National Institute for Health and Clinical Excellence

Headaches
Guideline Consultation Comments Table
25.04.12 – 7.06.12

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Allergan Ltd UK	1	NICE	14	5	Frequency of migraine is not mentioned in this 'Migraine' section and therefore the treatments are not related to the agreed definitions of both episodic or chronic migraine. For example, a patient is defined as having chronic migraine if he or she experiences headaches on at least 15 days per month for ≥ 3 months, where ≥ 8 of those days are with migraine (IHS 2011). Stratifying out the chronic migraine category would enable the inclusion of the NICE Botulinum toxinA (BOTOX®) STA appraisal for completeness of the evidence base and synergy with this STA.  RE Headaches draft guideline consultation	Thank you for your comment. The frequency of migraine in the studies included in the review was stated in the consultation guideline in the clinical introduction, confirming that the majority of the studies related to people suffering from migraine for less than 15 days per month (mean of 6 days per month), Section 14.1.1. At the time of going out to consultation on the clinical guideline the Final Appraisal Determination for the technology appraisal (TA) of BOTOX had not been issued and therefore was not included within the guideline. Since the publication of the TA we will now cross reference the TA in both the full and NICE versions of the guideline. The TA will also be included as a relevant treatment option within the Headaches pathway of recommendations. This will be available on the NICE website when the clinical guideline is published.
SH	Allergan Ltd UK	2	NICE	14	12	For completeness we suggest to include a rationale for using an anti emetic	Thank you for your comment. We agree. The recommendation has been amended accordingly.
SH	Allergan Ltd UK	3	Full	21	Top row of table	In this row/section of the table relating to "prophylactic treatment of migraine and chronic migraine" the review mentions: 'ACE inhibitors and angiotensin II receptor antagonists (ARBs), antidepressants (SNRIs, SSRIs, tricyclics), beta blockers, calcium channel blockers,	Thank you for your comment. At the time of going out to consultation on the clinical guideline the Final Appraisal Determination for the technology appraisal (TA) of BOTOX had not been issued and therefore was not included within the guideline. Since the

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						antiepileptics and other serotonergic modulators'. However the table does not mention BOTOX®. This needs to be rectified to be complete and to be in accord with the recent STA of BOTOX® in chronic migraine. The guidance for this STA should be in the public domain in June 2012.	publication of the TA we will now cross reference the TA in both the full and NICE versions of the guideline. The TA will also be included as a relevant treatment option within the Headaches pathway of recommendations. This will be available on the NICE website when the clinical guideline is published.
SH	Allergan Ltd UK	4	Full	40	29-32	Since topiramate is mentioned due to the licensed indication for prophylaxis of migraine, for completeness the licensed indication for BOTOX® should also feature in relation to chronic migraine and the recommendations of the TA for BOTOX®	Thank you for your comment. At the time of going out to consultation on the clinical guideline the Final Appraisal Determination for the technology appraisal (TA) of BOTOX had not been issued and therefore was not included within the guideline. Since the publication of the TA we will now cross reference the TA in both the full and NICE versions of the guideline. The TA will also be included as a relevant treatment option within the Headaches pathway of recommendations. This will be available on the NICE website when the clinical guideline is published.
SH	Allergan Ltd UK	5	Full	40	32	The draft document contains no mention of BOTOX® in prophylactic management of chronic migraine - this should feature here and should be in line with Technology appraisal recommendation	Thank you for your comment. At the time of going out to consultation on the clinical guideline the Final Appraisal Determination for the technology appraisal (TA) of BOTOX had not been issued and therefore was not included within the guideline. Since the publication of the TA we will now cross reference the TA in both the full and NICE versions of the guideline. The TA will also be included as a relevant treatment option within the Headaches pathway of recommendations. This will be available on the NICE website when the clinical guideline is published.
SH	Allergan Ltd UK	6	Full	42	9, able	Given that there is now a NICE approved and specifically licensed treatment for Chronic Migraine suggest the migraine column be sub-	Thank you for your comment. Chronic tension type headache and chronic migraine have been separated as suggested.

