



## Pizotifen for the treatment of migraine. A systematic review and meta-analysis

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**Edited by:**  
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**Keywords:**  
migraine  
pizotifen  
headache  
systematic review  
evidence-based medicine

### Abstract

#### Introduction

Pizotifen is an oral drug developed many years ago for the prophylaxis of migraine. Trials on pizotifen are decades old, and there has never been a systematic review and meta-analyses of data from these clinical studies.

#### Methods

This is a systematic review and meta-analyses on pizotifen's efficacy and safety for prophylactic migraine treatment. We considered for inclusion only randomized clinical trials (RCTs). A comprehensive electronic search was performed without language, date or publication status restrictions in the formal electronic databases, clinical trial registration platforms and grey literature.

#### Results

There were eight RCTs of pizotifen compared either to placebo or to other drugs. Very low certainty of evidence showed that pizotifen seems to be superior to placebo regarding clinical symptoms improvement (Relative risk [RR] 6.00; 95% Confidence interval [CI] 1.63 to 22.03;  $p = 0.007$ ), but not inferior to naproxen, flunarizine, valproate or clonidine. Weight gain was the most frequent adverse event of pizotifen but there was no difference with placebo (RR 1.92; 95% CI 0.30 to 12.38; 2 RCTs; 142 participants;  $I^2 = 67\%$ ;  $p = 0.49$ ).

#### Conclusion

The RCTs of pizotifen were decades old. It is a safe and potentially efficacious inexpensive drug that deserves a better designed, modern clinical trial before being dismissed as an option for migraine therapy. PROSPERO Register: CRD42020194347.

Received: April 9, 2021  
Accepted: September 30, 2021



## Introduction

Migraine affects over 10% of adults and can limit their activities both at home and at work.<sup>1</sup> The socioeconomic costs of migraine are remarkably high, and patients tend to overuse medications for the pain if the headache is not properly treated.<sup>2</sup> This disease is an important cause of absenteeism and presentism at work, missed days at school and excessive numbers of medical consultations and examinations.<sup>3</sup> Although several medications have been used for prophylaxis of migraine attacks, only two classes of drugs presently commercialized have been specifically developed for this condition. One of the drugs is the relatively old pizotifen and the other is the monoclonal antibody (MAb) anti-CGRP. Small oral molecules with anti-CGRP effect are undergoing clinical trials.

Anti-CGRP monoclonal antibodies have a strong placebo and weak nocebo effect.<sup>4</sup> This, in addition to their good safety profile [Hou], makes these drugs successful in controlling migraine. The complicating aspect of this treatment is its cost of circa USD 200/month per patient. In places with high *per capita* income and/or in countries with healthcare systems providing reimbursement of the drug, use of anti-CGRP MAbs can thrive.

Pizotifen, on the other hand, costs little. The only bothersome adverse event caused by pizotifen is weight gain, which can be tolerated by some patients if they know what to expect. It is hard to find pharmacies selling branded pizotifen: it is mostly available online and at compounding pharmacies. Pizotifen may decrease migraine attacks at a fraction of the price of some other drugs. There has never been a systematic review and meta-analysis on pizotifen for the treatment of migraine.

Apart from pizotifen and anti-CGRP MAbs, other drugs are used in migraine prophylaxis, like tricyclic antidepressants, calcium channel blockers, betablockers and anticonvulsants. For all these drugs, the profile of adverse events is worse than that of pizotifen or anti-CGRP MAbs.

Should pizotifen prove to be an efficient and safe prophylactic drug for migraine, many individuals who cannot afford the expensive new therapy could benefit from the older one. Thus, the objective of this systematic review was to assess the effects (benefits and harms) of pizotifen for treating migraine in adults.

## Methods

This systematic review followed the methodological recommendations of the Cochrane Handbook for Systematic Reviews of Interventions<sup>5</sup> and the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) to ensure the quality of the report.<sup>6</sup> This systematic review protocol was prospectively registered in the PROSPERO (International Prospective Register of Systematic Reviews) platform, under the number CRD42020194347.

### *Criteria for including studies for this review*

We considered randomized clinical trials (RCTs) with parallel design, assessing the effects (benefits and harms) of pizotifen for treating migraine in adults (over 18 years), who reported episodic or chronic migraine with or without aura. Studies that included any other headache condition were excluded if data were not presented separately for patients with migraine. The RCTs included compared any dose or scheme of pizotifen with placebo, no intervention, or another active drug treatment.

### *Types of outcome measurements*

#### *Primary outcomes*

- Reduction of frequency and/or severity and/or duration of migraine attacks.
- Reduction of medications taken to treat a migraine attack.
- Adverse events: proportion of participants with at least one adverse event resulting from the use of pizotifen (for example, any gastrointestinal events or allergy).

#### *Secondary outcomes:*

- Patients' satisfaction and preferences.
- Tolerability of weight gain.

We considered all time points reported by the RCTs, but we only pooled similar time points: short term (up to 8 weeks of treatment), intermediate-term (9 to 16 weeks of treatment) and long term (over 16 weeks of treatment).

### *Search methods for identification of studies*

A comprehensive electronic search was performed on July 20, 2020, and was updated on February 18, 2021. There were no restrictions regarding language, date or publication status. Sensitive search strategies were developed for



the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL) (via Wiley); MEDLINE (via PubMed); EMBASE (via Elsevier); Literatura Latino Americana em Ciências da Saúde e do Caribe - LILACS (via Biblioteca Virtual em Saúde - BVS); and PsycINFO (via EBSCO). We also searched for clinical trial registration platforms: ClinicalTrials.gov (<https://ClinicalTrials.gov/>) and WHO International Clinical Trials Registry Platform (ICTRP) (<https://www.who.int/ictip/search/en/>). The grey literature was searched via OpenGrey (<http://www.opengrey.eu/>). Hand searching was done by verifying the lists of references from relevant studies. Search strategies for each database were presented in the Supplementary material 1.

### Data collection and analysis

#### Selection of studies and data extraction

All titles and abstracts obtained through the search strategies were included in a reference management program (Endnote<sup>®</sup>) where duplicates were removed. Two authors independently selected titles and abstracts of the references retrieved using the software Rayyan.<sup>7</sup> All references classified as 'potentially eligible' were read in full text to confirm their eligibility.

