 (-1.34 to -0.24)
Charles 2008	-0.29 (-1.18 to 0.59)
Chua 1997	-0.85 (-1.34 to -0.35)
Eiser 1991	0.21 (-0.40 to 0.82)
Harris-Eze 1995	-0.06 (-0.60 to 0.47)
Hui 2014	-0.67 (-1.78 to 0.44)
Jankleson 1997	-0.22 (-0.58 to 0.14)
Jensen 2012	-0.12 (-1.11 to 0.88)
Johnson 1983	-0.25 (-0.40 to -0.09)
Leung 1996	-0.59 (-1.38 to 0.21)
Light 1996	0.00 (-0.67 to 0.67)
Mazzocato 1999	-1.22 (-2.06 to -0.38)
Noseda 1997	-0.04 (-0.50 to 0.43)
Oxberry 2011	0.02 (-0.49 to 0.52)
Poole 1998	-0.47 (-1.13 to 0.19)
Woodcock 1981	-0.40 (-0.81 to 0.00)
All studies	-0.32 (-0.47 to -0.18)

-2.0 -1.5 -1.0 -0.5 0.0 0.5 1.0

Favours Opioids Favours Placebo

Online supplement

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Appendix 1. Statistical analyses

Table S1. Included trials of and reasons for exclusion in meta-analyses of systemic opioids for chronic breathlessness

Appendix 1. Statistical analyses

The included trials were mostly (13 of 14) cross-over designs, but also included one parallel group study. The trials used a variety of measures of breathlessness including the Borg scale and visual analogue scales. To combine differences estimated on different scales, we standardized by dividing estimated treatment differences and their standard error by the standard deviation of the breathlessness index between participants. [1 2] We followed the recommendation of Curtin et al.[24] that "when combining standardized results from cross-over trials with those of parallel trials, the cross-over estimator s_b corresponds to s of parallel trials and only this standardization should be used." For cross-over trials, the standard deviation between participants was estimated by averaging the variances under the treatment conditions, or from a pre-treatment observation. For cross-over trials, the standard error was estimated using the cross-over information. This was done directly from the published report or calculated from significance test statistics or P values. For three studies,[3-5] all that was available was an upper limit for the P values, e.g. $P<0.05$. This upper limit was used to calculate the standard error, making the standard error slightly too large and the analysis slightly conservative. In three cases,[6-8] it was not possible find a standard error from the publication. As these all used the Borg scale, the variance of within-participant differences was found from the other cross-over studies which reported this scale and the average variance was used to impute the standard error for the studies where this was unavailable. As a sensitivity analysis, the meta-analysis was done including and excluding these studies. All estimates were expressed with 95% confidence intervals and, as the trials varied in treatment and medical condition of participants, a random effects estimate was used. This meant that any extra within-study variability produced by the standardization was automatically included in the error and did not need to be estimated explicitly.

Of the studies included by Barnes et al 2016, the study of Bar-Or et al.[9] was excluded as data suitable for the analysis were not found in the publication. The meta-analysis was also repeated including the study of Johnson et al [10] that was excluded in Barnes 2016 for reasons which were unclear, using the original raw data, with similar findings. Meta-analyses were using the software Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ). Data were entered as standardized differences and their standardized standard errors. Pooled estimates were obtained using a random effects model by the method of DerSimonian and Laird. The study and pooled estimates were presented as a forest plot drawn using Stata version 13 (StataCorp LP, College Station, TX).

Table S1. Included trials of and reasons for exclusion in meta-analyses of systemic opioids for chronic breathlessness

Trial	Jennings 2001 [11] n=9	Ekström 2015 [12] n=8	Barnes 2016 [13] n=12
Abernethy 2003	Not published yet	Yes	Yes
Bar-Or 1982	Letter only	Letter only	Yes
Bruera 1993	Yes	Not COPD	Yes
Chua 1997	Yes	Not COPD	Yes
Eiser 1991a	Yes	Yes	Yes
Eiser 1991b	Yes	Yes	Not stated
Hui 2014	Not published yet	Not COPD	Yes
Johnson 1983	Yes	Yes	Yes
Light 1996	Yes	Yes	Yes
Mazzocato 1999	Not published yet*	Not COPD	Yes
Oxberry 2011	Not published yet	Not COPD	Yes
Poole 1998	Yes	Yes	Yes
Woodcock 1981	Yes	Yes	Yes
Woodcock 1982	Yes	Yes	Not stated

Included studies and stated reasons for exclusion for trials in the published meta-analyses.

* Jennings 2001 performed the last search in May 1999.

Abbreviations: CHF = chronic heart failure;

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