Psychological treatment of panic disorder with or without agoraphobia: a meta-analysis
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CRD summary
This review found that a combination of exposure, relaxation training, and breathing-technique training was effective for treating panic disorder with or without agoraphobia, especially if treatment included homework during the intervention and a follow-up programme after it. There were limitations in the review, including weaknesses in the search and unexplained heterogeneity between studies, and the authors' conclusions require cautious interpretation.

Authors' objectives
To assess the efficacy of psychological interventions for panic disorder with or without agoraphobia and to explore the variables affecting treatment efficacy.

Searching
PsycINFO, MEDLINE, the Cochrane Library, and the Spanish databases of the CSIC and PSICODOC were searched, in June 2007, for articles conducted or published from 1980 to 2006, with search terms in their titles. The search terms were reported. Books, monographs, scientific journals, and the reference lists of 12 meta-analyses were searched and researchers in panic disorder were consulted. The search was restricted to studies in English, Spanish, or French.

Study selection
Controlled studies of psychological treatment for panic disorder with or without agoraphobia were eligible for inclusion, provided there were at least five participants in each group at follow-up. Participants had to be diagnosed using scientifically recognised criteria. Controls conditions were non-active, such as a waiting list, or active treatment, defined as a psychological and/or a pharmacological placebo. The intervention could not include psychoactive drugs.

Participants in the included studies had a mean age of 36 years and a mean illness duration of eight years; most of them were female. In most of the comparison groups, over half the participants had comorbid disorders, and they had all received previous treatment. Many participants were taking psychoactive drugs in controlled or reduced doses. The most common interventions (alone or in combination) were exposure (usually in real-life situations), cognitive therapy, relaxation training, and breathing techniques. Most studies had waiting list controls, while some used pill placebo, psychological placebo (e.g. empathic listening), or a combination of interventions. Outcomes reported in the review were panic (primary outcome), agoraphobia, general anxiety, depression, bodily sensations, global adjustment, and the overall results (mean of all measures). Studies used a range of scales and questionnaires to measure outcomes.

The authors did not state how many reviewers selected the studies.

Assessment of study quality
Studies were allocated up to nine points for quality, taking into account randomisation, sample size, use of pre-test measures, attrition, blinding of evaluators, full reporting of pre-test variables, homogeneity of treatment, reporting of follow-up, and use of normed and standardised outcomes measures. Two pairs of reviewers independently assessed study validity, resolving inconsistencies by consensus.

Data extraction
For each study, the standardised mean differences between treatment and control groups were calculated, with 95% confidence intervals. Effect estimates were calculated separately for self-reported and clinician assessments. Up to 24 indices were calculated for each study. Hedges' published methods were used to adjust for small sample sizes. Two pairs of reviewers independently extracted the data, using a code book and resolving inconsistencies by consensus.

Methods of synthesis
The data for each outcome and type of report were combined, using a random-effects inverse-variance model to calculate a pooled standardised mean difference and 95% confidence interval. Heterogeneity was assessed using the $\chi^2$
and $I^2$ tests. For panic-related outcomes, further analyses (including multiple regression) were conducted to investigate the impact of treatment type, participant characteristics, methodological variables, and extrinsic study qualities (e.g. publication year). The Egger and fail-safe N tests were used to assess publication bias in the overall results.

**Results of the review**

Forty-two studies, with 65 comparisons, were included (n=2,560 participants, 2,357 providing full data) and 36 of them were randomised. The comparison sample sizes, at post-test assessment, ranged from 11 to 140. Quality scores ranged from 4.5 to 8.5 out of nine points.

There was a significant improvement with the intervention for panic measures, both by patient and by clinician report. The combined (patient and clinician) standardised mean difference was 1.015 (95% CI 0.855 to 1.175; 61 comparisons; $I^2$=70%). There was also a significant improvement in the combined standardised mean difference for agoraphobia (SMD 0.856, 95% CI 0.679 to 1.033; 42 comparisons; $I^2$=65%), general anxiety (SMD 0.840, 95% CI 0.686 to 0.994; 44 comparisons; $I^2$=57%), depression (SMD 0.645, 95% CI 0.500 to 0.791; 42 comparisons; $I^2$=43%), global adjustment (SMD 0.895, 95% CI 0.663 to 1.126; 25 comparisons; $I^2$=72%), other outcomes (SMD 0.627, 95% CI 0.446 to 0.808; 24 comparisons; $I^2$=48%) and overall results (SMD 0.784, 95% CI 0.663 to 0.905; 65 comparisons; $I^2$=53%). Self-reported bodily sensations significantly improved (SMD 0.874, CI 0.656 to 1.092; 18 comparisons; $I^2$=49%). No significant evidence of publication bias was found.

In a multiple regression model, controlling for study quality and type of control group, the most effective treatment was exposure (SMD 1.90). The results of many other analyses were reported.

**Authors’ conclusions**

The combination of exposure, relaxation training, and breathing techniques was effective for treating panic disorder with or without agoraphobia, especially if treatment included homework during the intervention and a follow-up programme after it.

**CRD commentary**

The objectives and inclusion criteria were clear and relevant sources were searched for studies. Some studies might have been missed due to language restrictions, and limiting the electronic searches to the study titles, rather than including the abstract and other fields. Relevant tests were used to check for publication bias and none was found. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer check the study validity and extract the data, but it was unclear whether this applied for study selection. Very few details were given of the design, quality, and findings of each primary study; the within-study findings of comparisons between randomised treatment groups were not reported. Indirect comparisons were reported between groups from different studies and these have questionable validity due to the heterogeneity between studies. There were a large number of subgroup analyses, several of which did not appear to have been pre-specified. These were difficult to interpret and, as the authors acknowledged, they increased the risk of chance findings. There was marked heterogeneity, in the primary analyses, which was explored and partly explained, but the extent of residual heterogeneity was not clearly quantified. The large effect of placebo interventions (especially psychological placebos) was not acknowledged in the authors’ conclusions.

In view of the limitations in the review, including weaknesses in the search and unexplained heterogeneity between studies, the authors’ conclusions require cautious interpretation.

**Implications of the review for practice and research**

**Practice**: The authors stated that exposure was the treatment of choice for panic disorder and that the inclusion of relaxation and breathing-technique training was recommended, but might be too expensive for routine use.

**Research**: The authors stated that strategies that shorten the length of therapies for panic disorder should be explored, including new communication technologies for patient-therapist contact. They also stated that future studies should include active control groups and report follow-up data for all participants, with the details of any comorbidities, including agoraphobia.
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