Acupuncture for the prevention of migraine[1]

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Acupuncture Therapy, Migraine Disorders, Benefit Assessment, Systematic Review

This report was prepared with the involvement of an external expert. The responsibility for the contents of the report lies solely with IQWiG.

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed "Form for disclosure of potential conflicts of interest" from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A8 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

External expert

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IQWiG thanks the external expert for his collaboration in the project.

Patient and family involvement

Patients or family members were consulted during the preparation of the report.

Four people participated in the discussion.

The aim of the discussion was to obtain information on the following topics: experiences, wishes and concerns regarding the diagnostic procedures, impact of the disease on life and everyday life, and coping with the disease.

IQWiG would like to thank the participants for taking part in the discussion as well as the patient organization "MigräneLiga e. V. Deutschland" for its support. Neither party was involved in the actual preparation of the report.

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Key statement

Research question

The aim of this investigation is to assess the benefit of manual (conventional) acupuncture with needles for migraine prevention compared with

- pharmacological migraine prevention; or

- no pharmacological migraine prevention when pharmacological prevention is not indicated due to ineffectiveness, intolerance, or contraindications

in adult patients with migraine.

Conclusion

For a large proportion of the areas of application of manual acupuncture for migraine prevention, no relevant studies are available. This applies to both patients for whom drug therapy is not an option, as well as to those in whom conventional drug therapy does not adequately control symptoms and who are receiving or are being considered for calcitonin-gene-related-peptide (CGRP)-targeted escalation therapy. Therefore, there is currently no evidence to suggest that manual acupuncture using needles is beneficial in these areas of application.

Relevant studies are available only for comparisons of manual acupuncture with selected conventional drugs (flunarizine and topiramate). Based on the results of 3 randomized controlled trials on migraine prevention, which differed in design and compared conventional manual acupuncture using needles with guideline-compliant pharmacological migraine prevention using flunarizine or topiramate, there is a hint that acupuncture offers a greater benefit than flunarizine and topiramate in both episodic and chronic migraine. This conclusion is based particularly on hints of a greater benefit from acupuncture with regard to migraine symptoms and their consequences, such as the ability to cope with everyday life, as well as a hint of lesser harm with regard to adverse effects. The follow-up period lasted up to 4 months. Given the various restrictions on the use of topiramate and flunarizine in clinical practice, the advantages of manual acupuncture suggested by these studies can only be inferred for a limited range of applications. Topiramate should generally only be used after careful consideration of alternative treatments. Flunarizine should only be used if beta-blockers are contraindicated or if previous treatment with beta-blockers has been unsuccessful. No suitable studies comparing manual acupuncture with other conventional, approved medicines for migraine prevention, such as beta-blockers, amitriptyline, or onabotulinumtoxin A were identified.

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List of abbreviations

Abbreviation	Meaning
ADL	activities of daily living
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
BDI	Beck Depression Inventory
CGRP	calcitonin-gene-related-peptide
CI	confidence interval
CM	chronic migraine
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin e. V. (German Society for General Medicine and Family Medicine)
DGN	Deutsche Gesellschaft für Neurologie e. V. (German Society for Neurology)
EM	episodic migraine
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GERAC	German Acupuncture Trials
HADS	Hospital Anxiety and Depression Scale
HTA	health technology assessment
ICDH-3	International Classification of Headache Disorders – 3rd edition
IHS	International Headache Society
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
MD	mean difference
MIDAS	Migraine Disability Assessment
NICE	National Institute for Health and Care Excellence
NSAID	non-steroidal anti-inflammatory drugs
OR	odds ratio
PRO	patient-reported outcome
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short-Form 36
SMD	standardized mean difference
SmPC	Summary of Product Characteristics
SMS	Societas Medicinae Sinensis (International Society for Chinese Medicine)
SR	systematic review

Abbreviation	Meaning
TCM	Traditional Chinese Medicine
VAS	Visual Analogue Scale

1 Background

Migraine – the clinical picture

Migraine, as a primary headache disorder, is a very common neurological condition [1] which can cause major impairment for those affected. The exact cause of migraine is unknown. The most widely accepted explanation today is a partly hereditary neurobiological dysfunction of the brain and its blood vessels (particularly the trigeminovascular system), accompanied by increased excitability of nerve cells, which leads to a temporary but recurrent disruption of pain-regulating systems [2]. Various factors, such as emotional stress, certain foods, hormonal changes, lack of sleep or changes in the weather, can trigger migraine attacks. The attacks are characterized by moderate to severe, usually unilateral, throbbing headaches, which can last between 4 and 72 hours without treatment or if treatment is unsuccessful, and are usually exacerbated by physical activity. Nausea and vomiting, as well as hypersensitivity to light, sound and odours, are often associated with the headaches. In the case of migraine with aura – usually preceding the onset of the headache – there are also visual, speech and language disturbances and/or weakness, paralysis or numbness in an arm or leg.

A distinction is made between episodic migraine and the rarer chronic migraine. Chronic migraine is diagnosed when headaches have occurred on 15 or more days per month over a period of 3 months, and these were typical of migraine on at least 8 days per month [3]. There are also special forms such as menstrual migraine or vestibular migraine, which is characterized by paroxysmal dizziness and balance disorders [2].

Patients affected by migraine frequently suffer from additional somatic or mental health conditions such as back and neck pain, or depression and anxiety [1,4].

According to data from a representative survey in Germany [1], 14.8% of women and 6% of men in Germany were affected by migraine, provided all diagnostic criteria were met. Among 1.2% of respondents (corresponding to 9.1% of those affected by migraine), the condition was of a chronic nature; however, this can generally revert to an episodic form, for example, following successful prophylactic treatment or successful management of analgesic overuse (see next paragraph) [5]. According to this study, prevalence was highest in women in their third decade of life and in men in their fourth decade [1].

Acute treatment

Therapeutically, in addition to anti-nausea medication, acute migraine attacks are predominantly treated with analgesics from various drug classes, e.g. paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, diclofenac and ibuprofen, as well as triptans, which are used specifically for migraine. Some people develop a problem of overuse of the analgesics used for acute treatment due to too frequent and prolonged use.

This represents a risk factor for a (potentially reversible) transition to chronic migraine, as overuse in itself can also trigger headaches [6].

Migraine prevention

Various pharmacological and non-pharmacological approaches are used for the prevention of migraine. According to the current German S1 guideline on the treatment of migraine [4], recommended measures should be used in combination as part of a multimodal approach in cases of significant distress, impaired quality of life, a recognizable risk of medication overuse, or intolerable adverse effects from acute drug therapies. Their aim is to reduce the frequency, severity and duration of migraine attacks and, where applicable, to reduce the overuse of analgesics.

In the field of pharmacological prevention, the following medicines are used in Germany, each with different restrictions on use and contraindications:

- the beta-blockers propranolol and metoprolol,
- the calcium channel blocker flunarizine,
- the anti-epileptic drugs topiramate and valproic acid (the latter only for off-label use),
- the antidepressant amitriptyline and
- the botulinum toxin onabotulinumtoxin A

More recently, monoclonal antibodies against calcitonin gene-related peptide (CGRP) or its receptor have also been used, predominantly as second-line therapy following documented failure of the drugs for pharmacological prevention listed above.

Depending on the active ingredient, the range of adverse effects associated with medicines that have long been used for migraine prevention includes, for example, fatigue, dizziness, dry mouth, gastrointestinal symptoms such as nausea and stomach pain, weight gain or loss, and sleep and concentration disturbances.

