Does effect size in naltrexone trials for alcohol dependence differ for single-site vs. multi-center studies?

Feinn R, Kranzler H R

CRD summary
This review assessed the impact of study site and year of publication in trials of naltrexone for alcohol dependence. The authors concluded that the smaller effect sizes in multicentre studies may reflect random error due to differences among sites. It was difficult to assess the evidence since the review methods were not reported and study quality was not evaluated. Therefore, it is unclear whether the conclusions are reliable.

Authors' objectives
To assess the impact of study site and the year of publication on the results of trials assessing the effects of naltrexone for the treatment of alcohol dependence.

Searching
PubMed (incorporating MEDLINE, PREMEDLINE and HealthSTAR) was searched using the search terms reported; no search dates were stated. In addition, the references of retrieved articles and two recent meta-analyses were checked.

Study selection
Study designs of evaluations included in the review
Randomised, parallel-group, placebo-controlled trials were eligible for inclusion. Single-site studies were defined as those in which all patient assessments were obtained and treatment was provided at a single location. Multicentre studies were defined as those in which patient assessments were obtained and treatment was provided independently by investigators at more than one centre. In the multicentre studies the number of sites varied from 4 to 29 (average of approximately 11 per study).

Specific interventions included in the review
Studies that assessed naltrexone compared with placebo were eligible for inclusion.

Participants included in the review
Studies of patients receiving treatment for alcohol dependence were eligible for inclusion.

Outcomes assessed in the review
Studies that reported either the percentage of drinking days or the percentage of participants that experienced relapse (one or more heavy drinking days), or sufficient data for their calculation plus measures of variance, were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

For each study, the standardised mean difference (Cohen’s d) between the treatment and control group was calculated.
from test statistics or from the reported means and measures of variance.

**Methods of synthesis**

**How were the studies combined?**
The trials were combined in a meta-analysis using a random-effects model. The effect of each study was weighted by its approximated effect size variance. The authors did not assess publication bias.

**How were differences between studies investigated?**
Differences between the trials in terms of type of study (single-site or multicentre) and the year of publication were assessed using a hierarchical linear model.

**Results of the review**

Nineteen randomised controlled trials were included (n=2,691: 1,454 received naltrexone and 1,237 received placebo).

Twelve studies were single-site and seven were multi-site.

The average effect size for the percentage of drinking days was significantly greater than zero with naltrexone for both single site studies (d=0.33, 95% CI: 0.10, 0.56) and multicentre studies (d=0.17, 95% CI: 0.03, 0.36). There was no significant difference in the effect sizes between single-site studies and multicentre studies. The effect of the year of publication showed a non significant negative trend, with earlier studies showing larger effect sizes. The inclusion of both study type and year of publication as predictors of effect size reduced the magnitude of both effects.

The effect size estimates for the percentage of participants who relapsed to heavy drinking was significantly greater than zero with naltrexone for both single-site studies (d=0.41, 95% CI: 0.25, 0.55) and multicentre studies (d=0.17, 95% CI: 0.04, 0.29). The effect size estimates from multicentre studies were significantly smaller than the average effect size for single-site studies. The effect of the year of publication was also significant, with smaller effect sizes in more recent studies. The inclusion of both the type of study and the year of publication resulted in neither factor being a significant predictor of effect size.

**Authors' conclusions**
The smaller effect sizes seen in multicentre studies may reflect random error due to differences among the sites. However, since more recent publications also had smaller effect sizes, and multi-centre studies tended to be more recent than single-site studies, it was not possible to separate out the influence on effect size of study type and year of publication.

**CRD commentary**
The review question was clearly defined in terms of the interventions, outcomes and study designs. Only one database was searched for potentially relevant studies, and it was unclear whether any language restrictions were applied. No efforts were made to locate ongoing or unpublished studies, which may introduce publication bias into the review. It was unclear how studies were selected for the review and how the data were extracted, thus it is unknown whether any efforts were made to minimise reviewer bias and errors in these processes. The quality of the primary studies was not assessed, so the quality of the evidence base that underpins the review cannot be judged. In addition, as no details of the primary studies were presented, it is unclear whether combining the studies in a meta-analysis was appropriate, given the fact that there might have been clinically relevant differences between the participants included in the trials. The lack of a description of the review methods and the lack of a quality assessment make it difficult to comment on the reliability of the evidence underpinning the authors' conclusions.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.
Research: The authors stated that further research is needed to determine reasons for the influence on effect size of study type (single- or multi-site) and year of publication.

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