

Online supplement

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

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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 to 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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