In accordance with the S1 guideline on the treatment of migraine issued by the German Society of Neurology and the German Migraine and Headache Society [4], behavioural therapy measures (e.g. relaxation techniques, biofeedback), psychological pain therapy (e.g. pain management, stress management) or cognitive behavioural therapy are recommended for migraine prevention in addition to pharmacological prevention therapy. These should preferably be used as part of a multimodal approach, but may also be used as an alternative to pharmacological prevention in certain circumstances.

Real-life stories from people affected as a supplementary source of information

To complement the introduction to the clinical picture, IQWiG provides individual real-life stories from patients and/or their relatives. The anonymized real-life stories are intended to provide an insight into the individual experience of the condition and how to cope with its consequences. In this way, they can help to better understand the perspectives of people affected.

The real-life stories summarize interviews and are published on the IQWiG website at www.gesundheitsinformation.de / www.informedhealth.org. They are not representative, and statements made in the real-life stories do not constitute recommendations by IQWiG.

Further details on the methods used for the real-life stories can be found in the IQWiG methods paper [7].

You can find the real-life stories from people with migraine here: https://www.informedhealth.org/my-migraines-follow-a-certain-pattern.html.

Acupuncture

Acupuncture is a central component of Traditional Chinese Medicine (TCM) and has been used for over 2000 years to treat a wide range of conditions and illnesses. It is currently the most widely used complementary medical treatment worldwide [8]. Whilst TCM attributes the effects of acupuncture to the stimulation of specific areas of the body (acupuncture points) along the meridians (pathways through which “Qi” flows), modern science is increasingly providing insights into the biological mechanisms of action of acupuncture [9]. For the purposes of this review, “conventional” acupuncture is defined as manual acupuncture using needles at various specified points on the body: there are 361 anatomically defined acupuncture points located on the 12 main meridians and 2 extra meridians (Ren Mai and Du Mai) [10]. In addition, conventional acupuncture according to TCM also describes approximately 48 anatomically defined extra points (not located on the meridians) [11] as well as an unlimited, anatomically undefined number of tender points, which are referred to in TCM as Ah Shi points and in Western medicine as pain trigger points. Various technically assisted extensions, such as electro- and laser acupuncture, or independent microsystems such as auricular acupuncture – without combination with conventional TCM acupuncture points – are not classified as the “conventional” form and are therefore not the subject of this assessment.

Particularly in the field of pain relief, acupuncture is regarded as an evidence-based complementary medicine treatment option for various conditions and, following the results of randomized trials in Germany, was included in the statutory health insurance (SHI) health services catalogue in 2007 for the treatment of osteoarthritis of the knee and chronic lower back pain in the lumbar spine [12]. In Germany, acupuncture for migraine prevention is

currently offered only as an individual health service for self-paying patients [13]. Whilst the German S1 guideline does not make a clear recommendation for the use of acupuncture in migraine prevention, but merely refers to its “moderate, non-specific effects” [4], the National Institute for Health and Care Excellence (NICE) headache guideline [14], for example, recommends considering a course of acupuncture treatment lasting 5 to 8 weeks [13] if prevention with propranolol and topiramate has been shown to be ineffective or is not indicated.

The exact mechanisms of action of acupuncture in pain relief are still not fully understood and are highly complex. Among other mechanisms discussed for the treatment of migraine with acupuncture [9] are the suppression of neuroinflammatory processes, the suppression of peripheral and central sensitization (increased excitability), and the peripheral and central activation of the endorphin or serotonergic regulatory systems. Serious adverse effects from the treatment are very rare; common mild adverse effects include haematomas and pain at the insertion sites [15,16].

The diagnostic assessment preceding a traditional, conventional acupuncture treatment is highly individualized and, despite an identical “Western” diagnosis of a condition (e.g. migraine), can lead to different TCM treatment approaches involving different acupuncture treatments (e.g. even with regard to the selection of acupoints for each session).

Furthermore, the wide variety of practical applications of acupuncture in terms of style and technique [15] stems from

- the written body of clinical knowledge, which has been continuously modified over the course of more than two millennia by textbook authors,
- the emergence of national schools (e.g. China, Korea, Japan, Vietnam, France),
- the development of further sub-forms beyond whole-body acupuncture (e.g. microsystems such as ear, hand or cranial acupuncture), each with its own theoretical background,
- the corresponding expansions of the 361 conventional acupuncture points [15,17] that have accompanied these developments,
- through the range of variations in the methods of stimulation at the acupuncture points (e.g. insertion of sterile, fine needles with or without manipulation, moxibustion, electroacupuncture, laser acupuncture, acupressure, injection acupuncture) and
- the frequent combined use of acupuncture with other interventions such as massage (Tui Na), cupping treatments, Chinese pharmacotherapy and lifestyle counselling (including Qi Gong, Tai Chi and Chinese dietetics) within the framework of the main therapeutic practices of TCM [15,17].

The resulting diversity of acupuncture is not only evident in clinical practice but is also reflected in research.

Dealing with Chinese-language publications on acupuncture

The question of whether Chinese-language publications on RCTs should be included in benefit assessments of acupuncture is the subject of debate. Various authors [18,19] argue in favour of including them in order to avoid language bias.

To gain insights about the impact of Chinese-language publications, IQWiG conducted an exploratory review of 4 systematic reviews (SRs) of RCTs, both with [20-23] and without [13,24-26] the inclusion of Chinese-language RCTs on acupuncture for migraine. Regardless of whether Chinese-language publications were included or excluded, all SRs, when comparing acupuncture with various comparators, arrived at a qualitatively consistent, positive result in favour of acupuncture treatment. This is consistent with the findings of Jiao et al. [27], who found no differences in the rate of positive conclusions in Cochrane reviews on acupuncture, regardless of whether Chinese-language RCTs were included or excluded.

In this context, it should be noted that there is an important discussion regarding the quality (methods, reporting) of studies published in Chinese, as including these studies can lead to relevant limitations in the certainty of conclusions in systematic reviews [28-32]. The cited reviews show that it often remained unclear whether the Chinese-language studies were in fact RCTs. In one of the reviews, enquiries made to the authors of the Chinese-language study publications [32] clarified that only 6.7% of the cases were in fact RCTs. The fact that the methodological quality issues mentioned are likely to have persisted into more recent times is suggested by the conclusions of recent systematic reviews that (in some cases predominantly) included Chinese-language studies on acupuncture for migraine, which call for methodologically sounder and larger RCTs [20,21,23,33].

For the purposes of this review, therefore, no studies published in Chinese are included (see also Section A2.1.6 of the full report).

2 Research question

The aim of this investigation is to assess the benefit of manual (conventional) acupuncture with needles for migraine prevention compared with

- pharmacological migraine prevention; or
- no pharmacological migraine prevention when pharmacological prevention is not indicated due to ineffectiveness, intolerance, or contraindications

in adult patients with migraine.

3 Methods

The target population for the benefit assessment consisted of adult patients with migraine. The test intervention was conventional manual acupuncture using needles. The control intervention was, on the one hand, pharmacological migraine prevention. On the other hand, for patients for whom pharmacological migraine prevention was not indicated due to ineffectiveness, intolerance or existing contraindications, no pharmacological migraine prevention was administered in the control group.

The following patient-relevant outcomes were considered for the study:

- Morbidity
  - in particular, the frequency, duration and intensity of migraine attacks, as well as
  - psychological symptoms, depression and anxiety
- Activities of daily living, including ability to work
- Health-related quality of life
- Adverse effects

Only randomized controlled trials (RCTs) were included in the benefit assessment. Studies with a minimum treatment duration of 3 months were included.

