Medication-induced headache: overview and systematic review of therapeutic approaches

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Authors' objectives
To review medication-induced headache through a systematic evaluation of the literature regarding the pharmacologic management of this condition.

Searching
MEDLINE was searched from 1966 to June 1998 using the keywords: 'chronic daily headache', 'transformed migraine', 'analgesic withdrawal headache', 'analgesic rebound headache', 'drug-associated headache', 'medication-induced headache', 'detoxification' and 'dihydroergotamine'. Bibliographies of relevant literature were checked for additional references. Only English-language publications were included.

Study selection
Study designs of evaluations included in the review
All reports that specifically addressed the management of MIH were included, regardless of design. Articles were excluded if they evaluated only headache prophylaxis and did not identify whether the chronic daily headache (CDH) was drug associated.

Specific interventions included in the review
Abrupt discontinuation of analgesics, nonsteroidal anti-inflammatory drugs (NSAIDS), methylergonovine, dihydroergotamine, sumatriptin, amitriptyline and deamethasone, prothopendyl and piracetam, valproic acid.

Participants included in the review
Patients suffering from medication-induced chronic daily headache (MIH).

Outcomes assessed in the review
Proportion headache free, improvement in headache index (duration x severity), headache frequency, time to cessation of daily headache, subjective rating of headaches (better, much better etc).

How were decisions on the relevance of primary studies made?
All articles were evaluated independently by the authors for inclusion in the review.

Assessment of study quality
The authors do not report a method for assessing validity. All articles were evaluated independently by the authors for scientific validity.

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

Methods of synthesis
How were the studies combined?
A narrative approach was used to combine studies.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.
Results of the review

Nineteen studies were included in the review, 3 randomised controlled trials (RCTs), 2 controlled trials, 12 uncontrolled trials, 1 retrospective study and 1 case series.

Abrupt discontinuation of analgesics (n=6):

1 randomised trial, 3 groups, results at 4 weeks (improvement in headache index, HI): abrupt discontinuation, 60% improvement; amitriptyline added, 24% improvement; abrupt discontinuation with addition of amitriptyline, 72% improvement.

1 controlled trial, 5 groups. Results at 12 week (improvement in HI): continued medication, 24% improvement; symptomatic medications abruptly stopped, 58% improvement; symptomatic medications abruptly stopped and prophylactic medication started, 85% improvement; symptomatic medications abruptly stopped and prophylactic medication continued, 72% improvement; symptomatic medications abruptly stopped and prophylactic dose or drug changed 85% improvement.

3 uncontrolled trials, 2 abrupt discontinuation and 1 abrupt withdrawal and addition of beta-blocker or tricyclic antidepressant, all found improvement in patients compared to baseline: 45% headache free on discharge in one trial, 50% had <8 headaches per month in second trial and in trial with additional treatment all groups showed improvement ranging from 24-85% improvement in HI. One case series (5 subjects), abrupt withdrawal, all had cessation of daily headaches within 5 days.

Non-steroidal anti-inflammatory drugs (NSAIDS)(n=4):

1 RCT. Medication withdrawn and naproxen (500 mg po bid) versus symptomatic medications, at 8 days there were less headaches in naproxen group over the 8 d, no difference in HI between the groups. 3 uncontrolled trials, all abrupt withdrawal together with NSAIDs (naproxen 500 mg po prn + amitriptyline; tolfenamic acid 200mg po tid + chlorzoxazone 10-25mg po tid; naproxen 500 mg/d iv, delorazepam 2mg/d iv, pridinol 2mg/d iv), all showed some improvement (80%, 62% and not stated).

Methylergonovine (n=1):

1 uncontrolled trial, showed that after 6 months 43% rated headache as much better, 30% rated as better and 20% unchanged.

Dihydroergotamine (DHE)(n=3):

1 controlled trial, patients received either DHE + propranolol or diazepam, 89% of DHE patients and 13% diazepam patients H/A free at 48 hours, at 16 months 65% DHE patients had good/excellent response 1 retrospective study, rapid withdrawal + DHE + metoclopramide, 92% became headache free, most within 48 hours. 1 uncontrolled trial (3 patients), no overall improvements.

Sumatriptan (n=1):

Same authors report on RCT and uncontrolled trial. Uncontrolled trial showed brief benefit in migraine experiencers, none in non-migraine. In RCT all sumatriptan-treated patients had complete resolution of headache for 6-12 hours versus none in placebo.

Amitriptyline and deamethasone (n=1):

1 uncontrolled trial. At 6 months 61% very good responders, 39% responders.

Prothopendyl and piracetam (n=1):

1 uncontrolled trial. 90% headache free at discharge, 61% had significant relief at 17 months, 24% had no reduction in headache or medication use.
Valproic acid (n=1):

1 uncontrolled trial. 48% had >75% reduction in HI.

**Authors’ conclusions**

MIH is an under-recognised and difficult condition affecting headache-prone patients. The published literature concerning treatment of patients with MIH is scant and of poor quality, making it difficult for clinicians to decide on appropriate therapy, although some guidance can be gleaned from the available data. It appears that complete withdrawal of medications being overused is required for favourable long-term results to be achieved. The data also suggest that recognition and treatment of MIH may lead to long-term headache improvement for many patients.

**CRD commentary**

A reasonable review of an area in which little good evidence exists. The authors carried out a literature search however, restricting the search to published studies, searching only one database and only including studies published in English may have resulted in important studies being missed and the results may be subject to publication bias. Inclusion criteria were stated and individual study results clearly presented. The authors do not conduct a formal validity assessment, although they do comment on the generally poor standard of the studies. The evidence presented is very limited and most of the studies do not incorporate a control group thus it is very difficult to draw any conclusions from the data presented and the findings should be interpreted with caution.

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

Further good quality research is needed in this area.

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the reliability of the review and the conclusions drawn.