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Tricyclic antidepressants and headaches: systematic review and meta-analysis

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ABSTRACT

Objective To evaluate the efficacy and relative adverse effects of tricyclic antidepressants in the treatment of migraine, tension-type, and mixed headaches.

Design Meta-analysis.

Data sources Medline, Embase, the Cochrane Trials Registry, and PsycLIT.

Studies reviewed Randomised trials of adults receiving tricyclics as only treatment for a minimum of four weeks.

Data extraction Frequency of headaches (number of headache attacks for migraine and number of days with headache for tension-type headaches), intensity of headache, and headache index.

Results 37 studies met the inclusion criteria. Tricyclics significantly reduced the number of days with tension-type headache and number of headache attacks from migraine than placebo (average standardised mean difference −1.29, 95% confidence interval −2.18 to −0.39 and −0.70, −0.93 to −0.48) but not compared with selective serotonin reuptake inhibitors (−0.80, −2.63 to 0.02 and −0.20, −0.60 to 0.19). The effect of tricyclics increased with longer duration of treatment (β=−0.11, 95% confidence interval −0.63 to −0.15; P<0.0005). Tricyclics were also more likely to reduce the intensity of headaches by at least 50% than either placebo (tension-type: relative risk 1.41, 95% confidence interval 1.02 to 1.89; migraine: 1.80, 1.24 to 2.62) or selective serotonin reuptake inhibitors (1.73, 1.34 to 2.22 and 1.72, 1.15 to 2.55). Tricyclics were more likely to cause adverse effects than placebo (1.53, 95% confidence interval 1.11 to 2.12) and selective serotonin reuptake inhibitors (2.22, 1.52 to 3.32), including dry mouth (P<0.0005 for both), drowsiness (P<0.0005 for both), and weight gain (P<0.001 for both), but did not increase dropout rates (placebo: 1.22, 0.83 to 1.80, selective serotonin reuptake inhibitors: 1.16, 0.81 to 2.97).

Conclusions Tricyclic antidepressants are effective in preventing migraine and tension-type headaches and are more effective than selective serotonin reuptake inhibitors, although with greater adverse effects. The effectiveness of tricyclics seems to increase over time.

INTRODUCTION

Headaches are common and cause distress and disability. The prevalence of migraine headaches ranges between 8.4% and 18% worldwide.[1 2] Tension-type headaches are even more common, occurring in 16-30% of people worldwide, with 3% having headaches for more than 180 days a year.[2] Migraine headaches alone cost the United States $1bn (£0.64bn; €0.75bn) in medical costs and $13bn in lost productivity a year.[3]

Tricyclic antidepressants were first shown to be effective in preventing headaches in 1964[4] and have become a standard modality in headache prevention.[5] Based on current standards for preventive treatment in the United States, 43% of males and 34% of females who are candidates for such treatment are not receiving it.[6] This may result from insufficient understanding of the magnitude of beneficial effects, an overestimation of adverse effects, or the presumption that efficacy is only confined to migraine headaches. In a previous meta-analysis of antidepressants for headaches, we found that antidepressants were effective in preventing headaches, equally for tension-type headaches and migraine headaches.[7] This meta-analysis was limited by the relatively small number of available studies at the time. To expand on our previous systematic review we assessed the efficacy and tolerability of tricyclics in reducing the headache burden among adults with migraine or tension-type headache. We also compared tricyclics with other treatment modalities to assess whether the efficacy of tricyclics varies by type of headache, dose, and duration of treatment.

METHODS

This report closely adheres to the PRISMA method for reporting on systematic reviews. We searched, without language restrictions, Medline (1966-March 2010) and Embase (1974-March 2010) using the search strategy (antidepressive agents, tricyclic OR antidepressive$ OR tricyclic$ OR amitriptyline OR amoxapine OR clomipramine OR desipramine OR dibenzepin OR dothiepin OR doxepin OR imipramine OR lofepramine OR nortriptyline OR opipramol OR protriptyline OR trimipramine) AND (headache or headache disorders or headache$ OR migrain$ OR tension$ OR cephalgi$ OR cephalalgi$). We also searched CRISP and FEDRIP databases for unpublished

literature. In addition we searched the Cochrane Pain, Palliative and Supportive Care Trials Register; the Cochrane Central Register of Controlled Trials; PsycLIT (1974-2002); and PsycINFO (1974-March 2010), and carried out a review of the bibliographies of all articles retrieved. The last search date was 25 March 2010. The search was supplemented by searches carried out by medical librarians at our institution as well as the Cochrane clinical research group.

We included published, randomised clinical trials that evaluated the efficacy of tricyclic antidepressants in reducing the frequency or severity of migraine or tension-type headaches. Treatment groups were required to receive a tricyclic regularly at any dosing schedule as a single intervention for at least four weeks. Tricyclics could not be combined with other drugs with possible prophylactic benefit or effect augmentation. Comparison groups could receive placebo or a specified alternative drug or non-drug treatment. Additional inclusion criteria required studies to include only adults (>18 years) with migraine or tension-type headache (frequent episodic or chronic) that could reasonably be defined on the basis of diagnostic criteria described in 1988 by the International Headache Society[8] or earlier.[9 10] We excluded secondary headaches, such as those related to drug overuse, concussion, or lumbar puncture. Because the classification of headache has changed over time, two authors independently reviewed each included article's definition of headache and, where possible, classified it according to the most recent criteria of the International Headache Society.[8]

Study selection and data abstraction
We selected articles for inclusion in two stages. In the first stage two researchers (PGO'M, KJD) independently reviewed titles and abstracts to select full text articles for retrieval. A priori we decided to include all articles recommended by either reviewer for full text retrieval. Agreement was only modest during this stage ($\kappa=0.66$). During the second stage two other researchers (LS, MD) independently applied inclusion and exclusion criteria using standardised forms. Agreement was good ($\kappa=0.86$); during this stage, disagreements were resolved by consensus.

Two authors (WS, JLJ) independently abstracted data using standardised forms. Data abstracted included information about the study (setting, country, language, inclusion and exclusion criteria), information about the intervention (design, characteristics of treatment, such as dose and duration), characteristics of the participants (age, sex, ethnicity, assessment of comorbid psychiatric disease), and treatment related patient reported outcomes for headache (frequency, intensity or severity, duration, global improvement or relief, analgesics used, adverse events). For continuous outcomes we abstracted the number of participants, the mean, and the variance. We calculated missing variances from reported P values.[11] For dichotomous outcomes we abstracted data into 2×2 tables, requiring at least 50% clinical improvement in

headache. Studies reporting less than 50% improvement were not abstracted. We assessed article quality independently and in duplicate (DB, JLJ) using the risk of bias assessment tool developed by the Cochrane collaboration,[12] with good inter-rater agreement (Cochrane: $\kappa=0.83$). Disagreements were resolved by consensus.

Statistical analysis
Because reported measures for headache varied, a priori we preferentially abstracted and pooled data on headache measures in this order: frequency of headache, intensity of headache, and headache index, per the recommendations of the reviewers of our Cochrane protocol. For frequency we used the number of headache attacks for migraines and number of days with headache for tension-type headaches. Intensity was abstracted in the scale used by each study; some studies used visual analogue scales, others used other continuous measures of intensity. Many studies used a "headache index" to sum aspects of the burden of headache, usually derived by multiplying the frequency of the headache by intensity. In addition we pooled analgesic use. Because of differences in measurement of headache burden between studies, we pooled standardised differences between studies, a measure also known as an effect size. By convention, effect sizes greater than 0.8 are considered as large, those between 0.6 and 0.8 as moderate, and those between 0.2 and 0.6 as small.[13]

For studies with more than one arm, we pooled the data for all arms into one group; if this was not possible we reduced the sample size for each arm by 50% to prevent overweighting studies. We pooled data using the DerSimonian and Laird random effects model.[14] Regardless of headache type, we pooled all studies with stratified analysis to provide estimates for each subgroup, and used metaregression to test for differences between these groups. Heterogeneity was assessed visually using Galbraith plots[15] and the I^2 statistic.[16] For continuous data (such as headache frequency and index) we used standardised mean differences (absolute differences divided by the standard deviation). We calculated the percentage maximum dose by dividing the maximum dose in each study by the maximum dose allowed for the study drugs. Quality assessment was done using a component approach. In addition we tested the effect of study sponsorship, use of intention to treat analysis, and whether adherence was assessed. Because of the large number of analyses, we used P=0.01 as our threshold for significance. We assessed for small study effects (publication bias) using the methods of Peters[17] for dichotomous outcomes and Eggers[18] for continuous ones. We estimated the number of unpublished trials using Gleser's method[19] and assessed for the potential effects of bias using both the file drawer test[20] and the trim and fill method.[21] For the file drawer test we tested how many studies would be required to make our results clinically insignificant—that is, an effect size less than 0.30. We explored the potential source of

heterogeneity using stratified analysis and meta regression.[22] All analyses were done using Stata (v 11.2).