In parallel with the preparation of the protocol (“report plan”), a search for systematic reviews was conducted in the MEDLINE database (which also includes the Cochrane Database of Systematic Reviews) and the HTA Database, as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

A check was carried out to determine whether at least 1 high-quality and up-to-date systematic review (SR) was available that could be used as a basis for information retrieval (hereinafter referred to as the “base SR”).

If such a base SR was available, a supplementary search for studies covering the period not covered by the base SR was carried out in a second step. Otherwise, the search for studies was conducted without any time restrictions.

The systematic literature search for studies was carried out in the MEDLINE, Embase and Cochrane Central Register of Controlled Trials databases.

In addition, the following information sources and search techniques were taken into account: study registries, documents provided by the Federal Joint Committee (G-BA), screening of

reference lists from identified systematic reviews, documents made available during the commenting procedure on the preliminary report, and author enquiries.

The selection of relevant studies was carried out independently by 2 reviewers. Any discrepancies were resolved through discussion between them. Data extraction was carried out using standardized tables. To assess the certainty of the qualitative results, cross-outcome and outcome-specific criteria for risk of bias were evaluated, and the risk of bias was classified as either low or high in each case. The results of the individual studies were described, organized by outcome.

In addition to comparing the results of the individual studies, meta-analyses and sensitivity analyses were to be carried out, and effect modifiers investigated, provided that the methodological requirements were met.

For each outcome, a conclusion was drawn regarding the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter was the case if no data were available or the available data did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

Subsequently, an assessment of benefit and harm was carried out across outcomes.

4 Results

4.1 Results of information retrieval

No SR was included as a base SR for the purpose of identifying primary studies.

The literature search identified 5 relevant RCTs for the first sub-question (manual acupuncture versus pharmacological migraine prevention). For the second sub-question (conventional acupuncture versus no pharmacological prevention in patients for whom such prevention is not indicated due to ineffectiveness, intolerance or contraindications), the literature search and subsequent study selection did not yield any suitable studies.

No planned, ongoing or discontinued studies were identified for either sub-question. For the first sub-question, 1 study with an unclear status was identified.

The search strategies for bibliographic databases and study registries can be found in the appendix. The most recent search was carried out on 19 March 2025.

Table 1: Study pool for the benefit assessment

Study	**Available documents**	
	Full-text publication (in specialist journals)	**Registry entry / results report from study registries**
Studies included		
Allais 2002	Yes [34]	No
Nie 2019	Yes [35]	No
Yang 2011	Yes [36,37]	Yes [38] / no
Studies not included		
Diener 2006[a]	Yes [39-42]	Yes [43] / no
Streng 2006[a]	Yes [44]	Yes [45] / no
a. No usable data: the difference in the proportion of participants with missing data between the intervention and control groups was too great.		

4.2 Characteristics of the studies included in the assessment

For the subsequent, exclusive assessment of the first sub-question, 3 RCTs [34,35,37] were included, in which a total of approximately 300 patients were randomized to receive either conventional manual acupuncture with needles or pharmacological migraine prevention; 2 of the 5 RCTs [39,44] identified by the literature search were excluded from further assessment on methodological grounds, as more than 30% of the patients randomized to the medication group were not included in the analysis due to the immediate withdrawal of their consent to participate in the study [see also Section A3.1.3 in the full report], whereas this was considerably less common in the acupuncture group (the difference in the number of patients

excluded between the study arms was greater than 15 percentage points). In this respect, it cannot be assumed that the central aim of randomization – to achieve structural equivalence between the control groups – was fulfilled in these 2 studies.

The characteristics of the 3 RCTs analysed (see Table 1) are described in detail in Tables 9-12 of the full report. The 3 studies were published between 2002 and 2019. The sample size of the studies conducted in China, Italy and Taiwan ranged from 66 to 160 randomized patients.

The included studies differ in various respects. Whilst the proportion of women in the studies ranges from 72 to 100% – and, on average across all studies, stands at approximately 90%, which is higher than the roughly two-thirds typically seen in migraine – the duration of the condition among the included patients ranges from 4 to 20 years. In 1 study, patients with chronic migraine were treated (Yang 2011), and in 2 studies, those with episodic migraine (see Table 12 of the full report). The studies were categorized accordingly based on the authors' details regarding the study population, the reported inclusion and exclusion criteria, and a plausibility check involving a review of the reported baseline data on headache frequency and, additionally, the frequency of use of acute analgesics.

In the studies, manual acupuncture was compared with either flunarizine or topiramate as pharmacological migraine prevention. The duration of treatment in the studies was 3 or 6 months; in 1 of the 3-month studies, a further month of follow-up was added.

In the studies, acupuncture was performed either in a standardized or partially standardized manner by acupuncturists who were consistently described as highly experienced. With some overlap, various acupuncture points were selected, in some cases in different regions of the body (see Table 10 of the full report). The number and distribution of acupuncture sessions also varied.

4.3 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from the 3 studies. Table 2 provides an overview of the available data on patient-relevant outcomes from the included studies. The outcomes were sometimes recorded at different time points, depending on the varying durations of treatment or follow-up in the studies. In this assessment, results for the periods of 3 to 4 months and at 6 months after randomization are presented, where available. In 1 study (Nie 2019), results were recorded at 3 and 4 months; for this report, the results recorded at 4 months were used.

The outcomes in the studies were operationalized differently in some cases (e.g. headache frequency as headache days per month, migraine attacks per month; response defined as a reduction in the frequency of headache days by more than 50%). Health-related quality of life was assessed in 2 studies, but was only usable in the Yang 2011 study, as Nie 2019 presented

results from a Chinese-language migraine-specific scale whose validity and reliability could not be assessed due to a lack of suitable publications.

In the Nie 2019 study, a complex migraine score was used as the outcome, comprising the components of frequency, intensity and duration of migraine attacks, as well as the number of accompanying symptoms. In the analysis, these results were not included in a joint consideration and analysis of the outcomes of frequency, intensity and duration of migraine attacks, as the data (scores) are calculated in a specific manner (see footnotes, Table 19 of the full report) and cannot be meaningfully analysed together with the other operationalizations of these outcomes.

With regard to the aspect of harm from the compared interventions, it should be noted that the recording and reporting of adverse events in the studies varied greatly in terms of quality, and in one case (Nie 2019) the data were unusable. The information on harm in the studies was therefore not analysed quantitatively (meta-analysis) but only assessed in a qualitatively summarized manner in order to be considered in the weighing of benefits and harms.

During discussions with people affected, they explained that, on the one hand, acute analgesics more frequently triggered unpleasant adverse effects such as gastrointestinal complaints or “brain fog” with concentration problems, and, on the other hand, could lead in the longer term to a problem of overuse with increased migraine frequency (see Chapter 1). The results for the outcome “acute analgesic use” are therefore presented in addition to the actual benefit assessment (see Sections 4.7.2 as well as Section A3.4.2 of the full report).