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						divided into episodic and chronic migraine. Suggest to separate out chronic tension type headache into a separate box as it is treated differently from chronic migraine.	
SH	Allergan Ltd UK	7	Full	43	3	For completeness of the evidence base, there is a need to add chronic migraine as a section and include BOTOX® as a treatment option for those patients who fail 3 prophylactics and in whom medication overuse has been managed appropriately. This section should also include the stopping rules for BOTOX® treatment and refer to the recent STA. This section should also address the issue of patients who start on BOTOX® therapy and who become episodic after 2 cycles (as per guidance) and then regress back to chronic migraine. Currently the Final Appraisal Determination (FAD) does not address this question and clarification from the CG may be helpful to the clinical community.	Thank you for your comment. At the time of going out to consultation on the clinical guideline the Final Appraisal Determination for the technology appraisal (TA) of BOTOX had not been issued and therefore was not included within the guideline. Since the publication of the TA we will now cross reference the TA in both the full and NICE versions of the guideline. The TA will also be included as a relevant treatment option within the Headaches pathway of recommendations. This will be available on the NICE website when the clinical guideline is published. The GDG discussed the need for a stopping rule and agreed that a recommendation should be added stating that review for prophylactic treatment should be undertaken every six months (recommendation 1.3.20).
SH	Allergan Ltd UK	8	Full	45	Whole section	We suggest to include an ideal treatment algorithm for Headache & Chronic Migraine management highlighting the pathways adopted between interventions and the timescales required for review.	Thank you for your comment. This guideline will form part of the NICE pathways tool which will be on the NICE website when the guideline is published. The GDG agreed that a recommendation should be added stating that review for prophylactic treatment should be undertaken every six months (recommendation 1.3.20).
SH	Allergan Ltd UK	9	Full	45	7	We suggest to include a rationale for using an anti emetic	Thank you for your comment. We agree. The recommendation has been amended accordingly.
SH	Allergan Ltd UK	10	Full	45	16	There is currently no mention of BOTOX® in prophylactic management of chronic migraine -	Thank you for your comment. At the time of going out to consultation on the clinical

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						this should be in line with the recent Technology appraisal recommendation due to be issued as TAG in June 2012	guideline the Final Appraisal Determination for the technology appraisal (TA) of BOTOX had not been issued and therefore was not included within the guideline. Since the publication of the TA we will now cross reference the TA in both the full and NICE versions of the guideline. The TA will also be included as a relevant treatment option within the Headaches pathway of recommendations. This will be available on the NICE website when the clinical guideline is published.
SH	Allergan Ltd UK	11	Full	45	27	New TA for BotulinumtoxinA (BOTOX®) would suggest that there should be a new addition to this section which relates to patients with failure of 3 prophylactic agents and adequately managed medication overuse.	Thank you for your comment. At the time of going out to consultation on the clinical guideline the Final Appraisal Determination for the technology appraisal (TA) of BOTOX had not been issued and therefore was not included within the guideline. Since the publication of the TA we will now cross reference the TA in both the full and NICE versions of the guideline. The TA will also be included as a relevant treatment option within the Headaches pathway of recommendations. This will be available on the NICE website when the clinical guideline is published. A recommendation has also been added to indicate that prophylactic treatment should be reviewed every 6 months (recommendation 1.3.20).
SH	Allergan Ltd UK	12	Full	45	32	The BOTOX® TAG for Chronic Migraine should be in the public domain by end June, so this should be included in the section. Consider to offer guidance on timelines between each prophylactic agent before BOTOX® can be considered.	Thank you for your comment. At the time of going out to consultation on the clinical guideline the Final Appraisal Determination for the technology appraisal (TA) of BOTOX had not been issued and therefore was not included within the guideline. Since the publication of the TA we will now cross reference the TA in both the full and NICE versions of the guideline. The TA will also be