RESULTS

Overall, 1471 potential articles were identified. On the initial screen 443 full text articles were retrieved and assessed for eligibility (fig 1). Thirty seven studies met the inclusion criteria[4 23-58]; 13 focused on migraine headaches,[23 24 29 31 32 34 36 40 41 43 50 51 58] 17 on tension-type headaches,[4 25 26 28 33 35 37-39 42 44 45 47 53 55-57] six on chronic mixed headaches (components of migraine and tension-type headaches),[27 30 46 48 49 54] and one on psychogenic headaches.[52] Six studies used the 1988 criteria of the International Headache Society, 11 used the 1962 ad hoc committee criteria, and the remainder used the most recent criteria. All trials of migraine headaches would meet the most recent criteria. Among trials of tension-type headache, one met the criteria for infrequent episodic headaches, six for frequent episodic headaches, and 15 for chronic headache according to the most recent criteria. The six trials with mixed headaches were analysed as migraine headaches as they better met the criteria for migraine headache than for tension-type headache.

Twenty nine of the 37 studies used parallel group designs and eight crossover designs. None of the crossover studies provided sufficient data from which to calculate paired within patient results.[4 25 29 36 43 48 51 58 59] All eight were, however, included as one trial,[25] reported no carry-over effect, and the remainder had either more than four weeks of washout[43 58] or sufficiently long treatment durations to minimise carry-over effects.[36 43 48]

A total of 3176 participants were enrolled across the 37 studies (table 1). Studies lasted an average of 10 weeks (range 4-26 weeks). A mean 70 participants
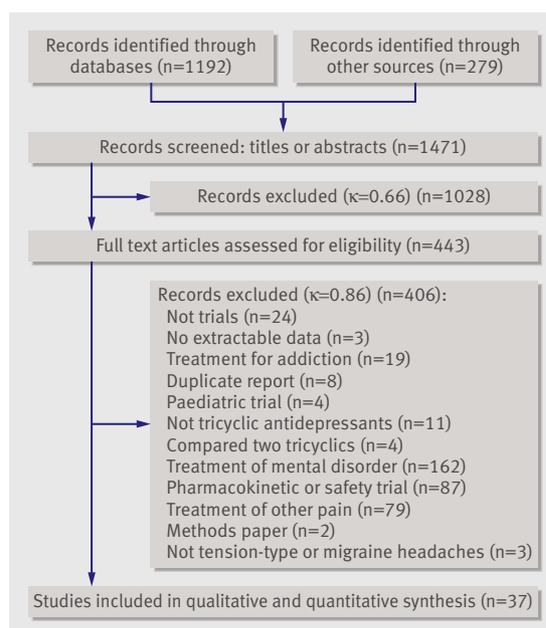
(range 10-554) took part in the studies. Seventy three per cent of participants were women (range 28-98%); all but one study[52] had more women than men. The mean age of participants was 39.6 years. Ten studies were carried out in the United States; five in Italy; four in the United Kingdom; three each in Denmark, Germany, and Turkey; two in Russia; and one each in Australia, Canada, Egypt, Greece, Hungary, Norway, and Spain. All but four studies were in English.[23 30 45 55] Nine trials were sponsored by industry, and in 16 the source of funding was not stated.

Among the 37 studies, 20 compared a tricyclic with placebo. Some studies had more than one comparison group. A few studies compared tricyclics with other modalities, including eight with selective serotonin reuptake inhibitors, three with β blockers, three with heterocyclics, and one each with buspirone,[47] dihydroergotamine,[27] flunarizine,[30] and ritanserin.[49] One study compared amitriptyline with cognitive behavioural therapy[37] and one with stress management,[38] one compared biofeedback with amitriptyline and propranolol,[46] three compared amitriptyline with spinal manipulation,[26 50 56] and one compared amitriptyline and fluvoxamine with transcranial brain electrostimulation.[55]

Measures of headache included frequency of headache (19 studies), headache intensity (n=5), and headache index (n=13). All the studies using headache index used frequency of headache as one component in the index calculation.

Most studies (n=29) titrated the study drugs. The maximum allowable daily dose for amitriptyline (30 studies) ranged from 10 mg[30] to 150 mg,[33 58] whereas the four studies of clomipramine ranged from 30 mg[43] to 150 mg.[42] Other maximum daily doses of tricyclics were opipramol 150 mg,[40] doxepin 100 mg,[48] amitriptylinoxide 90 mg,[48 53] and desipramine 150 mg.[57] Periods of dose titration ranged from none[24 27 30 45 49] to four weeks.[33 37 43 53 57 58] The mean pooled doses were amitriptyline 80.4 mg (95% confidence interval 70.1 to 90.7, range 25-150), amitriptylinoxide 90 mg (one study), clomipramine 116 mg (104 to 128, range 30-150), doxepin 50 mg (n=1), and opipramol 75 mg (n=1).

Seven studies excluded patients with depression.[25 28 29 35 47 53 56] Eleven studies reported the number of patients at trial entry meeting criteria for depression, ranging from 21% to 98%. The remaining studies did not measure or report on depression.

Dropout rates ranged from 0 to 52%. Four studies had less than 10% losses to follow-up,[28 49 53 54] eight between 10% and 20%,[25 26 37-39 41 47 55] nine between 20% and 30%,[23 24 27 30 36 42 44 46 50] eight between 30% and 40%,[29 31-35 48 57] and five more than 40%.[40 43 51 56 58] Losses to follow-up could not be determined in three studies.[4 38 45 52] Intention to treat analyses were done in only seven trials.[26 33 49 50 53 54 56]

Quality ratings
Although quality varied among the studies, most had important limitations with design or reporting (table 2).