The data extraction process was carried out by three independent authors using a pre-established data extraction form. Two other authors resolved all discordance in the selection and extraction process. When necessary, the authors of the trials included in the review were contacted for additional information.

#### Risk of bias (quality) assessment

Two independent authors assessed the methodological quality of the studies included using the Cochrane Risk of Bias (RoB) table<sup>5</sup>, which classify each of the following domains as presenting a high, low or unclear risk of bias: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessors; (5) incomplete outcome data; (6) selective reporting of outcomes; and (7) other potential sources of bias (for example, baseline imbalances). A third author was consulted in cases of disagreement.

#### Data synthesis

We planned to calculate risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, or the standard mean difference (SMD), if any outcome of interest had been measured using different scales or questionnaires (95% confidence interval). When

possible (if data were available and homogeneous), treatment effects were combined using a random-effects model meta-analysis in the Review Manager 5.4.1 software. The heterogeneity between the studies included was evaluated according to the clinical and methodological characteristics. Statistical heterogeneity was assessed through visual inspection of forest plots. We calculated a  $\chi^2$  test, considering  $p > 0.1$  as indicative of statistical heterogeneity, and an  $I^2$  test for measuring inconsistency across studies (we defined  $I^2 > 50\%$  as indicative of significant inconsistency).<sup>8</sup>

#### Subgroup and sensitivity analysis

We planned to assess subgroups for all primary outcomes, comparing separated results between adults and children. We also planned to conduct a sensitivity analysis in which RCTs with a high risk of bias (selection, detection and attrition bias) would be excluded from the meta-analysis.

#### Publication bias assessment

Publication bias would be investigated through analysis of funnel plots if there had been meta-analyses with at least ten studies.

#### Assessment of the certainty of the evidence

Two independent authors assessed the certainty of the body of evidence for primary outcomes from the main comparison: pizotifen versus placebo, using the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluations).<sup>9</sup> We summarized the evidence in the 'Summary of findings table' (SoF table) through the GRADEpro GDT platform.

## Results

#### Search results

The results from the search strategies, retrieved 749 records. After removing 104 duplicates, 645 were analyzed using the title and abstract. Of these, 623 did not fulfil the inclusion criteria and were excluded. Twenty-two studies were analyzed using the full text, and nine<sup>10-18</sup> were excluded (crossover trials). Five studies<sup>19,23</sup> were classified as 'awaiting classification studies' because their randomization was not clear, and we did not find the authors' contact details to request additional information. Contacts with the editors of the journals in which these papers were published were fruitless. Therefore, in the end, eight RCTs were included in this review.<sup>24-31</sup> Figure 1 summarizes the study selection process.

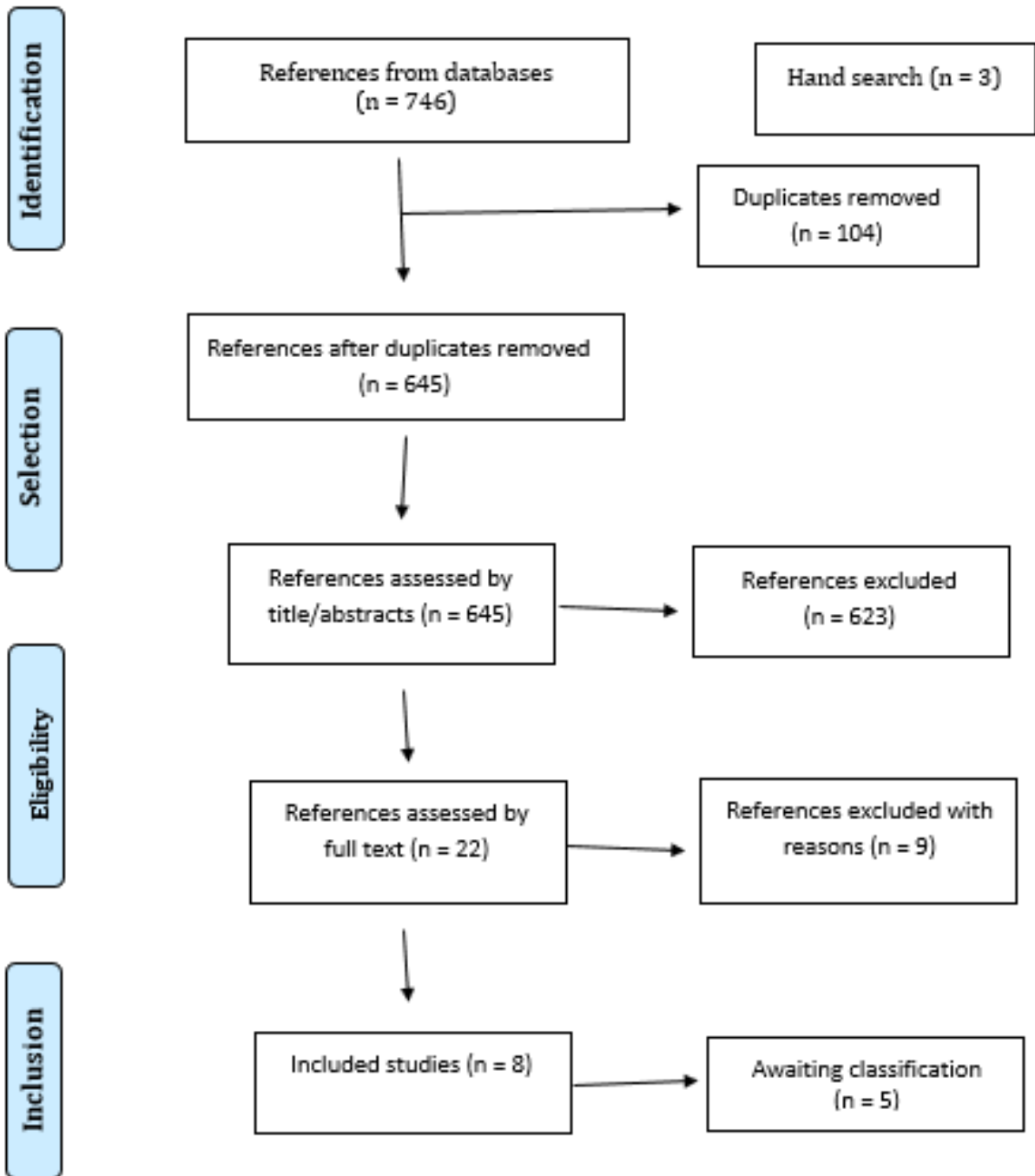


Figure 1. PRISMA flowchart.