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes								
	Morbidity							QoL	Adverse effects
	Headache frequency	Headache intensity	Migraine duration	Complex migraine score	Activities of daily living	Depression	Anxiety	Health-related quality of life	(S)AEs
Allais 2002	●	●	–	–	–	–	–	–	●
Never 2019	●	–	–	●	–	–	–	o[a]	o[b]
Yang 2011	●	–	–	–	●	●	o[c]	●	●

●: Data were reported and were usable.
o: Data were reported but were not usable for the benefit assessment.
x: Data were not reported despite data collection having been planned.
–: No data were reported (no further details) / The outcome was not measured.
a. The validity and reliability of the Chinese-language migraine-specific scale could not be assessed due to a lack of suitable publications.
b. Inadequate reporting on (S)AEs: blanket statement 'no adverse event occurred'.
c. It is unclear whether the HADS results refer to the anxiety or depression subscale.
HADS: Hospital Anxiety and Depression Scale; QoL: (health-related) quality of life; (S)AE: (serious) adverse event

4.4 Assessment of the risk of bias in the results

The risk of bias (see Table 13 of the full report) was rated as high across all outcomes for all 3 studies. Consequently, the reported results can only be considered to have moderate certainty of results. This is due, amongst other things, to the fact that in the comparisons examined between conventional manual acupuncture and pharmacological prevention, it was not possible to blind practitioners and patients, whilst at the same time a considerable proportion of the outcomes considered were based on information and documentation (migraine diary) provided by the patients themselves. Furthermore, Allais 2002 lacked a sufficiently detailed description of the concealment of group allocation during randomization (allocation concealment). Potential selective reporting could only be ruled out for Yang 2011 [37], as a prospective study registry entry [38] was available.

4.5 Results on patient-relevant outcomes

4.5.1 Results for the outcome “headache frequency”

Usable results were available for the outcome “headache frequency” from all 3 studies. These differed in terms of the time points and the operationalizations.

Results were reported for the following operationalizations:

- Number of headache days per month
  - Moderate/severe headaches
  - Headaches of any intensity
- Number of migraine attacks per month
- Response: Reduction in headache days by at least 50%
  - Moderate/severe headaches
  - Headaches of any intensity
- Response: No further migraine attacks

The relevant results are presented in detail in Tables 14 to 17 of the full report.

Statistically significant and clinically relevant differences, all in favour of manual acupuncture compared with pharmacological migraine prevention, are evident in the following operationalizations:

- Headache days per month: moderate/severe headaches, 3 to 4 months, chronic migraine, Yang 2011 study (MD: −2.70; 95% confidence interval [CI]: [−4.29; −1.11]; p = 0.001)
- Number of headache days per month: headaches of any intensity, 3 to 4 months, chronic migraine, Yang 2011 study (MD: −2.80; 95% CI: [−4.39; −1.21]; p < 0.001)
- Reduction in headache days by at least 50%: moderate/severe headaches, 3 to 4 months, chronic migraine, Yang 2011 study (odds ratio [OR]: 7.19; 95% CI: [2.42; 21.35]; p < 0.001)
- Reduction in headache days by at least 50%: headaches of any intensity, 3 to 4 months, chronic migraine, Yang 2011 study (OR: 9.80; 95% CI: [2.99; 32.11]; p < 0.001)

Furthermore, none of the 2 studies that included responder analyses showed statistically significant differences in the proportion of patients without migraine attacks. These 2 studies (Allais 2002, Nie 2019) had included patients with episodic migraine.

Overall, for patients with chronic migraine, there is a hint of a greater benefit from manual acupuncture compared with pharmacological migraine prevention (topiramate; Yang 2011) with regard to the outcome of headache frequency.

For patients with episodic migraine, there is no hint that manual acupuncture is more or less beneficial than pharmacological migraine prevention. This conclusion is based on the studies by Nie (2019) and Allais (2002) (flunarizine). In the Allais 2002 study, at the 3- to 4-month analysis point, when operationalized as migraine attacks per month, there was a statistically significant difference in favour of acupuncture, which, however, was not clinically relevant (the CI is close to a zero effect; it is therefore possible that this effect lies within an irrelevant range), and at the 6-month analysis point, no statistically significant difference was found.

4.5.2 Results for the outcome "headache intensity"

For this outcome (see Table 18 of the full report), the Allais 2002 study reported usable results:

In this study, 6 months after randomization, there was no statistically significant difference between the study groups (acupuncture vs. flunarizine) regarding the distribution of patients with episodic migraine across 3 intensity categories (mild, moderate, severe pain).

Consequently, with regard to headache intensity in patients with episodic migraine, there is no hint that manual acupuncture offers greater benefit compared with pharmacological migraine prevention at 6 months after randomization.

4.5.3 Results for the outcome "migraine duration"

No results were available for this outcome.

4.5.4 Results for the outcome "complex migraine score"

For the complex migraine score, which comprises the components of migraine frequency, intensity and duration, as well as the severity of accompanying symptoms, usable results were available from the Nie 2019 study – a study on episodic migraine. Nie 2019 reports only the results data for the 4 sub-components (see Table 19 of the full report).

In Nie 2019, statistically significant differences in favour of manual acupuncture compared with pharmacological migraine prevention were observed for all 4 sub-components of the complex migraine score, and the SMDs were all well below the irrelevance threshold of −0.2:

- Frequency of attacks: MD: −0.88; 95% CI: [−1.21; −0.55]; $p < 0.001$; SMD: −1.11 [−1.56; −0.67]
- Pain intensity: MD: −0.78; 95% CI: [−1.06; −0.50]; $p < 0.001$; SMD: −1.14 [−1.59; −0.70]

- Migraine duration: MD: −2.66; 95% CI: [−4.38; −0.94]; p < 0.003; SMD: −0.64 [−1.07; −0.22]
- Accompanying symptoms: MD: −0.78; 95% CI: [−0.83; −0.73]; p < 0.001; SMD: −6.52 [−7.58; −5.47]

This provides a hint that, for patients with episodic migraine, manual acupuncture offers greater benefit than pharmacological migraine prevention at 3 to 4 months after randomization.

4.5.5 Results for the outcome "activities of daily living"

This outcome encompasses migraine-related limitations in daily life, such as in work, social roles and leisure activities. Usable results were available from the Yang 2011 study, which operationalized "functional impairments in daily life" (MIDAS score – Migraine Disability Assessment) (see Table 20 of the full report).

A statistically significant difference was found in favour of manual acupuncture compared with pharmacological migraine prevention, with a difference in the MIDAS score at 3 to 4 months after randomization in patients with chronic migraine (MD: −12.60; 95% CI: [−17.53; −7.67]; p < 0.001].

Based on the Yang 2011 study, there is therefore a hint of a greater benefit of manual acupuncture compared with pharmacological migraine prevention for the outcome "activities of daily living" at 3 to 4 months after randomization in patients with chronic migraine.

4.5.6 Results for the outcome "depression"

For the outcome "depression", usable data were available from the Yang 2011 study, assessed using the Beck Depression Inventory II (BDI II) (Table 21 of the full report).

The analysis revealed a statistically significant effect in favour of acupuncture in patients with chronic migraine (MD: −2.10; 95% CI: [−3.97; −0.23]; p = 0.028). The SMD was −0.55; 95% CI [−1.04; −0.05]. This fell within the irrelevance threshold of −0.2. It is therefore possible that this effect lies within a clinically irrelevant range.

For the outcome of depression, therefore, no hint of a (greater) benefit of manual acupuncture compared with pharmacological migraine prevention can be inferred for patients with chronic migraine.

4.5.7 Results for the outcome "anxiety"

No usable results were available for this outcome, which was recorded in Yang 2011. Further details are provided in Section A3.3.7 of the full report.

4.5.8 Results for the outcome “health-related quality of life”

Usable data on health-related quality of life were available for the Yang 2011 study. This study reported results for the 8 domains of the SF-36, but no results for the 2 summary scores, the physical summary score and the mental summary score (see Table 22 of the full report).