Fig 1| Flow of articles through study

Table 1 | Characteristics of included studies

Study (country)	Design, intervention (maximum dose)	Duration of treatment (weeks)	Headache type	No of participants (% women)	Age (range)	Drop outs (%)	Depression
Amelin 2000[23] (Russia)	Parallel 3 arm comparing amitriptyline (25 mg), fluoxetine (20 mg), and maprotiline (25 mg)	12	Migraine	46 (95)	36 (21-57)	23	Hamilton depression rating scale
Bank 1994[24] (Hungary)	Parallel 2 arm comparing amitriptyline (25 mg) with fluvoxamine (50 mg)	12	Migraine	49 (80)	34 (20-62)	23	NS
Bendtsen 1996[25] (Denmark)	Crossover 3 arm comparing amitriptyline (75 mg), citalopram (20 mg), and placebo	8	Tension	34 (65)	40 (18-60)	15	Excluded
Boline 1995[26] (USA)	Parallel 2 arm comparing amitriptyline (30 mg) with spinal manipulation	6	Tension	126 (61)	42 (18-69)	16	NS
Bonuso 1983[27] (Italy)	Parallel 2 arm comparing amitriptyline (75 mg) with dihydroergotamine (10 mg)	8	Mixed*	30 (68)	NS (18-55)	27	NS
Boz 2003[28] (Turkey)	Parallel 2 arm comparing amitriptyline (25 mg) with sertraline (50 mg)	12	Tension	84 (89)	40.4 (19-64)	7	Excluded
Bulut 2004[29] (Turkey)	Crossover 2 arm comparing venlafaxine (150 mg) with amitriptyline (75 mg)	24	Migraine	52 (85)	31.9 (16-50)	32	Excluded
Canepari 1985[30] (Italy)	Parallel 3 arm comparing amitriptyline (10 mg), flunarizine (10 mg), and placebo	12	Mixed*	42 (98)	36 (15-65)	28	NS
Couch 1974[31] (USA)	Parallel 2 arm comparing amitriptyline (100 mg) with placebo	4	Migraine	73 (85)	NS (NS)	36	Hamilton depression rating scale, Zung depression scale
Couch 1976[32] (USA)	Parallel 2 arm comparing amitriptyline (100 mg) with placebo	8	Migraine	100 (84)	NS (NS)	38	Hamilton depression rating scale, Zung depression scale
Diamond 1971[33] (USA)	Parallel 3 arm comparing amitriptyline (60 mg), amitriptyline (150 mg), and placebo	4	Tension	85 (75)	46 (18-68)	32	Measured (unspecified)
Dodick 2009[34] (USA)	Parallel 2 arm comparing topiramate (100 mg) with amitriptyline (100 mg)	26	Migraine	331 (85)	38.8 (18-70)	40	NS
Gobel 1994[35] (Germany)	Parallel 2 arm comparing amitriptyline (75 mg) with placebo	6	Tension	53 (70)	43 (NS)	32	Excluded
Gomersall 1973[36] (UK)	Crossover 2 arm comparing amitriptyline (60 mg) with placebo	26	Migraine	20 (75)	42 (21-70)	23	Patients were asked if they were depressed
Holroyd 1991[37] (USA)	Parallel 2 arm comparing amitriptyline (75 mg) with cognitive behavioural therapy	12	Tension	41 (80)	32.3 (19-55)	12	Beck depression inventory
Holroyd 2001[38] (USA)	Parallel 4 arm comparing amitriptyline (100 mg) or nortriptyline (100 mg), stress management therapy, amitriptyline or nortriptyline plus stress management therapy, and placebo	24	Tension	203 (76)	37 (NS)	12	NS
Indaco 1988[39] (Italy)	Parallel 2 arm comparing amitriptyline (50 mg) with placebo	12	Tension	31 (52)	60.4 (41-70)	14	Zung depression scale
Jacobs 1972[40] (UK)	Parallel 2 arm comparing opipramol (150 mg) with placebo	12	Migraine	27 (78)	42 (23-67)	43	NS
Keskinbora 2008[41] (Turkey)	Parallel 3 arm comparing amitriptyline (150 mg), topiramate (200 mg), and combination of these two drugs	12	Migraine	63 (67)	37 (NS)	16	Beck depression inventory
Lance 1964[4] (Australia)	Crossover 2 arm comparing amitriptyline (75 mg) with placebo	4	Tension	27 (63)	NS (NS)	NS	NS
Langemark 1990[42] (Denmark)	Parallel 3 arm comparing clomipramine (150 mg), mianserin (60 mg), and placebo	6	Tension	82 (NS)	41 (18-69)	28	NS
Langohr 1985[43] (Germany)	Crossover 5 arm comparing all crossover combinations of clomipramine (100 mg), metoprolol (100 mg), and placebo	4	Migraine	36 (67)	44 (24-60)	43	NS
Loldrup 1989[44] (Denmark)	Parallel 3 arm comparing clomipramine (150 mg), mianserin (60 mg), and placebo	6	Tension	114 (64)	41 (17-69)	20	Measured (unspecified)
Martin-Araguz 2003[45] (Spain)	Parallel 2 arm comparing amitriptyline (25 mg) with mirtazapine (30 mg)	24	Tension	60 (70)	38 (NS)	NS	Hamilton depression rating scale
Mathew 1981[46] (USA)	Parallel 8 arm comparing multi-intervention: amitriptyline (75 mg), propranolol (160 mg), biofeedback, placebo, amitriptyline+propranolol, amitriptyline+biofeedback, propranolol+biofeedback, and amitriptyline+propranolol+biofeedback	24	Migraine and mixed	554 (95)	38 (19-57)	22	Zung depression scale
Mitsikostas 1997[47] (Greece)	Parallel 2 arm comparing amitriptyline (50 mg) with buspirone (30 mg)	12	Tension	49 (62)	43 (NS)	16	Hamilton depression rating scale
Morland 1979[48] (Norway)	Crossover 2 arm comparing doxepin (100 mg) with placebo	9	Mixed and tension	14 (86)	NS (20-50)	39	NS
Nappi 1990[49] (Italy)	Parallel 2 arm comparing amitriptyline (50 mg) with ritanserin (10 mg)	12	Migraine and tension	38 (79)	38 (20-50)	0	Hamilton depression rating scale
Nelson 1998[50] (USA)	Parallel 3 arm comparing amitriptyline (100 mg), spinal manipulation, and amitriptyline+spinal manipulation	8	Migraine	218 (79)	38 (NS)	23	NS
Noone 1980[51] (UK)	Crossover 2 arm comparing clomipramine (30 mg) with placebo	8	Migraine	10 (70)	NS (18-65)	52	Beck depression inventory
Okasha 1973[52] (Egypt)	Parallel 4 arm comparing amitriptyline (30 mg), doxepin (30 mg), diazepam (6 mg), and placebo	8	Psychogenic	80 (28)	NS (16-60)	NS	Hamilton depression rating scale
Pfaffenrath 1994[53] (Germany)	Parallel 3 arm comparing amitriptyline (75 mg), amitriptylinoxide (90 mg), and placebo	12	Tension	197 (56)	38 (18-68)	4.1	Excluded
Rampello 2004[54] (Italy)	Parallel 2 arm comparing amitriptyline (50 mg) with citalopram (20 mg)	16	Mixed*	88 (63)	39 (22-64)	0	Hamilton depression rating scale
Tarosova 2008[55] (Russia)	Parallel 3 arm comparing amitriptyline (100 mg), fluvoxamine (100 mg), and transcranial brain electrostimulation	4	Tension	44 (90)	44 (34-60)	18	Beck depression inventory
Vernon 2009[56] (Canada)	Parallel 4 arm comparing amitriptyline (25 mg), spinal manipulation, sham spinal manipulation, and amitriptyline+spinal manipulation	14	Tension	20 (80)	34.1 (18-48)	50	Excluded
Walker 1998[57] (UK)	Parallel 2 arm comparing desipramine (150 mg) with fluoxetine (40 mg)	12	Tension	25 (81)	35 (19-59)	32	Hamilton depression rating scale
Ziegler 1987[58] (USA)	Crossover 3 arm comparing amitriptyline (150 mg), propranolol (240 mg), and placebo	4	Migraine	30 (73)	38 (22-57)	44	Hamilton depression rating scale, Zung depression scale

NS=not stated.

*Analysed as migraine headache.

Few studies reported the method of randomisation or allocation concealment. Although trials were often reported as double blind, blinding success was reported in only one trial[57] and was often questionable, as treatment groups differed significantly in clinically recognisable adverse effects.

Headache outcomes
Tricyclics versus placebo
At baseline, participants with migraine averaged 4.7 headaches per month (95% confidence interval 4.3 to 5.1) and those with tension-type headaches 16.9 (15.8 to 18.0), with no difference between tricyclic and placebo groups (P=0.46). Tricyclics were more effective

than placebo in reducing the burden from both tension-type headaches (average standardised mean difference −0.99, 95% confidence interval −1.66 to −0.32; 11 arms, I^2=93.8%) and migraine headaches (−1.00, −1.52 to −0.48; 10 arms, I^2=89.4%, fig 2). Tricyclics were equally efficacious between the two headache types. The studies combined yielded an overall average standardised mean difference for tricyclics of −0.96 (95% confidence interval −1.39 to −0.53, I^2=90.1%). Therefore, regardless of the scale used to measure headaches, patients treated with a tricyclic experienced nearly 1 standard deviation of improvement, a clinically large effect. Efficacy did not differ among the different categories of tension-type

Table 2 | Quality of included studies

Study	Drop outs (%)	Adherence measured	Adequate sequence generation	Allocation concealment	Blinding	Incomplete data addressed	Free of selective reporting	Free of other bias	Industry sponsored
Amelin[23]	23	No	No	Unclear	No	No	Unclear	Yes	No
Bank[24]	23	No	Unclear	Unclear	Unclear	No	Unclear	Yes	NS
Bendtsen[25]	15	Yes	Unclear	Unclear	Yes	No	Unclear	Yes	No
Boline[26]	16	Yes	Yes	Yes	No	No	Unclear	No	No
Bonuso[27]	27	No	Unclear	Unclear	No	No	No	Yes	NS
Boz[28]	7	Yes	Unclear	Unclear	No	Yes	Unclear	Yes	No
Bulut[29]	32	No	Unclear	Unclear	Yes	No	Unclear	Yes	Yes
Canepari[30]	28	Yes	No	Unclear	Yes	No	Unclear	Yes	NS
Couch[31]	36	No	Unclear	Unclear	Yes	No	Unclear	Yes	NS
Diamond[33]	6	No	Unclear	Unclear	Yes	Yes	Unclear	Yes	NS
Dodick[34]	43	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gobel[35]	32	No	Unclear	Unclear	Yes	No	Unclear	Yes	NS
Gomersall[36]	23	No	Unclear	Unclear	Unclear	No	No	Yes	Yes
Holroyd 1991[37]	12	No	Unclear	Unclear	No	No	Unclear	Yes	NS
Holroyd 2001[38]	12	Yes	Yes	Unclear	No	Yes	Yes	Yes	No
Indaco[39]	14	Yes	Unclear	Unclear	Yes	No	Unclear	Yes	NS
Jacobs[40]	43	No	Unclear	Yes	Yes	No	No	Yes	Yes
Keskinbora[41]	16	Yes	Unclear	Yes	Yes	No	Yes	Yes	NS
Lance[4]	0	No	No	Unclear	Yes	Yes	Unclear	Yes	Yes
Langemark[42]	28	No	Unclear	Unclear	Yes	No	No	Yes	Yes
Langohr[43]	43	No	Unclear	Unclear	Unclear	No	No	Yes	Yes
Loldrup[44]	20	Yes	Unclear	Unclear	No	No	No	Yes	Yes
Martin-Araguz[45]	0	No	Unclear	Unclear	Unclear	No	Yes	Yes	NS
Mathew[46]	22	No	Unclear	Unclear	No	No	No	Yes	NS
Mitsikostas[47]	16	No	Unclear	No	No	No	No	Yes	NS
Morland[48]	39	No	Unclear	Unclear	Unclear	No	Unclear	Yes	NS
Nappi[49]	0	No	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes
Nelson[50]	23	No	Yes	Yes	No	No	Unclear	Yes	No
Noone[51]	52	No	Yes	Yes	Unclear	No	Unclear	Yes	NS
Okasha[52]	0	No	Yes	Unclear	Yes	Unclear	Unclear	Yes	NS
Pfaffenrath[53]	4.1	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	NS
Rampello[54]	0	No	Unclear	Unclear	No	Yes	Unclear	Yes	NS
Tarosova[55]	50	Yes	No	Unclear	Yes	No	Unclear	Yes	NS
Vernon[56]	50	No	Unclear	Unclear	Yes	No	Unclear	Yes	No
Walker[57]	32	No	Unclear	Unclear	No	No	Unclear	Yes	Yes
Ziegler[58]	44	Yes	Unclear	Unclear	Unclear	No	Unclear	Yes	No

NS=not stated.

headache (infrequent episodic *v* frequent episodic *v* chronic tension-type, P=0.39).