## Characteristics of the studies included

Table 1 summarizes the main characteristics of the eight RCTs included.

**Table 1.** Main characteristics of the included studies.

Study, year, country	Study design	Participants	Intervention	Comparator(s)	Outcomes of interest	Time points	Funding sources
Behan 1985 <sup>24</sup> Scotland	RCT	n = 60 common migraine >2 episodes/ month mean 30 years predominantly female (% NR)	Pizotifen 1.5 mg (once, at night) (n = 30)	Clonidine 25ug twice/d (n = 30)	* Number of episodes * Duration of episodes * Severity of episodes * Adverse events (weight gain)	2 mo	NR
Behan 1986 <sup>25</sup> Scotland	RCT	n = 67 common migraine (defined by WFN) frequent migraine episodes > 2 years age NR 82% female	Pizotifen 0.5 mg three times/d (n = 35)	Naproxen sodium 550 mg twice/d (n = 32)	* Number of episodes * Duration * Severity (excellent, moderate, mild, no change or worse) * Adverse events (weight gain, nausea, vomiting) * Analgesic medication required	3 mo	NR
Bellavance et al., 1990 <sup>26</sup> Canada	RCT	n = 176 Common migraine (defined by AHC), mean duration 11.9 years 6.7 episodes/month mean 32.5 years 79% female	Pizotifen 0.5 mg three times/d (0.5 mg at bedtime and gradually titrated up over 7 d to 0.5 mg three times/d) (n = 55)	Naproxen sodium 550 mg twice/d (n = 60) Placebo (n = 57)	* Frequency, duration and severity of episodes (Headache Unit Index) * Severity (rate of pain intensity, vomiting episodes) * Analgesic medication required * Adverse events (weight gain, gastrointestinal, skin effects) * Patient's global assessment	3 mo	NR
Cerbo et al., 1985 <sup>27</sup> Italy	RCT	n = 30 4 to 14 episodes/month > 6 episodes, last 6 months aged 23 to 54 years 53.3% male	Pizotifen 1.5 mg nightly, for 2 mo (n=15)	Flunarizine 15 mg nightly, for 2 mo (n=15)	* Number of episodes (per month) * Duration (per month) * Severity (total hours of intense pain per month) * Adverse events (weight gain, daytime sedation)	2 mo	NR
Chitsaz et al., 2012 <sup>28</sup> Iran	RCT	n = 42 Common migraine (defined by IHS) frequent migraine episodes > 1 year 4 to 14 episodes/month, last 3 months aged 23 to 54 years 57.1% female	Pizotifen 0.5 mg (bedtime) in the first week; 1.5 mg (bedtime) in the second and subsequent weeks (n = 21)	Sodium valproate 200 mg twice/d (n = 21)	* Number of episodes * Duration * Severity (VAS) * Adverse events (weight gain, nausea, vomiting)	3 mo	Isfahan University of Medical Sciences, Iran
Lawrence et al., 1977 <sup>29</sup> England	RCT	n = 36 Common migraine (defined by AHC), mean duration 15.9 years >4 episodes/ month mean age 16-64 years 72.2% female	Pizotifen 0.5 mg once/d (days 1-2), twice/d (days 3-4), three times (days 5-15), two tablets, three times/d for 10 wks (n=14)	Placebo same scheme (n = 14)	* Headache index (number of episodes x severity) * Adverse events (weight gain)	3 mo	NR
Louis et al., 1982 <sup>30</sup> Belgium and Netherlands	RCT	n = 75 Common migraine (defined by AHC) > 6 episodes, last 6 months mean age 37 years 55% female	Pizotifen 1 mg nightly, and after 5 d, additional 0.5 mg capsules twice/d, for 4 mo (n=37)	Flunarizine 10mg nightly, and after 5 d, additional placebo capsules twice/d for 4 mo (n=38)	* Number of episodes * Duration * Severity (4-point scale) * Adverse events (weight gain, daytime sedation) * Patient's global assessment	4 mo	NR
Rascol et al., 1986 <sup>31</sup> France	RCT	n = 35 Common migraine (defined by AHC), >2 years > 6 episodes, last 6 months mean age 38 years 71% female	Pizotifen 0.73 mg (days 1-2), 1.46 mg (days 4-6) and 2.19 mg (days 7-120), for 4 mo (n=14)	Flunarizine 10 mg /d, for 4 months (n=21)	* Number of episodes * Duration * Severity (4-point scale) * Adverse events (weight gain, changes in blood pressure, hot flushes, drowsiness, asthenia) * Patient's global assessment	4 mo	NR

RCT: randomized clinical trial; n: number of participants; mg: milligrams; h: hours; NR: not reported; AHC: Ad Hoc Committee on Classification of Headache; d: days; mo: months; WFN: World Federation of Neurology Research Group on Migraine and Headache; IHS: International Headache Society; VAS: visual analogue scale.



### Methodological quality assessment (risk of bias)

Figure 2 summarizes the review authors' judgments on each risk-of-bias domain for each study included. The reasons for each judgment are summarized in the "Risk of bias" is detailed in *Supplementary Material 2*.

Regarding selection bias, only one study<sup>31</sup> reported using an adequate method for generating the randomization sequence, and this study was judged as presenting a low risk of bias. In the other studies, insufficient information was provided, and these were classified as having an unclear risk of bias.

Regarding performance bias, three studies<sup>24,25,28</sup> were classified as having high risk of bias because they were single-blinded. Only one study<sup>27</sup> was considered as having a low risk of bias regarding blinding of participants, personnel and outcome assessors.