For all 8 domains, there were consistently statistically significant effects in favour of manual acupuncture compared with pharmacological migraine prevention in patients with chronic migraine over the period of 3 to 4 months after randomization:

- Physical functioning (MD: 9.50; 95% CI: [5.88; 13.12]; $p < 0.001$)
- Physical role functioning (MD: 9.40; 95% CI: [4.92; 13.88]; $p < 0.001$)
- Pain (MD: 5.60; 95% CI: [2.49; 8.71]; $p < 0.001$)
- General health perception (MD: 7.50; 95% CI: [2.72; 12.28]; $p = 0.003$)
- Vitality (MD: 5.30; 95% CI: [2.05; 8.55]; $p = 0.002$)
- Social functioning (MD: 6.20; 95% CI: [2.94; 9.46]; $p < 0.001$)
- Emotional role functioning (MD: 10.30; 95% CI: [6.00; 14.60]; $p < 0.001$)
- Psychological well-being (MD: 11.20; 95% CI: [8.03; 14.37]; $p < 0.001$)

For all 8 components, the SMDs were consistently fully outside the irrelevance range of [−0.20, 0.20].

Overall, for patients with chronic migraine, there is a hint of a greater benefit of manual acupuncture compared with pharmacological migraine prevention for the outcome of health-related quality of life.

4.5.9 Results for the outcome “adverse effects” ([serious] adverse events)

Of the 3 studies comparing manual acupuncture with pharmacological migraine prevention, 2 studies (Allais 2002, Yang 2011) reported usable results. In the Nie 2019 study, the data on adverse effects are insufficient. No serious adverse events (SAEs) were reported for manual acupuncture in any of the studies. In the 2 studies with usable results on adverse effects, these consistently favoured manual acupuncture in a clear and statistically significant manner. Furthermore, in these studies, the most common adverse effects of acupuncture were consistently less severe than the most common adverse effects associated with pharmacological prevention (flunarizine, topiramate).

This therefore provides a hint of lesser harm from manual acupuncture compared with pharmacological migraine prevention. Further details are provided in the Sections 5.1 as well as Section A3.3.9 of the full report.

4.6 Summary assessment of the results

Evidence map

The following Table 3 shows the evidence map for patient-relevant outcomes.

Table 3: Evidence map for patient-relevant outcomes

	Morbidity							QoL	Adverse effects
	Headache frequency	Headache intensity	Migraine duration	Complex migraine score[a]	Activities of daily living	Depression	Anxiety	Health-related quality of life	(S)AEs
Manual acupuncture versus pharmacological migraine prevention	⇗[b]	⇔[c]	–	⇗[c]	⇗[d]	⇔[d]	–	⇗[d]	⇗[e]

⇑: Indication of a greater benefit of manual acupuncture compared with pharmacological migraine prevention
⇗: Hint of a greater benefit of manual acupuncture compared with pharmacological migraine prevention
⇔: No hint, indication or proof of greater benefit of manual acupuncture compared with pharmacological migraine prevention
–: No data reported that can be used for a benefit assessment
a. The complex migraine score comprises the components of migraine frequency, intensity and duration, as well as the severity of accompanying symptoms.
b. Patients with CM (for patients with EM, there is no hint of a [greater] benefit of manual acupuncture compared with pharmacological migraine prevention).
c. For patients with EM (no usable data available for patients with CM).
d. For patients with CM (no usable data available for patients with EM).
e. For patients with EM and CM.

CM: chronic migraine; EM: episodic migraine; QoL: (health-related) quality of life; (S)AE: (serious) adverse event

Assessment of the extent of unpublished data

Table 8 in Section A3.1.4 of the full report shows that 1 study was identified in study registries that was intended to address a research question underlying this assessment [46,47]. The study registry entry for this study indicates that the plan was to enrol a total of 70 patients with migraine to compare acupuncture with flunarizine. Although the planned end date of the study was more than 12 months ago, the status is listed as “recruiting”. It is therefore unclear whether this study was actually carried out. Furthermore, there is no information on the duration of the study. Consequently, it is unclear whether this study would be relevant to the present benefit assessment, even if it had actually been carried out.

With regard to possible reporting bias, this can be ruled out for the outcomes listed in Table 2 for the Yang 2011 study, as a prospective study registration entry is available and a comparison with the reported results reveals no notable data gaps. For the other 2 studies, there is no study registry entry or published study protocol. A comparison of the outcomes planned in accordance with the methods section and those reported, based on the publications underlying this assessment, does not reveal any indications that results were selectively reported. In summary, the certainty of conclusions regarding the outcome-related results is not considered to be compromised by unpublished data.

Weighing of benefits and harms

For the outcome of migraine frequency, a hint from Yang 2011 on chronic migraine suggests a benefit of manual acupuncture at 3 to 4 months after randomization. For the complex migraine score, which comprises frequency, intensity, duration and accompanying symptoms of migraine, there is evidence from Nie 2019, based on results for all 4 components, of a hint of a greater benefit for episodic migraine at 3 to 4 months after randomization. With regard to limitations in daily life and health-related quality of life at 3 to 4 months after randomization, hints from one study (Yang 2011) suggest a greater benefit of manual acupuncture for patients with chronic migraine. For the outcome of migraine intensity and the outcome of depression as an aspect of psychological morbidity, there was no hint of a (greater) benefit of manual acupuncture compared with pharmacological migraine prevention. No usable data were available for the outcomes of migraine duration and anxiety.

None of the 3 studies showed a statistically significant disadvantage for manual acupuncture compared with pharmacological migraine prevention at any point in time for any of the patient-relevant outcomes on benefit.

As outlined in the Section 4.5.9 as well as Section A.3.3.9 of the full report, 2 studies show statistically significant and numerically large differences in the rates of adverse effects in favour of acupuncture, and no serious adverse events resulting from acupuncture occurred. Furthermore, the severity of the most frequently observed adverse effects of acupuncture is comparatively minor when compared with pharmacological prevention. In summary, this provides a hint of lesser harm acupuncture.

A summary of the results from 3 studies suggests that, for patients with migraine, the data provide a hint of a greater benefit of manual acupuncture compared with pharmacological migraine prevention (flunarizine, topiramate), because

- hints from various studies suggest a greater reduction in
  - the frequency, intensity and duration of migraine attacks,
  - the limitations on everyday activities caused by headaches, and
  - the impairment of health-related quality of life.
- there are hints of greater benefit for both chronic and episodic migraine,
- there were no disadvantages associated with acupuncture across all outcomes considered, and
- there is a hint that manual acupuncture carries a lower risk of harm.

For the second question underlying this benefit assessment (see Chapter 2), namely the comparison of acupuncture with no pharmacological prevention in patients for whom pharmacological prevention is not indicated due to lack of efficacy, intolerance or the presence of contraindications, no studies were identified during the study selection process. Consequently, for this population, there is no hint of benefit or harm from acupuncture for the prevention of migraine.

4.7 Additional results presented but not included in the benefit assessment

4.7.1 Results on patient-relevant outcomes collected before the 3-month treatment period was reached

The Allais 2002 study also recorded and reported results for the outcome “headache frequency” at the early time point of 2 months after randomization. This observation period is insufficient to demonstrate the duration of effect required for a chronic condition. However, insights can be gained from this regarding the time of the emergence of significant differences. These results are therefore reported as supplementary information. The results presented in Table 23 of the full report show that the differences in the number of headache attacks per month between acupuncture and pharmacological prevention (flunarizine) may fall within an irrelevant range.