The number of headaches per month among studies reporting it were reduced on average by 6.9 for tension-type headaches (95% confidence interval −21.6 to 7.7, three studies) and 1.4 for migraine headaches (−3.3 to 0.5, four studies). For both headache types this beneficial effect increased over time (tension-type: β=−0.16, 95% confidence interval −0.23 to −0.10, P<0.0005, migraine: β=−0.09, −0.14 to −0.04, P=0.001, fig 3). Therefore for every additional week of treatment with a tricyclic, the number of headaches were reduced by 0.16 standard deviations. Among these trials, a range of tricyclic doses was used, with an average dose that was 50% of the maximum for the particular tricyclic studied. The effect of doses less than 50% of the maximum dose was lower than those with higher doses (average standardised mean difference −0.73, 95% confidence interval −1.14 to −0.32 *v* −0.92, −1.50 to −0.34), although the difference was not significant (P=0.34).

Patients taking tricyclics were more likely to experience at least 50% improvement in their headaches than those taking placebo for both tension-type headaches (relative risk 1.41, 95% confidence interval 1.02 to 1.89, four studies, I²=48.8%) and migraine headaches (1.80, 1.24 to 2.62, four studies, I²=0.0%, fig 4). Therefore, patients treated with tricyclics had a 40% and 80% increase in the probability of having 50% improvement in tension-type and migraine headaches,

respectively. Overall, tricyclics improved the likelihood of achieving 50% improvement in headaches (1.53, 1.16 to 2.01, eight studies, I²=26.1%).

Tricyclics also reduced the number of doses of analgesics taken for acute headache pain for both tension-type headaches (average standardised mean difference −1.71, 95% confidence interval −3.37 to −0.05, six studies, I²=14.5%) and migraine headaches (−0.94, −1.87 to −0.02, four studies, I²=32.6%).

Individual adverse effects of tricyclics compared with placebo were variably reported among the studies. In seven comparison arms, patients taking tricyclics were more likely to report "any" side effect than those taking placebo (relative risk 1.89, 95% confidence interval 1.18 to 3.02, I²=85.9%, fig 5). Among 10 individual adverse effects, only dry mouth (2.34, 1.63 to 3.35, I²=43.3%) and drowsiness (1.87, 1.25 to 2.70, I²=55.1%) were statistically more frequent in patients receiving tricyclics than in those receiving placebo (table 3). The likelihood of withdrawing due to adverse effects, however, did not differ among 16 placebo controlled trials (1.21, 0.80 to 1.82, I²=74.1%, fig 5).

Tricyclics versus selective serotonin reuptake inhibitors
In a limited number of trials the effectiveness between tricyclics and selective serotonin reuptake inhibitors did not differ for tension-type headaches (average standardised mean difference −0.80, 95% confidence interval −1.63 to 0.02, four studies, I²=89.5%, fig 6) or

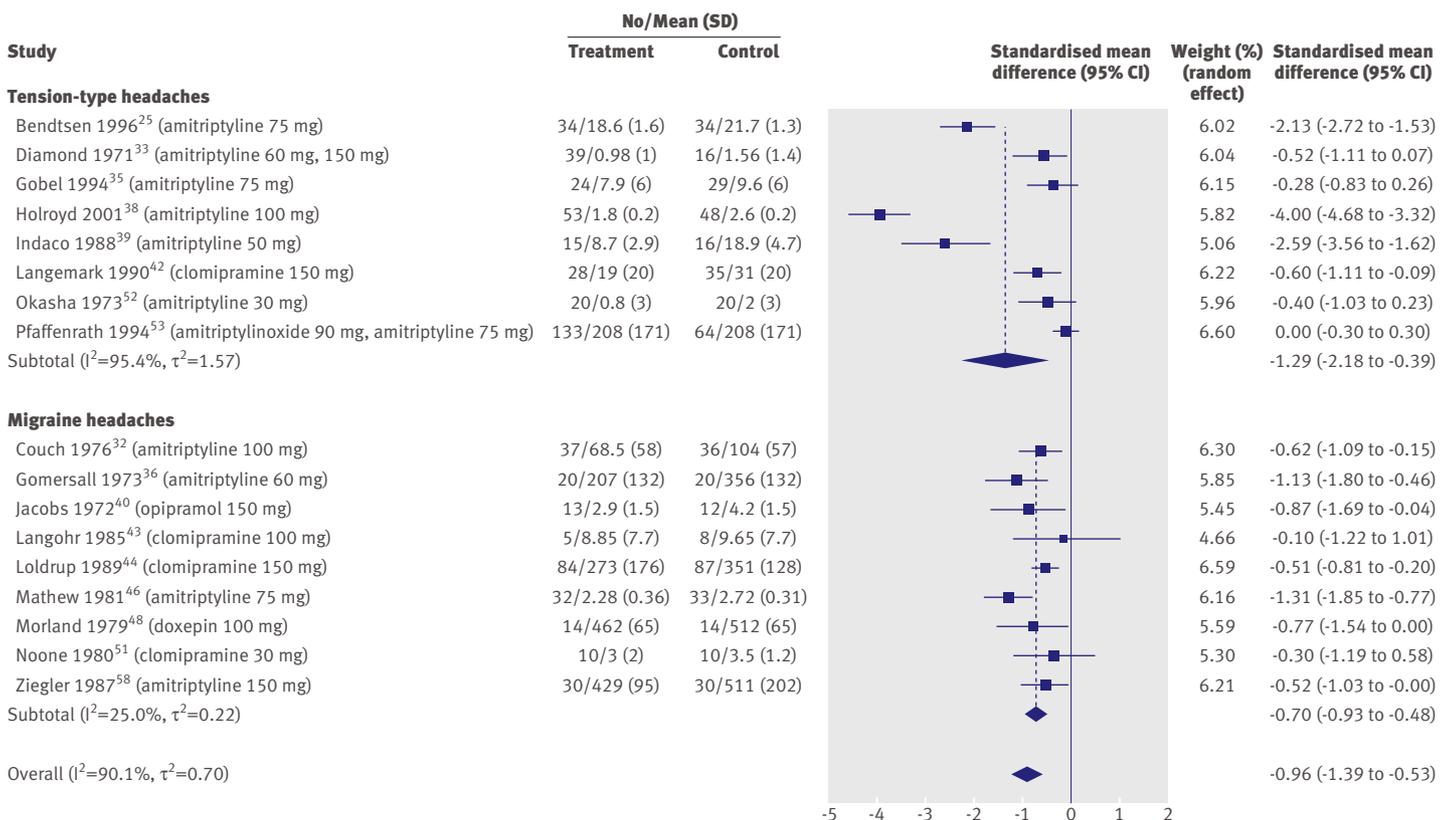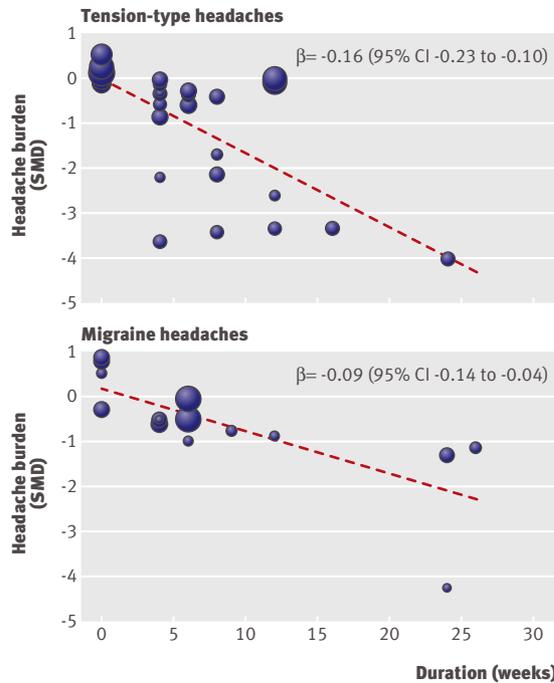| Study	No/Mean (SD)		Standardised mean difference (95% CI)	Weight (%) (random effect)	Standardised mean difference (95% CI)
	Treatment	Control			
Tension-type headaches					
Bendtsen 1996[25] (amitriptyline 75 mg)	34/18.6 (1.6)	34/21.7 (1.3)		6.02	-2.13 (-2.72 to -1.53)
Diamond 1971[33] (amitriptyline 60 mg, 150 mg)	39/0.98 (1)	16/1.56 (1.4)		6.04	-0.52 (-1.11 to 0.07)
Gobel 1994[35] (amitriptyline 75 mg)	24/7.9 (6)	29/9.6 (6)		6.15	-0.28 (-0.83 to 0.26)
Holroyd 2001[38] (amitriptyline 100 mg)	53/1.8 (0.2)	48/2.6 (0.2)		5.82	-4.00 (-4.68 to -3.32)
Indaco 1988[39] (amitriptyline 50 mg)	15/8.7 (2.9)	16/18.9 (4.7)		5.06	-2.59 (-3.56 to -1.62)
Langemark 1990[42] (clomipramine 150 mg)	28/19 (20)	35/31 (20)		6.22	-0.60 (-1.11 to -0.09)
Okasha 1973[52] (amitriptyline 30 mg)	20/0.8 (3)	20/2 (3)		5.96	-0.40 (-1.03 to 0.23)
Pfaffenrath 1994[53] (amitriptylinoxide 90 mg, amitriptyline 75 mg)	133/208 (171)	64/208 (171)		6.60	0.00 (-0.30 to 0.30)
Subtotal (I²=95.4%, τ²=1.57)					-1.29 (-2.18 to -0.39)
Migraine headaches					
Couch 1976[32] (amitriptyline 100 mg)	37/68.5 (58)	36/104 (57)		6.30	-0.62 (-1.09 to -0.15)
Gomersall 1973[36] (amitriptyline 60 mg)	20/207 (132)	20/356 (132)		5.85	-1.13 (-1.80 to -0.46)
Jacobs 1972[40] (opipramol 150 mg)	13/2.9 (1.5)	12/4.2 (1.5)		5.45	-0.87 (-1.69 to -0.04)
Langohr 1985[43] (clomipramine 100 mg)	5/8.85 (7.7)	8/9.65 (7.7)		4.66	-0.10 (-1.22 to 1.01)
Loldrup 1989[44] (clomipramine 150 mg)	84/273 (176)	87/351 (128)		6.59	-0.51 (-0.81 to -0.20)
Mathew 1981[46] (amitriptyline 75 mg)	32/2.28 (0.36)	33/2.72 (0.31)		6.16	-1.31 (-1.85 to -0.77)
Morland 1979[48] (doxepin 100 mg)	14/462 (65)	14/512 (65)		5.59	-0.77 (-1.54 to 0.00)
Noone 1980[51] (clomipramine 30 mg)	10/3 (2)	10/3.5 (1.2)		5.30	-0.30 (-1.19 to 0.58)
Ziegler 1987[58] (amitriptyline 150 mg)	30/429 (95)	30/511 (202)		6.21	-0.52 (-1.03 to -0.00)
Subtotal (I²=25.0%, τ²=0.22)					-0.70 (-0.93 to -0.48)
Overall (I²=90.1%, τ²=0.70)					-0.96 (-1.39 to -0.53)