Four studies<sup>24-26,29</sup> had substantial losses of participants during the study (16 to 44%) and were classified as presenting high risk of attrition bias. Trial register protocols were not available for any of the studies included, leading to an overall unclear risk of reporting bias. Lastly, two studies<sup>27,29</sup> did not describe the baseline characteristics between groups and were judged as having unclear risk of other sources of bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Behan 1985	?	?	●	?	●	?	●
Behan 1986	?	?	●	?	●	?	●
Bellavance 1990	?	?	?	?	●	?	●
Cerbo 1985	?	?	●	●	●	?	?
Chitsaz 2012	?	?	●	●	?	?	●
Lawrence 1977	?	?	?	●	●	?	?
Louis 1982	?	?	?	?	●	?	●
Rascal 1986	●	?	?	?	●	?	●

**Figure 2.** Risk-of-bias summary: review authors' judgments about each risk-of-bias item for each study included.

### Effects of interventions

#### Comparison 1. Pizotifen versus placebo

##### - Frequency, intensity and duration of episodes

Two studies<sup>26,29</sup> evaluated these outcomes, and it was not feasible to pool their results in a meta-analysis due to their clinical diversity and the unavailability of data. When possible, estimated effects were calculated using individual study data.

Bellavance et al.<sup>26</sup> (112 participants) assessed a headache unit index (sum of severity x duration of each episode/number of treatment days) and reported that use of pizotifen led to improvement after three months of treatment, compared with placebo (mean of 3.27 versus 5.08 episodes per week). No difference was observed regarding pain intensity (mean 1.80 versus 1.86), severity of disability (mean 1.67 versus 1.77), duration of episodes (mean 1.59 versus 1.55), use of migraine rescue medication per week (mean 0.82 versus 1.26) and vomiting episodes per week (mean 0.08 versus 0.48).

Lawrence et al. (1977)<sup>29</sup> (36 participants) assessed a weekly headache index by multiplying the number of episodes by their intensity, according to the following scale: severe = 3, moderate = 2 and mild = 1. In the pizotifen group, 85.7% (12/14) achieved complete resolution of symptoms or progressive improvement after three months of treatment, compared with 14.2% (2/14) reporting slight improvement in the placebo group. Pizotifen seemed to improve compared with placebo, but this result was considered very imprecise due to the wide confidence interval (RR 6.00; 95% CI 1.63 to 22.03; p = 0.007).

##### - Adverse events

The meta-analysis results showed no difference between pizotifen and placebo regarding weight gain (ranging from 0.5 to 4 kg) after three months of treatment. However, an imprecision in this estimated effect was observed due to the wide confidence interval (RR 1.92; 95% CI 0.30 to 12.38; 2 RCTs; 142 participants; I<sup>2</sup> = 67%; p = 0.49) (Figure 3). Moreover, there was a slight statistical heterogeneity (67%), which can be explained as possible clinical differences between participants, including in the treatment scheme with pizotifen.

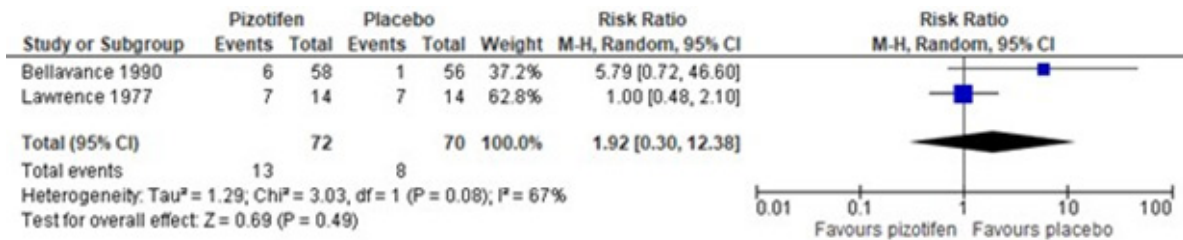


Figure 3. Meta-analysis of pizotifen versus placebo. Outcome: adverse events (weight gain).

Bellavance et al. (1990)<sup>26</sup> also presented a non-significant difference between their groups regarding the following adverse events: gastrointestinal (7/58 versus 3/56); skin (0/58 versus 1/56), and other (2/58 versus 4/56). The adverse events informed by patients were generally of mild or moderate intensity.

- Patients' overall evaluation

In one study<sup>26</sup>, good or excellent ratings in the patients' overall evaluation were reported by 68% of pizotifen-treated participants and 36% of placebo-treated participants (p = 0.005).

Comparison 2: Pizotifen versus flunarizine

- Frequency, intensity and duration of episodes

Regarding the severity of episodes measured on a pain intensity scale, in one study<sup>27</sup> an improvement of 81% in the flunarizine group was observed, compared with 40% in the pizotifen group (p < 0.01). The episodes' duration was not significantly changed by either pizotifen or flunarizine (mean 8.5 versus 31, respectively). Louis et al.<sup>30</sup> used a 4-point scale to assess the severity of the episodes, and no difference was noted between pizotifen and flunarizine, considering the number of participants with migraine grade 1 (mild) after four months of treatment (RR 0.14; 95% CI 0.02 to 1.06; p = 0.06). This effect was uncertain, given the breadth of the confidence interval. These authors also stated that the episodes' duration was not changed by either drug (no numerical data provided).

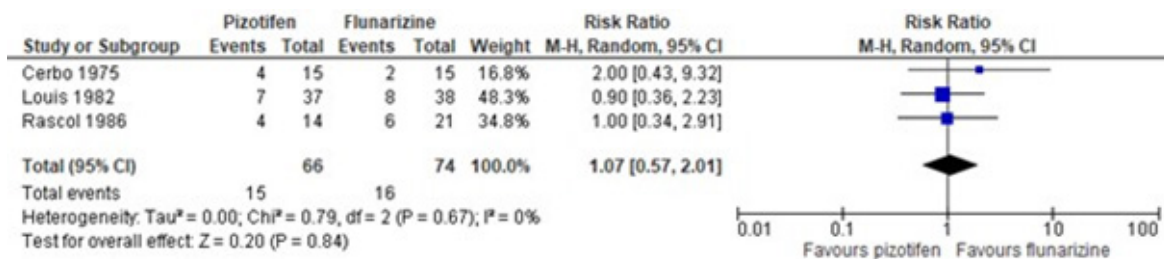


Figure 4. Meta-analysis of pizotifen versus flunarizine. Outcome: adverse events (weight gain).

Three studies<sup>27,30,31</sup> assessed these outcomes, but it was not possible to group their data in a meta-analysis or calculate the estimated effects for most individual studies due to missing numerical data.