4.7.2 Acute analgesic use

The outcome “acute analgesic use” has not been sufficiently validated as a surrogate for the occurrence of medication-overuse headache and chronic migraine (see Section A4.2.1 of the full report). Therefore, the results from all 3 studies for 3 time points are presented for supplementary purposes only in Tables 24 and 25 of the full report. The outcome was operationalized in the studies as follows:

- Number of days or occasions per month on which acute analgesics were taken for migraine
- Number of patients who no longer took any acute analgesics at all

The overall picture of the results regarding acute analgesic use is characterized by a benefit of acupuncture for patients with chronic migraine in terms of the frequency of analgesic use at the analysis point relevant to this assessment, namely 3 to 4 months after randomization. Furthermore, a statistically significant effect in favour of acupuncture was also observed for patients with episodic migraine, specifically at the analysis point of 2 months after randomization, but not at 3 to 4 months or 6 months after randomization. With regard to the complete cessation of acute analgesic use, results were available only for the analysis point of 6 months after randomization from 1 study (Allais 2002) (Table 25 of the full report). No statistically significant effect was observed here. Overall, these results on acute analgesic use do not contradict the findings included in the actual benefit assessment.

5 Classification of the assessment result

5.1 (Serious) adverse events

The predominantly inadequate recording and reporting of SAEs suggests that the finding of a hint of a lower risk of harm from acupuncture compared with pharmacological prevention should be classified further. The fact that, despite statistically significantly lower AE rates in the acupuncture groups in 2 RCTs, only a hint and no indication of lesser harm is derived is due to the fact that the AE rates were reported without categorization according to the severity of the adverse effects, and only examples or the 2 to 3 most common adverse effects were cited.

The following contextual information is also relevant for classifying the assessment results on adverse effects: Results from large cohort studies, such as those involving nearly 100,000 participants in Germany in the former pilot projects on acupuncture [16], show that minor adverse events such as minor bleeding, local haematomas and short-term pain already account for almost the entire AE spectrum associated with conventional acupuncture. SAEs such as a pneumothorax caused by an acupuncture needle are very rare clinical treatment complications [48]. In contrast, according to their respective Summary of Product Characteristics (SmPC), the various drugs for pharmacological prevention are associated with frequent adverse effects, including SAEs. Flunarizine, for example, is frequently associated with fatigue, weight gain and nausea, and can trigger depression and extrapyramidal symptoms such as parkinsonism and tremor [49]. Topiramate can also cause depression, including suicidal tendencies, and may lead to further serious adverse effects such as kidney stones, metabolic acidosis, and cognitive and visual disturbances [50].

5.2 Acupuncture treatment protocol for migraine prevention

The following Table 4 provides an overview of the total number of acupuncture sessions, as well as the duration of treatment and follow-up, in the individual studies. In combination with the information from Table 10 of the full report regarding the distribution, frequency and duration of manual acupuncture sessions, the following can be inferred:

The number of acupuncture sessions ranges from a total of 12 sessions in Allais 2002, spread over 6 months, to 14 sessions in Nie 2019, spread over 3 months, up to a total of 24 sessions in Yang 2011, also spread over 3 months. In the studies by Allais 2002 and Nie 2019, the frequency of sessions decreased over time, whereas in Yang 2011 it remained consistently high:

- In Allais 2002, patients received 1 treatment per week in the first and second months and only 1 treatment per month in the remaining 4 months. Each session lasted 20 minutes, with 18 needles inserted on each occasion. This is the study with the lowest total number of acupuncture treatments and the lowest treatment frequency, but the highest total number of needles inserted.
- In Nie 2019, patients received 2 treatments per week in the first month, 1 treatment per week in the second month, and 1 treatment every 14 days in the final month. Each session lasted 30 minutes, with 12 needles inserted in each session, plus optional additional needles depending on the TCM syndrome, selected from a range of 24 acupoints.
- In Yang 2011, patients received the highest total number of treatments and – at a rate of 2 treatments per week throughout the entire 3-month treatment period – a consistently high frequency of treatment. Consequently, from the second month onwards, the frequency of acupuncture treatments in the Yang 2011 study was consistently higher than the respective treatment frequencies in the other 2 studies:
  - In the second month of treatment, the frequency in Yang 2011 – at 2 treatments per week – was twice as high as that in the Allais 2002 and Nie 2019 studies during the same month of treatment.
  - In the third month of treatment, the frequency of acupuncture treatment in Yang 2011 was ultimately 4 times higher than that in the Nie 2019 study and as much as 8 times higher than that in the Allais 2002 study during the same month of treatment.

  Each session lasted 30 minutes, with 7 needles inserted in each case.

Table 4: Number of acupuncture sessions and needles inserted, as well as duration of treatment and observation

Study		**Number of acupuncture sessions, needles and duration of treatment (time of data collection)**						
	Number of sessions	**Number of needles per session**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**
Allais 2002	12	18	(X)			(X)		(X)
Never 2019	14	12+ others from a selection of 24 points)[a]			(X)	(X)		
Yang 2011	24	7			(X)			

Month of treatment
Month of follow-up
(X): Time of data collection
a. See Table 10 of the full report.

If we now consider the treatment and analysis periods for which statistically significant sub-results were obtained for patients with chronic and episodic migraine, the following emerges:

- As outlined in the supplementary results text in Section 4.7.1, results for the outcome of headache frequency are available from1 included study (Allais 2002) at 2 months after randomization; these show a difference in favour of acupuncture between the study groups that may be clinically irrelevant.
- At 3 to 4 months after randomization, there are hints of a greater benefit from manual acupuncture compared with pharmacological migraine prevention, based on results relating to the complex migraine score, health-related quality of life, migraine-related limitations in activities of daily living, and headache frequency.

Regarding the question of when the effects of manual acupuncture and pharmacological migraine prevention can be expected to take effect, in addition to the data outlined above from Allais 2002, there are results from 2 RCTs [51,52] [51,52] involving a 4-week treatment period with flunarizine – a duration that is too short for this assessment. These results show, for various patient-relevant outcomes (e.g. migraine intensity, complex migraine score), that statistically significant and clinically relevant differences in favour of acupuncture can already be observed after 4 weeks.

With regard to the long-term effectiveness of acupuncture as a migraine prevention, usable results are available from the Nie 2019 study: The study reports that, at the analysis point 1 month after the end of the 3-month course of acupuncture treatment, the differences in favour of acupuncture observed at the end of treatment remained at a similar magnitude for all 4 components of the complex migraine score (headache frequency, intensity and duration, as well as accompanying symptoms).

From the facts presented, it can be inferred regarding the presumed duration of effectiveness of acupuncture for migraine prevention that

- the data on the onset of the effect of acupuncture are heterogeneous, as results from an early analysis point (2 months) in one of the included RCTs show benefits of questionable clinical relevance, whilst data from 2 studies – which were too short for this benefit assessment – already suggest benefits of acupuncture after 4 weeks of treatment,
- there is a hint of a greater benefit of acupuncture involving at least 12 sessions for various patient-relevant outcomes at 3 to 4 months after randomization, and
- there is no evidence available for the period beyond 6 months after randomization.

The 3 studies used for the assessment also differ significantly in terms of the acupuncture treatment, specifically regarding the number and location of the acupuncture points (for details, see Table 10 of the full report).

Due to this heterogeneity in the studies and the way acupuncture was administered, no clear pattern can be identified regarding which locations of acupuncture points, which exact number of treatment sessions at what frequency, and which distribution over time are suitable for generating a (particularly) high benefit from acupuncture in migraine prevention.

5.3 Possible influence of the cultural contexts in which the studies included in the review were conducted

The question here is whether a pattern can be identified whereby the positive results in favour of manual acupuncture in this benefit assessment stem predominantly from studies conducted in the Chinese-Asian or Western cultural spheres.

No cultural bias can be identified with regard to the quality of the studies and their results: across all outcomes, the risk of bias is high in all 3 studies. Furthermore, the results from the Italian study (Allais 2002) contribute to the conclusion in this assessment that manual acupuncture offers greater benefit and lesser harm, albeit not to the same extent as the 2 studies from Taiwan and China (Yang 2011, Nie 2019).