-5 -4 -3 -2 -1 0 1 2

Fig 2 | Effect of tricyclic antidepressants on burden of headache for tension-type and migraine headaches compared with placebo. Trials of mixed and migraine headaches are combined

Fig 3 | Effect of tricyclic antidepressants compared with placebo over time. SMD=standardised mean difference

migraine headaches (−0.22, −0.75 to 0.31, four studies, I^2=89.5%). Seven of these trials used amitriptyline and one used desipramine. The doses used were relatively low: the maximum dose of amitriptyline averaged 50 mg, ranging from 25 mg to 75 mg; the dose of desipramine was 150 mg. Despite low doses, tricyclics were more likely than selective serotonin reuptake inhibitors to produce at least 50% improvement in tension-type headaches (relative risk 1.73, 95% confidence interval 1.34 to 2.22, I^2=0.0%, three studies, fig 7), and migraine headaches (1.72, 1.15 to 2.55, I^2=9.2%, three studies). Tricyclic arms had higher
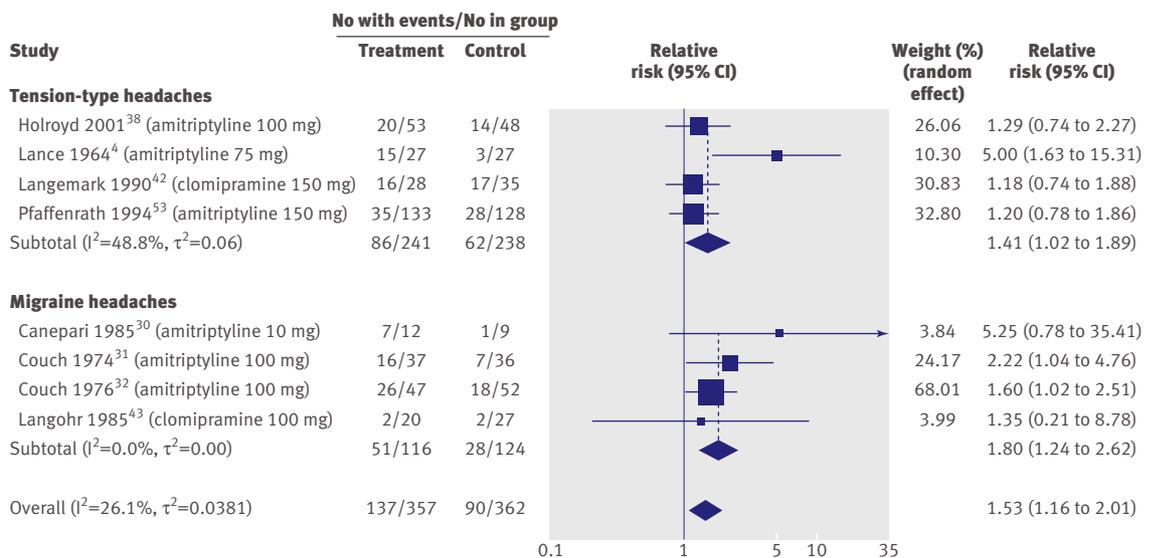
rates of several adverse effects such as drowsiness and dry mouth (table 3), although they did not have higher withdrawal rates for tension-type headaches (1.05, 0.92 to 1.19, two studies, I^2=0.0%) or migraine headaches (2.0, 0.90 to 4.47, three studies, I^2=0.0%).

Among three trials, tricyclic arms were more likely to have "any" side effect than the selective serotonin reuptake inhibitor arms (2.25, 1.52 to 3.32, I^2=0.0%).[25 28 57] Specific side effects more common among tricyclics included abdominal distress (2.34, 1.31 to 4.95, four studies, I^2=6.6%), dizziness (2.52, 0.77 to 8.23, five studies, I^2=63.0%), and dry mouth (4.88, 2.26 to 10.52, five studies, I^2=67.8%), although the risk of withdrawing from the study did not differ (1.16, 0.81 to 2.97, five studies, I^2=19.0%).

Tricyclics versus other drugs
Few studies compared tricyclics with other modalities. No studies compared β blockers and tricyclics for tension-type headaches; among three studies of migraine headaches, tricyclics and β blockers did not differ in reduction of number of headaches or attacks (average standardised mean difference 0.90, 95% confidence interval −0.38 to 2.18, I^2=93.8%) and in two studies did not differ in the likelihood of experiencing at least 50% reduction in the number of headaches (relative risk 0.78, 95% confidence interval 0.42 to 1.44, I^2=0.0%). Three of the studies used amitriptyline and one used clomipramine; the average dose for both was 100 mg.

Two studies of tension-type headaches compared tricyclics with buspirone (amitriptyline 50 mg) and found no differences (buspirone: average standardised mean difference −1.01, 95% confidence interval −1.83 to −0.18, I^2=0.00%, table 4). Two studies compared tricyclics (amitriptyline 25 mg, clomipramine 150 mg) with tetracyclics and found no difference (average standardised mean difference −0.21, −0.65 to 0.22,

Study	No with events/No in group		Relative risk (95% CI)	Weight (%) (random effect)	Relative risk (95% CI)
	Treatment	Control			
Tension-type headaches					
Holroyd 2001[38] (amitriptyline 100 mg)	20/53	14/48		26.06	1.29 (0.74 to 2.27)
Lance 1964[4] (amitriptyline 75 mg)	15/27	3/27		10.30	5.00 (1.63 to 15.31)
Langemark 1990[42] (clomipramine 150 mg)	16/28	17/35		30.83	1.18 (0.74 to 1.88)
Pfaffenrath 1994[53] (amitriptyline 150 mg)	35/133	28/128		32.80	1.20 (0.78 to 1.86)
Subtotal (I^2=48.8%, τ^2=0.06)	86/241	62/238			1.41 (1.02 to 1.89)
Migraine headaches					
Canepari 1985[30] (amitriptyline 10 mg)	7/12	1/9		3.84	5.25 (0.78 to 35.41)
Couch 1974[31] (amitriptyline 100 mg)	16/37	7/36		24.17	2.22 (1.04 to 4.76)
Couch 1976[32] (amitriptyline 100 mg)	26/47	18/52		68.01	1.60 (1.02 to 2.51)
Langohr 1985[43] (clomipramine 100 mg)	2/20	2/27		3.99	1.35 (0.21 to 8.78)
Subtotal (I^2=0.0%, τ^2=0.00)	51/116	28/124			1.80 (1.24 to 2.62)
Overall (I^2=26.1%, τ^2=0.0381)	137/357	90/362			1.53 (1.16 to 2.01)

