Behavioral and prophylactic pharmacological intervention studies of pediatric migraine: an exploratory meta-analysis

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Authors' objectives
To review the effectiveness of behavioural and pharmacological treatments for paediatric migraine.

Searching
MEDLINE, PsycLit, Psychological Abstracts, Dissertation Abstracts and Current Contents were searched from 1970 to 1993. The keywords were listed. Conference proceedings were searched. Handsearches were undertaken of recent volumes of relevant journals: Headache, Cephalalgia, Pain, Biofeedback and Self-Regulation, and bibliography checks done of available reviews.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), controlled trials and case controls were included.

Specific interventions included in the review
Behavioural treatments:
Electromyographic biofeedback, progressive muscle relaxation, cognitive therapy (autogenic therapy, hypnosis).

Pharmacological interventions:
Beta-blockers (Propranolol), serotoninergic drugs (Pizotifen, Cyproheptadine, Amitriptyline), calcium-channel blockers (Flunarizine, Nimodipine), anti-convulsants (Phenobarbital, Phenytoin), psychological placebo and wait-list control.

Participants included in the review
Vascular headache sufferers aged 5 to 18 years were included.

Outcomes assessed in the review
Headache reduction of at least 50% reflected by headache frequency, or a headache index combining frequency and duration or severity.

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

Assessment of study quality
Studies which included samples consisting of vascular headache sufferers (migraine or mixed headache) between the ages of 5 and 18 with the following design features:

1. Adequate sample size: If group design sample size >=3 or if case reports or experiments sample size >=2.

2. If findings presented in more than one reference, the most recent report was included in the meta-analysis.

3. The patient sample should not be pre-selected.

4. Studies should provide adequate diagnostic and statistical information as to obtain the effect size.
The studies were reviewed and scored using a set of a priori defined criteria, including treatment type, randomisation, adequacy of baseline periods, type of headache, sample selection, sample description, age range and mean, proportion of pure migraineurs versus children suffering from mixed headache, use of standardised diagnostic criteria, chronicity of headache problem, drop-out/take-out rate, treatment length, assessment of palliative medication consumption, adequacy of statistical analysis and overall quality. Relevant studies were independently reviewed by the first two authors.

Data extraction
The overall quality was coded on a scale from 0 (poor) to 2 (good) and reflects a global rating of procedural quality (internal and external validity).

The authors derived the effect size of each treatment independently and then compared results.

Methods of synthesis
How were the studies combined?
The studies were combined using both a narrative review and effect size meta-analyses (using Hedges and Olkin's meta-analytical model). Within-group analyses of the behavioural interventions and the drug interventions were performed. Behavioural interventions were compared with drug treatments, and a between-groups meta-analysis was carried out.

How were differences between studies investigated?
Tests for homogeneity were carried out. Outlier analysis were carried out for each treatment category. Potential moderator variable (treatment characteristics, sample characteristics and statistical features) were examined.

Results of the review
Seventeen behavioural studies:

Thermal biofeedback (BFB) n=5
Progressive muscle relaxation (PMR) n=5
Progressive muscle relaxation in combination with thermal biofeedback (PMR and BFB) n=4.
Multi-component packages n=3
Hypnosis n=1
Cognitive therapy, Autogenic therapy n=1
Autogenic training combined with progressive muscle relaxation (Augenic training and PMR) n=1
Psychological placebo and wait-list control ES n=8

24 studies of drug treatments were identified:

Propranolol n=2
Flunarizine n=8
Nimodipine n=3
Serotonergic drugs (Amitriptyline Trazodone, Cyproheptadine, Pizotifen, 5-HTP Dopaminergic drugs, Clonidine, Papaverine, Acetylsalicylic Acid) n=29.
Drug Vs Placebo n=6

Behavioural intervention: All the non-pharmacological treatment modalities were shown to be superior to placebo or wait-list controls. Thermal BFB, and PMR in combination with BFB, were found to lead to better outcomes than the other modalities.

Pharmacological interventions: Contrasts between the frequently-evaluated drugs (calcium-channel blockers, serotonergic drugs, placebo) demonstrated better treatment outcome for all drugs than for the placebo, but no evidence for differential effectiveness of calcium-channel blocking drugs. There is some (limited) evidence to suggest that propranolol has superior effectiveness than placebo and other active prophylactic drugs.

Comparison of behavioural and drug treatment studies: Pharmacological and non-pharmacological control conditions were not associated with different outcomes. Thermal BFB, as well as PMR + BFB, led to more headache reduction in comparison to calcium-channel blockers and serotonergic drugs. PMR alone, multi component treatment programmes and both calcium-channel blockers as serotonergic drugs did not yield different treatment effects. Propranolol was not found to be significantly more efficacious than any other behavioural and drug intervention.

Between-group meta-analysis: In the second meta-analysis which excluded studies without a comparison group consisting of placebo or no-treatment control, the findings from the first review were only partially replicated. Individual a priori contrasts indicated that only BFB was associated with a significantly higher treatment success than serotonergic drugs ($Z^2 = 6.5$, $p<0.05$) and PMR displayed a tendency to be more effective than calcium-channel blockers ($Z^2 = 2.0$, $p<0.09$). There were no significant differences between multi-component behavioural treatment and all three types of prophylactic medications.

Authors' conclusions
A first meta-analysis based on treatment outcome within treatment conditions revealed that thermal BFB and interventions combining BFB and PMR seem to be significantly more efficacious than other behavioural treatment modalities. Though there is some evidence suggesting good effectiveness of propranolol, the lack of systematic data precludes more definitive conclusions. A second meta-analysis which included only studies providing data on the comparison between controls and active treatment groups only partially replicated the initial findings. In the light of the relative small numbers of studies that met basic inclusion requirements, conclusions regarding the differential effectiveness of treatment types have to be drawn with caution.

Overall, the review clearly demonstrates the need for direct comparisons between behavioural and pharmacological treatments and the need for a more theory-driven research in order to determine the most promising approach to paediatric migraine.

CRD commentary
This is a thorough review of the literature to date. The authors have completed a comprehensive search of the literature and have reviewed the evidence carefully, highlighting the need for more well-designed research projects in this area.

The usefulness of the scoring system is questionable. The second meta-analysis which included only well-designed studies negates the need for the scoring system employed in the earlier analyses.

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