As several hints of a greater benefit of acupuncture compared with pharmacological migraine prevention were derived from the results of the Nie 2019 study and those of the Yang 2011 study, these studies are classified separately once again in terms of quality aspects.

The methodological descriptions in the publications provide no indication that these were not randomized trials, as was the case in the past, for example, with Chinese studies [32]. This is because both the generation of the randomization sequence and the blinding of group allocation are adequately described for both studies, whereas this was not the case for the other RCTs in the study pool with regard to the latter. Whilst there was no prospective study registration for Nie 2019, this does exist for Yang 2011 (on ClinicalTrials.gov), meaning that reporting bias could be reliably ruled out. Furthermore, the Yang 2011 study is the only one of the 3 included RCTs in which all criteria for risk of bias were rated as low – with the exception of blinding, which was not possible in this case. The risk of bias in the study was classified as high solely because, in the absence of blinding, all the outcomes assessed were subjective in nature or were documented by the patients themselves. The study also used assessment tools that are frequently employed in Western cultures, such as the SF-36, the BDI II and the MIDAS scale. Overall, the 2 studies – Nie 2019 and Yang 2011 – which can certainly be regarded as RCTs, contribute considerably to the positive assessment of manual acupuncture. The Yang 2011 study from Taiwan is to be regarded as the highest-quality study from a methodological perspective amongst the pool of RCTs considered.

5.4 Transferability of the results to health care in Germany – pharmacological prevention in the control groups

Control intervention: Use of conventional medicines only

A limitation regarding generalizability arises from the fact that, in the 3 studies with usable data, only conventional medicines such as flunarizine and topiramate were used; furthermore, identified German studies involving beta-blockers were not included in the assessment for methodological reasons. No RCTs were identified that compared manual acupuncture with the newer CGRP antibodies, which can now be prescribed in Germany for migraine prevention in cases where older medicines are ineffective or not tolerated, or where there are contraindications to their use, and which have fewer adverse effects whilst offering similar efficacy (e.g. [53-57]). It is therefore possible that a body of evidence incorporating studies comparing acupuncture with the new CGRP antibodies or with beta-blockers would lead to a different conclusion when weighing benefits and harms.

Usability of the evidence from 2 German studies

There were 2 RCTs that had been carefully designed and conducted in Germany. These studies had investigated the comparison of acupuncture with beta-blockers alone as pharmacological migraine prevention (Streng 2006 [44]) and with beta-blockers as first-line medication (Diener 2006 [39]). In particular, the 2006 Diener study, with its more than 620 randomized patients, could potentially have made a significant contribution to the assessment. However, the results from both studies were unusable due to high drop-out rates in the respective drug treatment arms, meaning they could not be taken into account for the assessment. Further information on this can be found in Section A3.1.3 of the full report and in the list of arguments in row 1, Table 26 of the full report.

Doubts regarding the authorized use of flunarizine

The doubts regarding the use of flunarizine in accordance with its marketing authorization – and thus the generalizability of the results from 2 RCTs – relate to the following aspect: In Germany, the prescription of flunarizine is conditional upon the patient having a contraindication to the use of beta-blockers – such as severe bronchial asthma, marked bradycardia or insulin-dependent diabetes mellitus with marked fluctuations in blood glucose levels – or upon prophylactic treatment with beta-blockers having been unsuccessful. For the studies by Allais 2002 and Nie 2019, the publications lack explicit information on whether there had been unsuccessful treatments with beta-blockers, whether a contraindication was present in the study population, or how many of the included patients were affected by this. It therefore remains unclear for these 2 studies on episodic migraine whether flunarizine was used in accordance with the German marketing authorization status or off-label. However, the finding of this review – that acupuncture offers greater benefit than pharmacological prevention with older drugs – would only be called into question, and only in the case of

episodic migraine, if flunarizine were more effective in the population authorized in Germany than in the presumably unselected populations of the 2 RCTs. With regard to the outcome of headache frequency, a systematic review of unselected populations demonstrated that flunarizine and beta-blockers had the same prophylactic efficacy [58]. The idea that the observed advantages of acupuncture are entirely absent in the population for which the drug is authorized, or that there might even be a reversal of effect, seems implausible, particularly in the absence of a corresponding (e.g. biological) rationale.

Effect of flunarizine dosage on the assessment result

Flunarizine is used as pharmacological migraine prevention in the Allais 2002 and Nie 2019 studies. According to the SmPC [49], the approved initial dose of flunarizine for patients up to 65 years of age is 10 mg/day. According to the SmPC for migraine prevention, this initial dose should not be administered for longer than is necessary to relieve symptoms (usually no longer than 2 months). Thereafter, if the patient responds to the treatment and further treatment is required for maintenance therapy, the dose should be reduced by having the patient take flunarizine only every other day, or by having the patient take flunarizine for 5 days followed by 2 treatment-free days.

In the Allais 2002 study, all patients received flunarizine at a dose of 10 mg/day for the first 2 months – in accordance with the SmPC – and a maintenance dose of 10 mg on 20 days per month (with daily interruptions) for the following 4 months. This dosing regimen is assumed to correspond in principle to a maintenance therapy regimen specified in the SmPC (5 days at 10 mg/day, followed by 2 days without medication).

In the Nie 2019 study, all patients received 5 mg twice daily for the entire 12 weeks of the study intervention. This results in a higher dose of flunarizine for the final 4 weeks of the treatment phase than that specified as the maintenance dose in the SmPC. No medication was administered during the subsequent 4-week follow-up period (see also Table 4).

With regard to the potentially distorting effect on morbidity outcomes and the outcome of adverse effects ([serious] adverse events), therefore, only the Nie 2019 study warrants closer examination due to the higher dose of 10 mg flunarizine daily – as opposed to administration 5 days a week – in the third month of treatment, which exceeds the recommendation in the SmPC.

A higher dose of flunarizine during the maintenance phase than that specified in the SmPC potentially leads to an enhanced drug effect. The results for the morbidity outcomes are therefore potentially biased against acupuncture. Consequently, the observed positive effects of acupuncture compared with pharmacological migraine prevention are not called into question by a higher maintenance dose of flunarizine.

With regard to adverse effects, the failure to reduce the dose may lead to a higher rate in the flunarizine arm. This may result in a bias in favour of acupuncture for the outcome of adverse effects.

However, firstly, as Nie 2019 reports that no "significant" adverse effects occurred in the study arms either during the 3-month treatment period or during the 1-month follow-up period, there appear to have been no negative effects of the failure to reduce the flunarizine dose in the third month of treatment.

Secondly, it should be noted that the result from Nie 2019 regarding adverse effects – which was reported only in general terms in the text – was not suitable for joint analysis with the data reported by Allais 2002 and Yang 2011, and was therefore not included in the assessment of this outcome.

In light of the adverse effects that occurred in the flunarizine group during the 6-month treatment period in Allais 2002, the finding in Nie 2019 that there were no "significant" AEs can be called into question. However, the following information from the publication suggests that the finding in Nie 2029 was probably accurate:

- Only patients who had no serious pre-existing conditions or contraindications to the study medication were included in the study;
- Before the start and after the completion of the study treatment, the participants in both arms underwent a medical examination – a meticulous procedure that is unique among the other RCTs of acupuncture versus medication included in this assessment;
- In the event of "significant" AEs – all of which were explicitly required to be recorded – treatment should have been discontinued immediately; however, there were no drop-outs in either study arm over the 4-month period.