Fig 4 | Likelihood of experiencing at least 50% reduction in tension-type and migraine headaches compared with placebo. Trials of mixed and migraine headaches are combined
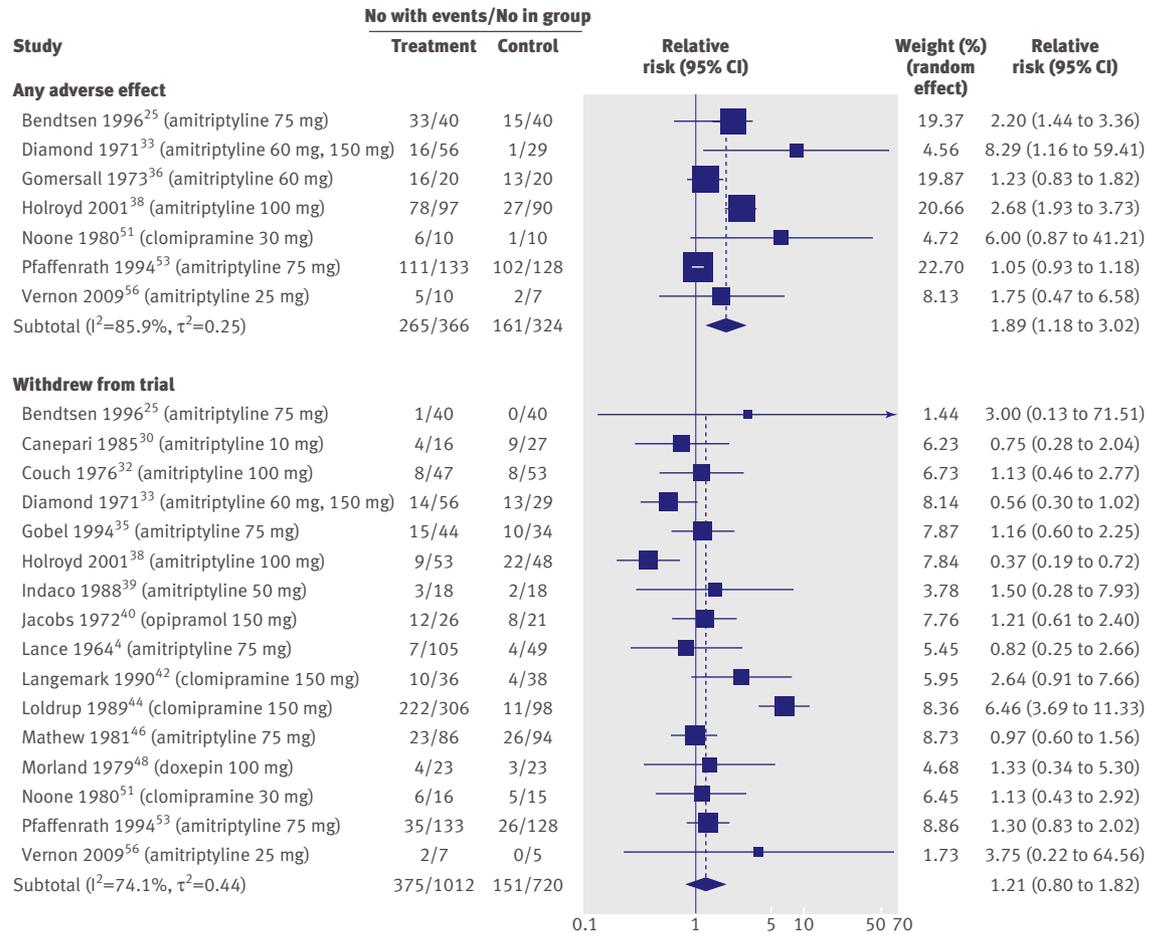
	No with events/No in group				
Study	Treatment	Control	Relative risk (95% CI)	Weight (%) (random effect)	Relative risk (95% CI)
Any adverse effect					
Bendtsen 1996[25] (amitriptyline 75 mg)	33/40	15/40		19.37	2.20 (1.44 to 3.36)
Diamond 1971[33] (amitriptyline 60 mg, 150 mg)	16/56	1/29		4.56	8.29 (1.16 to 59.41)
Gomersall 1973[36] (amitriptyline 60 mg)	16/20	13/20		19.87	1.23 (0.83 to 1.82)
Holroyd 2001[38] (amitriptyline 100 mg)	78/97	27/90		20.66	2.68 (1.93 to 3.73)
Noone 1980[51] (clomipramine 30 mg)	6/10	1/10		4.72	6.00 (0.87 to 41.21)
Pfaffenrath 1994[53] (amitriptyline 75 mg)	111/133	102/128		22.70	1.05 (0.93 to 1.18)
Vernon 2009[56] (amitriptyline 25 mg)	5/10	2/7		8.13	1.75 (0.47 to 6.58)
Subtotal (I^2=85.9%, τ^2=0.25)	265/366	161/324			1.89 (1.18 to 3.02)
Withdrew from trial					
Bendtsen 1996[25] (amitriptyline 75 mg)	1/40	0/40		1.44	3.00 (0.13 to 71.51)
Canepari 1985[30] (amitriptyline 10 mg)	4/16	9/27		6.23	0.75 (0.28 to 2.04)
Couch 1976[32] (amitriptyline 100 mg)	8/47	8/53		6.73	1.13 (0.46 to 2.77)
Diamond 1971[33] (amitriptyline 60 mg, 150 mg)	14/56	13/29		8.14	0.56 (0.30 to 1.02)
Gobel 1994[35] (amitriptyline 75 mg)	15/44	10/34		7.87	1.16 (0.60 to 2.25)
Holroyd 2001[38] (amitriptyline 100 mg)	9/53	22/48		7.84	0.37 (0.19 to 0.72)
Indaco 1988[39] (amitriptyline 50 mg)	3/18	2/18		3.78	1.50 (0.28 to 7.93)
Jacobs 1972[40] (opipramol 150 mg)	12/26	8/21		7.76	1.21 (0.61 to 2.40)
Lance 1964[4] (amitriptyline 75 mg)	7/105	4/49		5.45	0.82 (0.25 to 2.66)
Langemark 1990[42] (clomipramine 150 mg)	10/36	4/38		5.95	2.64 (0.91 to 7.66)
Loldrup 1989[44] (clomipramine 150 mg)	222/306	11/98		8.36	6.46 (3.69 to 11.33)
Mathew 1981[46] (amitriptyline 75 mg)	23/86	26/94		8.73	0.97 (0.60 to 1.56)
Morland 1979[48] (doxepin 100 mg)	4/23	3/23		4.68	1.33 (0.34 to 5.30)
Noone 1980[51] (clomipramine 30 mg)	6/16	5/15		6.45	1.13 (0.43 to 2.92)
Pfaffenrath 1994[53] (amitriptyline 75 mg)	35/133	26/128		8.86	1.30 (0.83 to 2.02)
Vernon 2009[56] (amitriptyline 25 mg)	2/7	0/5		1.73	3.75 (0.22 to 64.56)
Subtotal (I^2=74.1%, τ^2=0.44)	375/1012	151/720			1.21 (0.80 to 1.82)

0.1 1 5 10 50 70

Fig 5| Likelihood of adverse effects between tricyclic antidepressants and placebo

I^2=32.8%). A single study of tension-type headache found no difference between low dose amitriptyline (25 mg) and the serotonin antagonist ritanserin (−0.49, −1.70 to 0.71). One study found that amitriptyline (75 mg) was better than timed release dihydroergotamine for migraines (−6.57, −8.44 to −4.71). In addition, two trials compared amitriptyline (maximum doses 100 mg and 150 mg) with the anticonvulsant topiramate (0.05, −0.32 to 0.33, I^2=29.2%, table 4) and one (amitriptyline 75 mg) with the calcium channel blocker flunarazine (relative risk 1.60, 95% confidence interval 0.83 to 3.10, table 5) in migraine headaches, and found no differences.

Tricyclics versus non-drug treatments
No differences were found between spinal manipulation and tricyclics in two studies of tension-type headaches (average standardised mean difference −0.25, 95% confidence interval −0.59 to 0.09, I^2=0.0%, table 4) and one study of migraine headaches (−0.31, −0.69 to

Table 3| Relative risk of adverse effects among tricyclic antidepressants compared with placebo or selective serotonin reuptake inhibitors

Adverse effect	Placebo	No of studies	Heterogeneity (I^2) %	Selective serotonin reuptake inhibitors	No of studies	Heterogeneity (I^2) %
Anxiety or irritability	0.44 (0.15 to 1.31)	2	0.0	0.67 (0.23 to 1.91)	2	0.0
Blurred vision	1.05 (0.56 to 1.97)	4	0.0	NR		
Constipation or abdominal pain	1.07 (0.61 to 1.86)	7	6.4	2.34 (1.31 to 4.95)	4	6.6
Diaphoresis	1.09 (0.38 to 3.08)	3	73.0	NR	NR	NR
Dizziness	1.20 (0.77 to 1.86)	7	0.0	2.52 (0.77 to 8.23)	5	63.0
Drowsiness	1.87 (1.25 to 2.70)	10	55.1	2.64 (1.84 to 3.78)	6	17.0
Dry mouth	2.34 (1.63 to 3.35)	10	43.3	4.88 (2.26 to 10.52)	5	67.8
Nausea or vomiting	1.18 (0.42 to 3.31)	4	22.8	0.62 (0.26 to 1.48)	4	57.8
Sleep disturbance	0.64 (0.37 to 1.09)	5	0.0	0.52 (0.17 to 1.58)	3	0.0
Weight gain	1.69 (0.74 to 3.88)	6	49.2	7.45 (0.99 to 56.37)	4	72.0

NR=not reported.