One study<sup>31</sup> (75 participants) presented a mean reduction in the number of migraine episodes of 54% for the flunarizine group and 45% for the pizotifen group after four months. The authors stated that there was a significant difference between the groups (p < 0.001). Cerbo et al.<sup>27</sup> (30 participants) reported that there was no difference between drug treatments regarding the mean reduction in the number of episodes per month (mean 2.67 pizotifen versus 3.56 flunarizine). Rascol et al.<sup>31</sup> (35 participants) reported that the reduction in the flunarizine group (65%) was slightly greater than in the pizotifen group (45%), but the intergroup difference was not significant after two months of treatment (p = 0.10).

Adverse events

Weight gain was reported in the three studies comparing pizotifen with flunarizine<sup>27,30,31</sup>, ranging from 4 to 11 kg. The results from a meta-analysis showed that there was no difference between the groups (RR 1.07; 95% CI 0.57 to 2.01; 3 RCTs; 140 participants; I<sup>2</sup> = 0%; p = 0.84) (Figure 4).

In two studies<sup>27,30</sup>, daytime sedation among the participants in both groups was reported. The results from a meta-analysis showed no difference between groups (RR 0.49; 95% CI 0.24 to 1.01; 2 RCTs; 105 participants; I<sup>2</sup> = 0%; p = 0.48). Rascol et al.<sup>31</sup> found no difference between the groups regarding occurrences of other adverse events, including changes in blood pressure, hot flushes, drowsiness and severe asthenia (1/14 versus 2/15; RR 2.00; 95% CI 0.20 to 19.78; p = 0.55). However, both effect estimates had wide confidence intervals and were



highly imprecise.

*Patients' overall evaluation*

The participants in two studies<sup>30,31</sup> reported that the effects from both treatments were positive, but there was no significant difference between the groups after 4 months of treatment (RR 0.90; 95% CI 0.61 to 1.32; 2 RCTs; I<sup>2</sup> = 0%; 101 participants; p = 0.40) (Figure 5).

The pooled results from two studies<sup>26,27</sup> showed that subjects who received naproxen presented less weight gain than those who received pizotifen. However, this meta-analysis was very imprecise (RR 11.45; 95% CI 1.52 to 86.21; 2 RCTs; I<sup>2</sup> = 0%; 183 participants; p = 0.90) (Figure 6).

In two studies<sup>26,27</sup>, other adverse events relating to the treatments were reported. These included nausea,

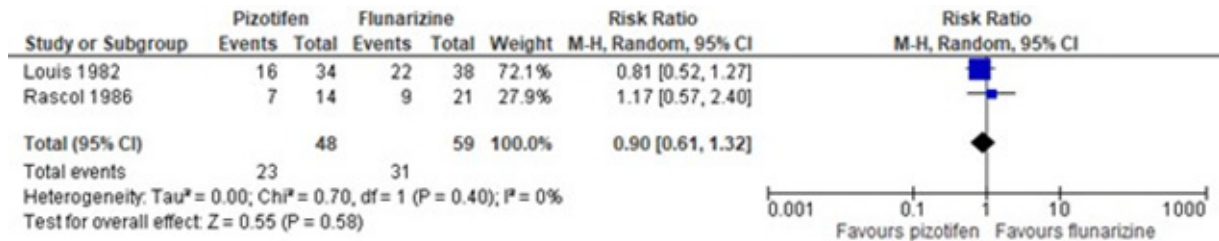


Figure 5. Meta-analysis on pizotifen versus flunarizine. Outcome: patients' overall evaluation.

*Comparison 3: Pizotifen versus naproxen*

*- Frequency, intensity and duration of episodes*

Two studies<sup>25,26</sup> assessed these outcomes, but it was not possible to group their data in a meta-analysis because the outcomes were measured using different methods. In one study<sup>25</sup> (67 participants), no significant differences between the groups were found regarding frequency (MD -0.10; 95% CI -0.68 to 0.48) or severity of episodes (MD -0.20; 95% CI -0.93 to 0.53), after 3 months of treatment. There were no significant differences between the groups regarding the duration of attacks or use of rescue medication (no numerical data provided).

vomiting and gastrointestinal effects. However, there were no differences between the groups observed.

*Comparison 4: Pizotifen versus sodium valproate*

*- Frequency, intensity and duration of episodes*

One study<sup>28</sup> (60 participants) assessed this comparison. Significant mean reductions in the frequency (MD 2.80; 95% CI 1.42 to 4.18) and severity (RR 1.30; 95% CI 0.61 to 1.99) of headaches were observed in the pizotifen group, compared with the sodium valproate group, at the end of three months. No difference in reducing headache duration was found (RR 1.10; 95% CI -1.94 to 4.14).

In another study<sup>27</sup> (115 participants), a headache unit index (sum of severity and duration of each episode/number of treatment days) was assessed, and no difference was found between the groups after three months (mean of 3.27 versus 2.85 episodes per week). There were also no differences regarding pain intensity (mean 1.80 versus 1.64), severity of disability (mean 1.67 versus 1.58), duration of episodes (mean 1.59 versus 1.35), migraine rescue medication per week (mean 0.82 versus 0.73) or vomiting episodes per week (mean 0.08 versus 0.25).

*- Adverse events*

Regarding safety, 30 participants presented one or more adverse events during the study<sup>28</sup>: 18 in the pizotifen group and 12 in the sodium valproate group. No difference in weight gain was observed (RR 0.33; 95% CI 0.04 to 2.95). Sedation, nausea, and increased appetite were the other adverse events observed after three months of treatment, but no difference was noted between groups.