Use of topiramate as pharmacological migraine prevention

In the Yang 2011 study, patients in the control group received topiramate. This is contraindicated, amongst other reasons, due to teratogenic risks during pregnancy and in women of childbearing age – i.e. the main target group for migraine prevention – unless highly effective contraception is used; a pregnancy test must be carried out before starting treatment with topiramate; the Federal Institute for Drugs and Medical Devices (BfArM) highlighted this in a Direct Healthcare Professional Communication ("Rote Hand Brief") at the end of 2023, together with the overall need for careful consideration of possible alternative treatments [50,59]. Topiramate is therefore authorized for migraine prevention provided that women of childbearing age use highly effective contraception. In the Yang 2011 study, it can be assumed that the drug was used in accordance with the marketing authorization, as pregnancy and breastfeeding were exclusion criteria, and participating patients of

childbearing age were required to undergo a pregnancy test as part of the safety assessment. Indeed, there were no cases of study withdrawal due to confirmed pregnancy in the study.

5.5 Indications of the significance of the analysed outcomes from discussions with patients

Discussions with patients, the majority of whom suffered from chronic and severe migraine, gave the impression that reducing the frequency of headaches (migraine attacks, days with headaches) is a particularly important goal of prophylactic treatment. The importance of reducing the frequency of migraine days and attacks is also confirmed by results from patient preference studies [60] involving several thousand participants in total.

Several people affected reported a lack of understanding, “being put under pressure”, conflicts and stigmatization in the workplace due to the more frequent inability to work and days off associated with migraine attacks. This aspect of reduced work capacity – which, based on impressions from the interviews, is highly relevant from the patients’ perspective, with concrete consequences such as a change of career or job, or early retirement, and which is subsumed under the outcome “activities of daily living” – was reported in a way that could be analysed in only 1 of the 3 studies.

Another aspect discussed with migraine patients was the use of acute analgesics, which would be reduced through effective migraine prevention. With a reduction in migraine attacks, they could more often avoid the use of triptans or NSAIDs, which, in their experience, frequently triggered unpleasant adverse effects such as gastrointestinal complaints or “brain fog” with concentration problems. Furthermore, according to the subjective assessment of those affected, the use of acute analgesics could, in the long term, lead to a problem of overuse with an increased frequency of migraine attacks. Several participants reported their own experiences in this regard, having undergone (multiple) inpatient withdrawal treatments over the course of their migraine condition, which in some cases had lasted for decades. Consequently, the results relating to the outcome “acute analgesic use” are presented in supplementary form in Section 4.7.2 and Section A3.4.2 of the full report, although, as outlined in Section A4.2.1, this outcome was not included in the benefit assessment.

6 Conclusion

For a large proportion of the areas of application of manual acupuncture for migraine prevention, no relevant studies are available. This applies to both patients for whom drug therapy is not an option, as well as to those in whom conventional drug therapy does not adequately control symptoms and who are receiving or are being considered for CGRP-targeted escalation therapy. Therefore, there is currently no evidence to suggest that manual acupuncture with needles is beneficial in these areas of application.

Relevant studies are available only for comparisons of manual acupuncture with selected conventional drugs (flunarizine and topiramate). Based on the results of 3 RCTs on migraine prevention, which differed in design and compared conventional manual acupuncture using needles with guideline-compliant pharmacological migraine prevention using flunarizine or topiramate, there is a hint that acupuncture offers a greater benefit than flunarizine and topiramate in both episodic and chronic migraine. This conclusion is based particularly on hints of a greater benefit from acupuncture with regard to migraine symptoms and their consequences, such as the ability to cope with everyday life, as well as a hint of lesser harm with regard to adverse effects. The follow-up period lasted up to 4 months. Given the various restrictions on the use of topiramate and flunarizine in clinical practice, the advantages of manual acupuncture suggested by these studies can only be inferred for a limited range of applications. Topiramate should generally only be used after careful consideration of alternative treatments. Flunarizine should only be used if beta-blockers are contraindicated or if previous treatment with beta-blockers has been unsuccessful. No suitable studies comparing manual acupuncture with other conventional, approved medicines for migraine prevention, such as beta-blockers, amitriptyline, or onabotulinumtoxin A were identified.

References for English extract

Please see full final report for full reference list.

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The full report (German version) is published under

https://www.iqwig.de/en/projects/n25-01.html.

Appendix A Search strategies

A.1 Searches in bibliographic databases

Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to January 13, 2025

The following filter was adopted:

- Systematic review: Wong [61] – High specificity strategy (adopted)

#	Searches
1	exp migraine disorders/
2	migrain*.ti,ab.
3	exp acupuncture therapy/
4	acupunctur*.ti,ab.
5	(prophyla* or prevent* or control* or reduc*).ti,ab.
6	(pc or tu or ae).fs.
7	1 or 2
8	3 or 4
9	5 or 6
10	7 and 8 and 9
11	Cochrane database of systematic reviews.jn.
12	(search or MEDLINE or systematic review).tw.
13	(meta analysis or systematic review).pt.
14	or/10-13
15	14 not (exp animals/ not humans.sh.)
16	and/10,15
17	16 and (english or german or multilingual or undetermined).lg.
18	..l/ 17 yr=2020-current

2. International HTA Database

Search interface: INAHTA

#	Searches
1	("migraine disorders"[mh])
2	migrain*
3	"acupuncture therapy"[mh]
4	acupunctur*
5	#2 OR #1
6	#4 OR #3
7	(*) FROM 2020 TO 2025
8	#7 AND #6 AND #5

Search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to March 07, 2025

The following filter was adopted:

- RCT: Lefebvre [62] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2023 revision)

#	Searches
1	exp Migraine Disorders/
2	(headache* or migrain*).ti,ab.
3	or/1-2
4	exp Acupuncture Therapy/
5	Acupuncture/
6	(acupuncture or acupoint*).ti,ab.
7	or/4-6
8	and/3,7
9	exp Randomized controlled Trial/
10	controlled clinical trial.pt.
11	(randomized or placebo or randomly or trial or groups).ab.
12	drug therapy.fs.
13	or/9-12
14	13 not (exp animals/ not humans.sh.)
15	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/

#	Searches
16	hi.fs. or case report.mp.
17	15 or 16
18	14 not 17
19	18 and (english or german or multilingual or undetermined).lg.
20	and/8,19

2. Embase

Search interface: Ovid

- Embase 1974 to 2025 March 07

The following filter was adopted:

- RCT: Wong [61] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	exp Migraine/
2	migrain*.ti,ab.
3	((chronic or primary) adj3 headache*).ti,ab.
4	or/1-3
5	exp Acupuncture/
6	Acupuncture Needle/
7	(acupuncture or acupoint*).ti,ab.
8	or/5-7
9	and/4,8
10	(random* or double-blind*).tw.
11	placebo*.mp.
12	or/10-11
13	and/9,12
14	13 not medline.cr.
15	14 not (exp animal/ not exp human/)
16	15 not (Conference Abstract or Conference Review or Editorial).pt.
17	16 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 2 of 12, February 2025

#	Searches
#1	[mh "Migraine Disorders"]
#2	(headache* OR migrain*):ti,ab
#3	#1 OR #2
#4	[mh "Acupuncture Therapy"]
#5	[mh ^Acupuncture]
#6	(acupuncture or acupoint*):ti,ab
#7	#4 OR #5 OR #6
#8	#3 AND #7
#9	#8 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#10	#9 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
#11	#10 in Trials

A.2 Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Expert Search

Search strategy
AREA[ConditionSearch](migraine OR headache) AND AREA[InterventionSearch]acupuncture

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Basic Search

Search strategy
(migrain* OR headache*) AND (acupuncture* OR acupoint*)