Study	No/Mean (SD)		Standardised mean difference (95% CI)	Weight (%) (random effect)	Standardised mean difference (95% CI)
	Tricyclics	SSRI			
Tension-type headaches					
Bendtsen 1996[25] (amitriptyline 75 mg, citalopram 20 mg)	34/18.6 (1.6)	34/21.5 (1.4)		24.85	-1.93 (-2.51 to -1.35)
Boz 2003[28] (amitriptyline 25 mg, sertraline 50 mg)	43/13 (5.5)	41/13.8 (4.2)		26.30	-0.16 (-0.59 to 0.27)
Rampello 2004[54] (amitriptyline 50 mg, citalopram 20 mg)	44/5.6 (3.25)	44/10.1 (5)		26.13	-1.07 (-1.52 to -0.62)
Walker 1998[57] (desipramine 150 mg, fluoxetine 40 mg)	13/4.2 (2.9)	13/4.2 (2.9)		22.71	0.00 (-0.77 to 0.77)
Subtotal (I^2=89.5%, τ^2=0.056)					-0.80 (-1.63 to 0.02)
Migraine headaches					
Amelin 2000[23] (amitriptyline 25 mg, fluoxetine 20 mg)	14/1.4 (1)	16/1.6 (1.8)		20.74	-0.13 (-0.85 to 0.58)
Bank 1994[24] (amitriptyline 25 mg, fluvoxamine 50 mg)	20/0.09 (0.06)	24/0.07 (0.05)		23.48	0.37 (-0.23 to 0.96)
Bulut 2004[29] (amitriptyline 75 mg, venlaxafine 150 mg)	52/1.38 (0.98)	52/1.52 (1.15)		28.51	-0.13 (-0.51 to 0.26)
Rampello 2004[54] (amitriptyline 50 mg, citalopram 20 mg)	44/2.32 (0.86)	44/3.41 (1.5)		27.27	-0.89 (-1.33 to -0.45)
Subtotal (I^2=89.5%, τ^2=0.412)					-0.22 (-0.75 to 0.31)
Overall (I^2=85.85%, τ^2=0.4069)					-0.51 (-0.99 to -0.02)

Scale: -3, -2, -1, 0, 1

Fig 6 | Comparison of effectiveness of tricyclic antidepressants with selective serotonin reuptake inhibitors for tension-type and migraine headaches. Trials of mixed and migraine headaches are combined. SSRI=selective serotonin reuptake inhibitor

0.08). All three studies used amitriptyline, with maximum doses of 25 mg, 30 mg, and 100 mg. Tricyclics were compared with cognitive behavioural therapy in one study of tension-type headaches and in two studies of migraine headaches, with no differences (tables 4 and 5). All three used amitriptyline at a dose of 75 mg.

Assessment of bias and sensitivity analyses

The Cochrane criteria seemed to show considerable risk of bias (table 2). On analysis of the components, we found no difference in effects between studies meeting or not meeting any Cochrane criteria for bias. We also found no effect of industry sponsorship or assessment of adherence on outcomes. We found evidence of publication bias for continuous outcomes (P=0.06) and dichotomous outcomes (P=0.04). Estimates based on Gleser's method suggested that up to 10 unpublished trials reporting continuous outcomes and four unpublished

trials reporting dichotomous outcomes could exist. Rosenthal's fail safe suggests that 1467 unpublished trials with continuous outcomes and 691 unpublished trials with dichotomous outcomes with no effect would be required to reduce our effect to clinical insignificance (effect size <0.3). The meta-trim test did not affect the continuous outcome summary effect, but reduced the dichotomous outcome from a relative risk of 1.53 (95% confidence interval 1.16 to 2.01) to one of 1.50 (1.13 to 1.99). Metaregression found no effect of any other variables abstracted on summary outcomes, with the exception of study duration. Duration explained 32.4% of the heterogeneity for continuous outcomes and 27.3% of the variance for dichotomous outcomes.

DISCUSSION

We found that tricyclic antidepressants substantially reduced the pain from both migraine and tension-

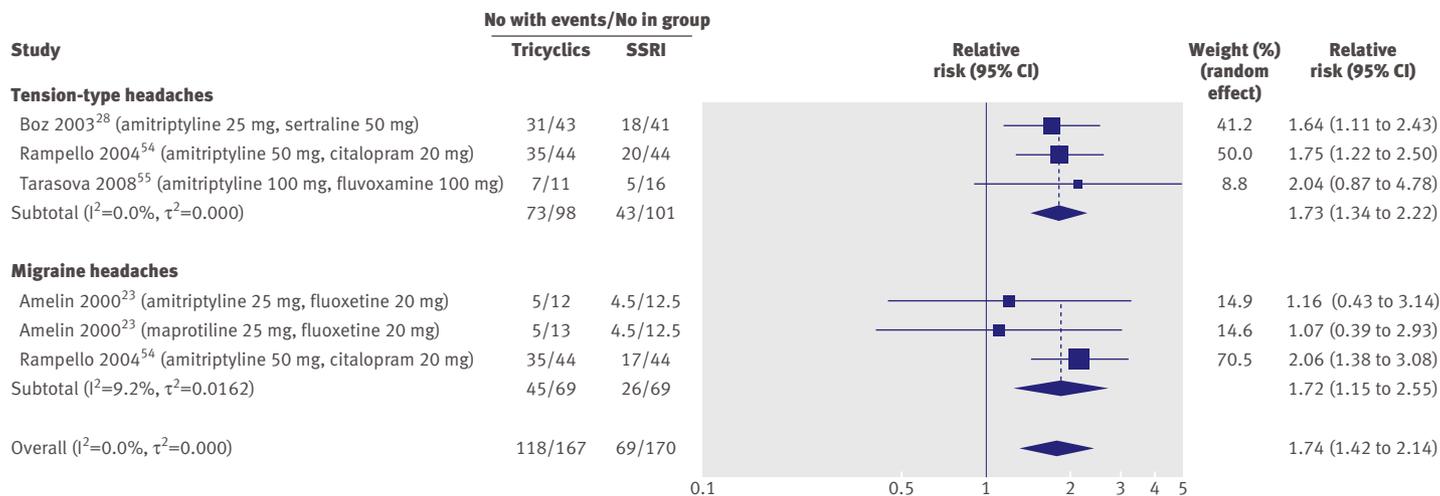| Study	No with events/No in group		Relative risk (95% CI)	Weight (%) (random effect)	Relative risk (95% CI)
	Tricyclics	SSRI			
Tension-type headaches					
Boz 2003[28] (amitriptyline 25 mg, sertraline 50 mg)	31/43	18/41		41.2	1.64 (1.11 to 2.43)
Rampello 2004[54] (amitriptyline 50 mg, citalopram 20 mg)	35/44	20/44		50.0	1.75 (1.22 to 2.50)
Tarasova 2008[55] (amitriptyline 100 mg, fluvoxamine 100 mg)	7/11	5/16		8.8	2.04 (0.87 to 4.78)
Subtotal (I^2=0.0%, τ^2=0.000)	73/98	43/101			1.73 (1.34 to 2.22)
Migraine headaches					
Amelin 2000[23] (amitriptyline 25 mg, fluoxetine 20 mg)	5/12	4.5/12.5		14.9	1.16 (0.43 to 3.14)
Amelin 2000[23] (maprotiline 25 mg, fluoxetine 20 mg)	5/13	4.5/12.5		14.6	1.07 (0.39 to 2.93)
Rampello 2004[54] (amitriptyline 50 mg, citalopram 20 mg)	35/44	17/44		70.5	2.06 (1.38 to 3.08)
Subtotal (I^2=9.2%, τ^2=0.0162)	45/69	26/69			1.72 (1.15 to 2.55)
Overall (I^2=0.0%, τ^2=0.000)	118/167	69/170			1.74 (1.42 to 2.14)

Scale: 0.1, 0.5, 1, 2, 3, 4, 5

Fig 7 | Likelihood of experiencing 50% clinical improvement with tricyclics compared with selective serotonin reuptake inhibitors. Trials of mixed and migraine headaches are combined. SSRI=selective serotonin reuptake inhibitor

Table 4 | Average standardised mean differences between tricyclic antidepressants and non-placebo treatments for tension-type and migraine headaches

Comparison class	Tension-type headache				Migraine headache			
	Drugs compared	Average SMD (95% CI)	No of studies	Heterogeneity (I_2) %	Drugs compared	Average SMD (95% CI)	No of studies	Heterogeneity (I_2) %
Anticonvulsant	—	—	—	—	Topiramate	0.05 (−0.32 to 0.33)	2	29.2
β blocker	—	—	—	—	Propranolol (×3), metoprolol	0.90 (−0.38 to 2.18)	4	93.8
Biofeedback	—	—	—	—	—	−0.93 (−2.76 to 0.91)	2	95.5
Buspirone	Buspirone	−1.01 (−1.83 to −0.18)	2	0	—	—	—	—
Cognitive behavioural therapy	—	0.59 (−0.08 to 1.26)	1	—	—	—	—	—
Ergotamine	—	—	—	—	—	−6.57 (−8.40 to −4.71)	1	—
Serotonin antagonist	Ritanserin	−0.49 (−1.70 to 0.71)	1	—	—	—	—	—
Spinal manipulation	—	−0.25 (−0.59 to 0.09)	2	0	—	−0.31 (−0.69 to 0.08)	1	—
Tetracyclic	Mianserin, mirtazapine	−0.212 (−0.65 to 0.22)	2	32.8	Maprotiline	−0.15 (−0.87 to 0.57)	1	—

type headaches. Patients treated prophylactically with tricyclics experienced about 1 standard deviation of improvement in headache burden, a clinically large effect. Patients with tension-type or migraine headaches were 40-70% more likely to report at least a 50% improvement in headaches, and patients taking tricyclics for tension-type headaches used fewer analgesics. Moreover, the effect seems to increase over time; patients in the first month of treatment had less improvement than those treated for six months. Some adverse effects, particularly dry mouth and drowsiness, were more likely with tricyclics, although this did not result in significantly greater dropout rates, implying a tolerable side effect profile given the benefit. Tricyclics were more effective than selective serotonin reuptake inhibitors in achieving 50% reduction in headaches in a small number of comparative studies. People taking tricyclics were more likely to experience dry mouth, drowsiness, and abdominal distress than those taking selective serotonin reuptake inhibitors, but were not more likely to withdraw from the study.