*Comparison 5: Pizotifen versus clonidine*

*- Frequency, intensity and duration of episodes*

One study<sup>24</sup> (60 participants) assessed this comparison

*- Adverse events*

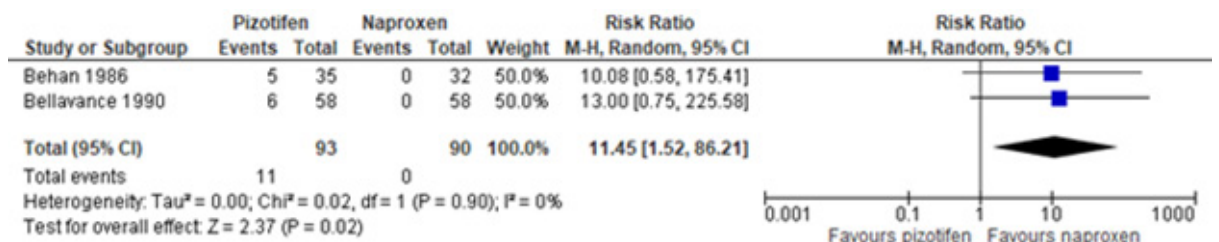


Figure 6. Meta-analysis on pizotifen versus naproxen. Outcome: adverse events (weight gain).





and showed an overall greater improvement through use of pizotifen than clonidine. After two months of treatment, the authors reported that approximately 50% of the participants who received pizotifen (6/14) had no headaches, whereas only one participant who received clonidine was completely headache-free (1/19). There were overall reductions in the pizotifen group regarding frequency, severity and duration of episodes and the number of associated symptoms in most patients (RR 5.88; 95% CI 2.06 to 16.78;  $p = 0.0002$ ).

#### - Adverse events

The participants in the study by Behan et al.<sup>24</sup> presented weight gains. However, no numerical data were provided, and the authors reported that only in one case, was it sufficient to cause the patient's withdrawal from the study. No adverse events were seen in the clonidine group.

### Certainty of the evidence

Based on the GRADE approach, the certainty the evidence regarding pizotifen *versus* placebo was classified as 'very low'. It indicated that we had little confidence in the effect estimate. The evidence was downgraded due to methodological limitations, inconsistency (substantial heterogeneity between studies) and imprecision (wide confidence intervals and small sample size). The findings are summarized in a table of assessment details, which is presented as *Supplementary Material 3*.

## Discussion

Migraine is a burden for patients and society. The socioeconomic costs of migraine are immense<sup>32</sup>, with average direct costs of €2427/patient/year in the USA and Canada<sup>33</sup> and €1222 to €1482/patient/year in Europe.<sup>34,35</sup> These societies will invest in newer drugs and will reimburse the costs of anti-CGRP MABs so that migraineurs will have lower financial burdens and less absenteeism and presenteeism. The same cannot be said for developing countries, where treating migraine at the cost of circa €1600/patient/year is unrealistic. Poorer countries require efficient but inexpensive drugs that provide effective migraine treatments. For this situation, pizotifen may be an alternative. This systematic review has shown that pizotifen is superior to placebo and not inferior to naproxen, flunarizine, valproate or clonidine. The ensuing weight gain is not tolerated by all patients<sup>36</sup>, but it may be acceptable in some cases and situations. An additional benefit of pizotifen is a very safe profile in pregnancy cases (category B in the Food and Drug Administration

- FDA). All other prophylactic migraine treatments are at least category C by the FDA.<sup>37</sup>

The adverse events reported in pizotifen trials are essentially restricted to weight gain. The profile of adverse events of most prophylactic drugs for migraine leads to high rates of discontinuation.<sup>38</sup> Even for erenumab, an anti-CGRP MAB, the discontinuation rate over six months was 27.7% in real life.<sup>39</sup>

Trials on pizotifen were conducted decades ago, with low numbers of participants and unclear risks of bias. The patients with migraine included in most pizotifen studies were not selected to take the International Headache Society criteria into consideration criteria.<sup>40</sup> It is unlikely that an inexpensive drug-like pizotifen will be tested in modern trials. In an ideal scenario, a new trial should compare pizotifen's efficacy and safety compared to another drug.

Despite the limitations mentioned above, we believe that these meta-analyses' results are sufficient for pizotifen to be considered in treatments for migraine for patients who are not preoccupied with weight gain.

## Conclusion

Pizotifen was superior to placebo and not inferior to naproxen, flunarizine, valproate or clonidine, for treating migraine. The adverse events from the use of pizotifen were restricted to weight gain. The clinical trials on pizotifen are now a few decades old, and the body of evidence was classified as 'very low' due to methodological limitations. A new trial in the 21<sup>st</sup> century could render good evidence for this inexpensive drug's safety and efficacy.

**Funding:** none.

**Conflicts of interest/competing interests:** none.

**Authors contribution:** all authors contributed to the study concept and design and participated in searching and selecting articles. ALCM, carried out meta-analyses; YDF, paper draft and final version.

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**Supplementary material 1.** Search strategy for each electronic database (on 20 July 2020 and updated on 18 February 2021).

<p><b>MEDLINE</b> (via Pubmed)</p>	<p>#1 "Migraine Disorders"[Mesh] OR (Disorder, Migraine) OR (Disorders, Migraine) OR (Migraine Disorder) OR Migraine OR Migraines OR (Migraine Headache) OR (Headache, Migraine) OR (Headaches, Migraine) OR (Migraine Headaches) OR (Acute Confusional Migraine) OR (Acute Confusional Migraines) OR (Migraine, Acute Confusional) OR (Migraines, Acute Confusional) OR (Status Migrainosus) OR (Hemicrania Migraine) OR (Hemicrania Migraines) OR (Migraine, Hemicrania) OR (Migraines, Hemicrania) OR (Migraine Variant) OR (Migraine Variants) OR (Variant, Migraine) OR (Variants, Migraine) OR (Sick Headache) OR (Headache, Sick) OR (Headaches, Sick) OR (Sick Headaches) OR (Abdominal Migraine) OR (Abdominal Migraines) OR (Migraine, Abdominal) OR (Migraines, Abdominal) OR (Cervical Migraine Syndrome) OR (Cervical Migraine Syndromes) OR (Migraine Syndrome, Cervical) OR (Migraine Syndromes, Cervical)                  #2 "Migraine with Aura"[Mesh] OR (Migraine with Auras) OR (Familial Hemiplegic Migraine) OR (Familial Hemiplegic Migraines) OR (Hemiplegic-Ophthalmoplegic Migraine) OR (Hemiplegic Migraine, Familial) OR (Migraine with Typical Aura) OR (Classical Migraine) OR (Migraine, Classical) OR (Migraine, Classic) OR (Classic Migraine) OR (Migraine with Acute Onset Aura) OR (Acute Onset Aura Migraine) OR (Migraine with Prolonged Aura) OR (Migraine, Prolonged Aura) OR (Prolonged Aura Migraine) OR (Complicated Migraine) OR (Migraine, Complicated) OR (Basilar-Type Migraine) OR (Basilar Type Migraine) OR (Migraine, Basilar-Type) OR (Basilar Migraine) OR (Basilar Migraines) OR (Migraine, Basilar) OR (Basilar Artery Migraine) OR (Migraine, Basilar Artery) OR (Migraine Aura without Headache) OR (Typical Aura without Headache)                  #3 "Migraine without Aura"[Mesh] OR (Common Migraine) OR (Common Migraines) OR (Migraines, Common) OR (Migraine, Common)                  #4 #1 OR #2 OR #3                  #5 "Pizotyline"[Mesh] OR Pizotifen OR Polomigran OR Sandomigran OR (BC-105) OR (BC 105) OR (BC105)                  #6 #3 AND #4 (236)</p>
<p><b>Embase</b> (via Elsevier)</p>	<p>#1 'migraine'/exp OR 'Disorder, Migraine' OR 'Disorders, Migraine' OR 'Migraine Disorder' OR Migraine OR Migraines OR 'Migraine Headache' OR 'Headache, Migraine' OR 'Headaches, Migraine' OR 'Migraine Headaches' OR 'Acute Confusional Migraine' OR 'Acute Confusional Migraines' OR 'Migraine, Acute Confusional' OR 'Migraines, Acute Confusional' OR 'Status Migrainosus' OR 'Hemicrania Migraine' OR 'Hemicrania Migraines' OR 'Migraine, Hemicrania' OR 'Migraines, Hemicrania' OR 'Migraine Variant' OR 'Migraine Variants' OR 'Variant, Migraine' OR 'Variants, Migraine' OR 'Sick Headache' OR 'Headache, Sick' OR 'Headaches, Sick' OR 'Sick Headaches' OR 'Abdominal Migraine' OR 'Abdominal Migraines' OR 'Migraine, Abdominal' OR 'Migraines, Abdominal' OR 'Cervical Migraine Syndrome' OR 'Cervical Migraine Syndromes' OR 'Migraine Syndrome, Cervical' OR 'Migraine Syndromes, Cervical'                  #2 'migraine with aura'/exp OR 'migraine without aura'/exp                  #3 #1 OR #2                  #4 'pizotifen'/exp OR pizotyline OR polomigran OR sandomigran OR 'bc 105' OR bc105                  #5 #3 AND #4                  #5 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) (469)</p>
<p><b>Cochrane Central Register of Controlled Trials (CENTRAL)</b></p>	<p>#1 MeSH descriptor: [Migraine Disorders] explode all trees                  #2 "Disorder, Migraine" OR "Disorders, Migraine" OR "Migraine Disorder" OR Migraine OR Migraines OR "Migraine Headache" OR "Headache, Migraine" OR "Headaches, Migraine" OR "Migraine Headaches" OR "Acute Confusional Migraine" OR "Acute Confusional Migraines" OR "Migraine, Acute Confusional" OR "Migraines, Acute Confusional" OR "Status Migrainosus" OR "Hemicrania Migraine" OR "Hemicrania Migraines" OR "Migraine, Hemicrania" OR "Migraines, Hemicrania" OR "Migraine Variant" OR "Migraine Variants" OR "Variant, Migraine" OR "Variants, Migraine" OR "Sick Headache" OR "Headache, Sick" OR "Headaches, Sick" OR "Sick Headaches" OR "Abdominal Migraine" OR "Abdominal Migraines" OR "Migraine, Abdominal" OR "Migraines, Abdominal" OR "Cervical Migraine Syndrome" OR "Cervical Migraine Syndromes" OR "Migraine Syndrome, Cervical" OR "Migraine Syndromes, Cervical"                  #3 MeSH descriptor: [Migraine with Aura] explode all trees                  #4 "Migraine with Auras" OR "Familial Hemiplegic Migraine" OR "Familial Hemiplegic Migraines" OR "Hemiplegic-Ophthalmoplegic Migraine" OR "Hemiplegic Migraine, Familial" OR "Migraine with Typical Aura" OR "Classical Migraine" OR "Migraine, Classical" OR "Migraine, Classic" OR "Classic Migraine" OR "Migraine with Acute Onset Aura" OR "Acute Onset Aura Migraine" OR "Migraine with Prolonged Aura" OR "Migraine, Prolonged Aura" OR "Prolonged Aura Migraine" OR "Complicated Migraine" OR "Migraine, Complicated" OR "Basilar-Type Migraine" OR "Basilar Type Migraine" OR "Migraine, Basilar-Type" OR "Basilar Migraine" OR "Basilar Migraines" OR "Migraine, Basilar" OR "Basilar Artery Migraine" OR "Migraine, Basilar Artery" OR "Migraine Aura without Headache" OR "Typical Aura without Headache"                  #5 MeSH descriptor: [Migraine without Aura] explode all trees                  #6 "Common Migraine" OR "Common Migraines" OR "Migraines, Common" OR "Migraine, Common"                  #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6                  #8 MeSH descriptor: [Pizotyline] explode all trees                  #9 Pizotifen OR Polomigran OR Sandomigran OR BC-105 OR "BC 10 5" OR BC105                  #10 #8 OR #9                  #11 #7 AND #10 (in Trials) (78)</p>
<p><b>Literatura Latino-Americana em Ciências da Saúde e do Caribe - LILACS (via Biblioteca Virtual em Saúde - BVS)</b></p>	<p>#1 MH: "Transtornos de Enxaqueca" OR "Migraine Disorders" OR "Transtornos Migrañosos" OR C10.228.140.546.399.750                  #2 MH: Pizotilina OR Pizotyline OR Pizotilina OR D02.886.778.580 OR D03.383.903.580                  #3 #1 AND #2 (4)</p>
<p><b>PsycINFO (APA)</b></p>	<p>Any Field: migraine disorders AND Any Field: Pizotyline (10)</p>
<p><b>ClinicalTrials.gov</b></p>	<p>Pizotifen AND Migraine (0)</p>
<p><b>WHO/ICTPR</b></p>	<p>Pizotifen AND Migraine (0)</p>