In a previous meta-analysis, we found that antidepressants reduced headache burden compared with placebo.[7] This study expands that work in several important ways. Previously we included only English language articles and only compared antidepressants with placebo. This study has a greater number of trials and includes comparisons with modalities other than placebo. This allowed us to show that longer treatment improved the efficacy of tricyclics. We were also able

to show that tricyclics are superior to selective serotonin reuptake inhibitors. A recent Cochrane review found that selective serotonin reuptake inhibitors were no more effective than placebo for tension-type headaches. They found some indicators that selective serotonin reuptake inhibitors were less effective than tricyclics for migraines (likelihood of taking >5 analgesic doses per month, number of hours per day with headache).[60] They concluded that tricyclics were favoured over selective serotonin reuptake inhibitors, consistent with the findings reported here.

It is difficult to reach firm conclusions on the relative efficacy of tricyclics compared with other treatment modalities. There were relatively few studies and most were underpowered to assess clinical equivalence.

Tricyclics seem equally effective for tension-type, migraine, and mixed headaches. This is useful information for clinicians as differentiating these headache types may not always be straightforward, especially in patients with frequent headaches. While this similar efficacy lends support to the clinical practice of using the same treatment approaches for recurrent tension, mixed and migraine headache, it does not address important underlying theoretical issues. A similarity in the magnitude of effect does not prove that the mechanisms underlying these headache types are the same, that they converge on some final common pathway, or that the different classes of antidepressants act through some common mechanism. Neither the

Table 5 | Effect of tricyclic antidepressants compared with non-placebo treatments on reduction in headache burden by 50%

Comparison class	Tension-type headache		Migraine headache	
	Drugs	Relative risk (95% CI)	Drugs	Relative risk (95% CI)
Anticonvulsant	—	—	Topirimate	0.82 (0.61 to 1.09)*
β blocker	—	—	Metoprolol, propranolol	0.78 (0.42 to 1.44)*
Calcium channel blocker	—	—	Flunarazine	1.60 (0.83 to 3.10)*
Cognitive behavioural therapy	—	1.09 (0.65 to 1.82)*	—	0.48 (0.14 to 1.57)*
Tetracyclic	Mianserin	1.07 (0.67 to 1.71)*	—	—
*One study.				

studies we examined, nor this study, were designed to resolve issues of nosology and mechanism.

We also found evidence that the benefit of tricyclics for headaches increased with longer study duration. This is consistent with clinical practice and treatment recommendations suggesting that tricyclics need to be taken for several months before reaching any conclusion on effectiveness for any given patient. The scarcity of studies with longer duration is problematic and casts suspicion on the reliability of any conclusions about the long term efficacy of tricyclics.

Strengths and weaknesses of the study

This study's strengths include its methodological rigor and the care taken in study design, data abstraction, and data analysis. However, our meta-analysis has several limitations. Firstly, one of the most important questions is whether tricyclics are better than other commonly used prophylactic treatments, such as β blockers or anticonvulsants. Unfortunately, few trials compare tricyclics head to head against other modalities and many of these comparisons seem to have been designed to put tricyclics at a disadvantage—for example, the average dose of tricyclics used in the comparison with selective serotonin reuptake inhibitors is lower than most clinicians would use in treating headaches. More comparative effectiveness trials are needed.

Secondly, because of the large number of analyses, caution is required in interpreting our finding of an association between treatment duration and efficacy. This analysis should be viewed as exploratory rather than definitive. Moreover, most trials were relatively short, particularly since headaches tend to be a chronic problem. The average duration of the trials in our study was 11 weeks and the longest only 26 weeks; consequently our timeline was constrained to four to 26 weeks. This finding is consistent with clinical experience. Many clinicians encourage their patients to take tricyclics for several months, during which the dose is slowly increased, before deciding to try a different prophylactic agent. This also suggests that treatment trials of longer duration are urgently needed.

Thirdly, it is impossible to differentiate whether treatment effect was independent of depression. The relation between depression and physical symptoms is well described. Patients with depression have more physical symptoms and report those symptoms as more severe and disabling than patients without depression.[61 62] Depressed patients experience improvement in somatic problems when underlying depression is successfully treated.[63] Patients with depression have also been found to have more headaches,[64] although others have argued that this is a result of chronic underlying pain rather than the cause of it.[65] The effects of tricyclic antidepressants on pain syndromes that are considered unrelated to depression, such as neuropathy, have led investigators to suggest a direct analgesic effect.[66 67] Serotonin has been found to be an active neurotransmitter in the central modulation of pain,[68] so there is a possible effect on

pain mechanisms other than through depression. Given the short duration and low doses of tricyclics used for headaches compared with those needed to treat depression, it seems unlikely that the mechanism for the success of headache treatment in these trials is entirely due to the treatment of depression.

A fourth limitation is the lack of reporting on concomitant use of direct, "as needed," drugs. Although most of the studies included patient diaries on the use of analgesics during or before the study period, only four placebo controlled studies and two comparisons with selective serotonin reuptake inhibitors provide any results, all showing insignificantly greater reduction in analgesic use among patients receiving tricyclics. When data are combined across headache types, there is evidence of reduction in analgesic use. However, it is possible that other trials collected but did not report their data; there may be a bias against presenting data suggesting less treatment benefit. Reducing the need for patient use of analgesics is an important goal of prophylactic therapy in general, and has the additional benefit of helping to prevent "rebound" or drug overuse headaches.

A fifth limitation is that it is impossible to tell from our data what the optimal dose is for preventing headaches. Meta-analysis is limited by the problem of aggregate data. Optimal dosing is a question that could be answered only with the availability of patient level data, given the relatively large number of trials that have been carried out and the fact that nearly all trials included titration of tricyclics.

Sixthly, study quality was low in general. Few studies did an intention to treat analysis. This is particularly worrisome since some trials experienced up to 50% losses to follow-up. It is easy to imagine that patients who either had tremendous adverse effects or had lack of improvement would be particularly likely to drop out. We found no difference in effect estimates between those who did and did not do an intention to treat analysis, but our sample was relatively small.

Finally, heterogeneity in our results was considerable, particularly among people with tension-type headaches. Study duration explained some, but not all, of the variance. In addition, there was evidence of small study effects on our results, also known as publication bias. Tests to estimate the number of unpublished trials to calculate the number of unpublished trials necessary to obviate results and tests to "fill in" missing studies have been criticised for lack of underlying theory, poor performance in simulations, and a tendency to overestimate effects, particularly in the face of heterogeneity.[69] Since small, negative trials are less likely to be published, such missing trials would generally decrease the efficacy estimate. It is important to keep in mind, however, two important potential sources of confounding. Firstly, the treatment effect is real. Effective treatments would also seem to have evidence of publication bias. Secondly, tests for publication bias tend to overestimate risk of bias in the face of heterogeneity.[69] It is possible, indeed probable, that

WHAT IS ALREADY KNOWN ON THIS TOPIC

Tricyclic antidepressants are effective in treating tension-type and migraine headaches

Selective serotonin reuptake inhibitors are not more effective in the treatment of migraine headaches than tension-type headaches

WHAT THIS STUDY ADDS

Tricyclics are more effective over time

Tricyclics are more effective than selective serotonin reuptake inhibitors for both migraine and tension-type headaches

The number of trials comparing tricyclics with other treatment modalities is inadequate

unpublished trials exist. The effect we report is therefore possibly an overestimation.

Despite these limitations, our meta-analysis shows the efficacy of tricyclics in people both with migraine headache and with tension-type headache. The benefit seems moderate to large in magnitude. Helpful studies would be those that determine whether particular subgroups of patients are more likely to respond to treatment with tricyclics, such as depressed patients or those with high use of analgesics. It would also be useful to better define more effective treatment regimens, in terms of target doses, treatment duration, or interaction with direct analgesics. Trials directly comparing treatment between tricyclics and other prophylactic regimens are needed.

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