**Supplementary material 2.** Judgments and justifications for risk of bias assessments.

Study (author year)	Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome	Selective reporting	Other bias
Behan 1985	UNCLEAR No information on random sequence generation	UNCLEAR No information on allocation concealment	HIGH Quote: "A randomised, single-blind study"	UNCLEAR Blinding of outcome assessors was unconfirmed. Judgement of subjective outcomes is likely to be influenced by the lack of blinding.	HIGH Substantial losses (26.6%), with reasons: no data at all were available for 6 and a further 2 did not return after the admission interview. No ITT analysis.	UNCLEAR Unavailable trial protocol	LOW No other potentially sources of bias.
Behan 1986	UNCLEAR No information on random sequence generation.	UNCLEAR No information on allocation concealment	HIGH Quote: "A randomised, single-blind study"	UNCLEAR Blinding of outcome assessors was unconfirmed. Judgement of subjective outcomes is likely to be influenced by the lack of blinding.	HIGH Substantial losses (44%), with reasons: 16 in the naproxen, 15 pizotifen (due to poor response, adverse event, loss to follow up, remission). No ITT analysis.	UNCLEAR Unavailable trial protocol	LOW No other potentially sources of bias.
Bellavance 1990	UNCLEAR Quote: 'patients were assigned to receive, according to a predetermined randomization code'. Comment: Insufficient information on random sequence generation.	UNCLEAR No information on allocation concealment	UNCLEAR Quote: "The drugs were taken three times daily using a double placebo method." Comment: There was insufficient information on how blinding of participants and personnel was performed.	UNCLEAR Quote: "The drugs were taken three times daily using a double placebo method." Comment: There was insufficient information on how blinding of outcome assessors was performed.	HIGH Substantial losses (16.4%), with reasons: 7 dropped out due to adverse reactions, 4 were lost to follow-up, 4 were noncompliant and 10 dropped out due to reasons unrelated to therapy. No ITT analysis.	UNCLEAR Unavailable trial protocol	LOW No other potentially sources of bias.
Cerbo 1985	UNCLEAR Quote: 'i pazienti sono stati assegnati in maniera randomizzata a due gruppi, per effettuare un trattamento di due mesi'. Comment: Insufficient information on random sequence generation.	UNCLEAR No information on allocation concealment	LOW Quote: 'i farmaci erano stati consegnati in boccette di plastica indentiche, denominate A (pizitifene) e B (flunarizina). All'inizio dello studio né i medici né il paziente sapevano quali farmaci fossero presenti nelle boccette A e B.'. Comment: adequate blinding	LOW Quote: 'La valutazione dell'effetto profilattico è stata effettuata per mezzo di controlli mensili dei pazienti, mettendo in evidenza le variazioni di frequenza, intensità e durata degli attacchi.' Comment: outcome assessment was conducted by the patients, that were blinded by the allocation group.	LOW No substantial losses (10%), with reasons	UNCLEAR Unavailable trial protocol	UNCLEAR The study did not describe the baseline characteristics between groups.
Chitsaz 2012	UNCLEAR No information on random sequence generation.	UNCLEAR No information on allocation concealment	HIGH Quote: 'This was a single blind, randomized, parallel-group study.'	LOW Quote: 'A research assistant who was blind to the type of intervention made all evaluations.'	UNCLEAR It was not clear if there were no losses after randomization.	UNCLEAR Unavailable trial protocol	LOW No other potentially sources of bias.
Lawrence 1977	UNCLEAR No information on random sequence generation.	UNCLEAR No information on allocation concealment	UNCLEAR Blinding of outcome participants and personnel was unconfirmed. Judgement of subjective outcomes is likely to be influenced by the lack of blinding.	HIGH Quote: 'Information about migraine attacks was recorded daily on record cards'. Comment: Outcomes results could be influenced by this fact.	HIGH Substantial losses (22%), with reasons: '5 on active treatment stopped because of failure to improve, symptoms resolved, complained of depression, and felt "muzzy", bad tempered and was excessively hungry. Three patients on placebo stopped treatment because it was ineffective. No ITT analysis.	UNCLEAR Unavailable trial protocol	UNCLEAR The study did not describe the baseline characteristics between groups.



Louis 1982	UNCLEAR No information on random sequence generation.	UNCLEAR No information on allocation concealment	UNCLEAR Blinding of outcome participants and personnel was unconfirmed. Judgement of subjective outcomes is likely to be influenced by the lack of blinding.	UNCLEAR Blinding of outcome assessors was unconfirmed. Judgement of subjective outcomes is likely to be influenced by the lack of blinding.	LOW No substantial losses (8%), with reasons.	UNCLEAR Unavailable trial protocol	LOW No other potentially sources of bias.
Rascoll 1986	LOW Quote: 'According to a computer-made randomization list'. Comment: Insufficient information on random sequence generation.	UNCLEAR No information on allocation concealment	UNCLEAR Blinding of outcome participants and personnel was unconfirmed. Judgement of subjective outcomes is likely to be influenced by the lack of blinding.	UNCLEAR Blinding of outcome assessors was unconfirmed. Judgement of subjective outcomes is likely to be influenced by the lack of blinding.	LOW No substantial losses (8.5%), with reasons.	UNCLEAR Unavailable trial protocol	LOW No other potentially sources of bias.

**Supplementary material 3.** Summary of findings table: pizotifen versus placebo.

Pizotifen compared to placebo for migraine						
Patient or population: migraine						
Setting: outpatient						
Intervention: pizotifen						
Comparison: placebo						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Pizotifen				
<b>Frequency, intensity and duration of migraine episodes</b> assessed with: Headache index follow up: mean 3 months	143 per 1.000	857 per 1.000 (233 to 1.000)	RR 6.00 (1.63 to 22.03)	28 (1 RCT)	⊕○○○ VERY LOW a,b	
<b>Adverse events (weight gain)</b> follow up: mean 3 months	114 per 1.000	219 per 1.000 (34 to 1.000)	RR 1.92 (0.30 to 12.38)	142 (2 RCTs)	⊕○○○ VERY LOW a,b,c	
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio						
GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect						

**Explanations**

- a. We downgraded 2 levels due to methodological limitations (unclear risk for selection and performance bias; and high risk for detection and attrition bias.
- b. We downgraded 2 levels due to a wide CI and small sample size.
- c. We downgraded one level due to substantial heterogeneity (I<sup>2</sup>=67%)