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							included as a relevant treatment option within the Headaches pathway of recommendations. This will be available on the NICE website when the clinical guideline is published. The GDG agreed that a recommendation should be added to state that the need for prophylactic treatment should be reviewed every six months (recommendation 1.3.20).
SH	Allergan Ltd UK	13	Full	180	32	BotulinumtoxinA (BOTOX®) should be included in this section	Thank you for your comment. At the time of going out to consultation on the clinical guideline the Final Appraisal Determination for the technology appraisal (TA) of BOTOX had not been issued and therefore was not included within the guideline. Since the publication of the TA we will now cross reference the TA in both the full and NICE versions of the guideline. The TA will also be included as a relevant treatment option within the Headaches pathway of recommendations. This will be available on the NICE website when the clinical guideline is published.
SH	Allergan Ltd UK	14	Full	181	21	BotulinumtoxinA (BOTOX®) should be included in this section. NICE reviewed comparator trials with topiramate, Placebo and Amytryptiline	Thank you for your comment. At the time of going out to consultation on the clinical guideline the Final Appraisal Determination for the technology appraisal (TA) of BOTOX had not been issued and therefore was not included within the guideline. Since the publication of the TA we will now cross reference the TA in both the full and NICE versions of the guideline. The TA will also be included as a relevant treatment option within the Headaches pathway of recommendations. This will be available on the NICE website when the clinical guideline is published.
SH	Allergan Ltd UK	15	Full	212		Insert section for patients failing 3 prophylactic agents and clinical evidence to support this for botulinumtoxinA (BOTOX®)	Thank you for your comment. At the time of going out to consultation on the clinical guideline the Final Appraisal Determination for

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							the technology appraisal (TA) of BOTOX had not been issued and therefore was not included within the guideline. Since the publication of the TA we will now cross reference the TA in both the full and NICE versions of the guideline. The TA will also be included as a relevant treatment option within the Headaches pathway of recommendations. This will be available on the NICE website when the clinical guideline is published. A recommendation has also been added to indicate that prophylactic treatment should be reviewed every 6 months (recommendation 1.3.20).
SH	Association of Anaesthetists of Great Britain and Ireland	1	Full	307	General	We would ask you to consider specifically mentioning post-dural puncture headache (PDPH) in the immediate postpartum period within the 'pregnancy' section. This occurs in approximately 1 in 100 epidurals used for pain relief in childbirth, and around 1 in 200 – 1 in 500 spinals, used for pain relief or operative delivery (although it should be noted that PDPH is not confined to pregnancy, but is a risk in any patient who has undergone a spinal or epidural injection). PDPH is usually benign, but can progress to a chronic pain syndrome. In a small proportion of cases, reduced intracranial pressure can result in meningeal stretching with subsequent subdural or extradural haemorrhage, and several maternal deaths have been attributed to this mechanism. PDPH is very amenable to treatment (blood patch), especially if caught early, so it is important that GPs, midwives and others involved in the care of postpartum women are aware of this condition. Not all headaches following epidural or spinal	Thank you for your comment. Post-dural puncture headache falls outside the scope of the guideline. Therefore we could not provide a response.

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						headache are PDPH; most are benign but rarely serious, life threatening conditions such as cortical vein thrombosis may co-exist.	
SH	BASH	1				We find no strong reason to recommend parenteral anti-emetics as an alternative if the oral treatment does not work, considering the comparison was based on a low quality study of 62 patients. Intramuscular Non-steroidal anti-inflammatory drugs (NSAID) were far superior to intramuscular paracetamol in a bigger study of 149 patients. Subcutaneous triptan was inferior to anti-emetics but that does not mean the anti-emetics should be used in preference to parenteral NSAID (Page 141)	Thank you for your comment. We do not know which comparison your comment refers to. The evidence reviewed for non-oral drugs is outlined in section 11.3. The recommendation was influenced by a number of evidence reviews including the comparison between intravenous antiemetic and subcutaneous triptan which was of moderate quality.
SH	BASH	2				We are not convinced that telmisartan is recommended ahead of lisinopril. The evidence was based on a small, low quality study and the estimated ICER for this treatment is well above the NICE threshold of £ 20,000. A randomized double blind study on lisinopril has demonstrated efficacy (Schrader et al 2001) (Page 209) and the drug should be ahead of telmisartan in recommendations. The recommendation to use Topiramate as a first line migraine prophylaxis is difficult to justify. The drug is poorly tolerated, has teratogenecity and interferes with oral contraceptive pill. The fact this drug has published evidence of efficacy does not mean the first line treatments namely beta-blockers and amitriptyline are not effective. These drugs have been in the market for a long time and are much cheaper to	Thank you for your comments. After careful consideration we agree that telmisartan should not be recommended. It has now been removed from the recommendation. The GDG have reworded the recommendation to 'Offer topiramate or propranolol…' A statement has also been added stating according to patient preference, comorbidities and risk of adverse events. No evidence relevant to the review protocol was identified for Lisinopril, amitriptyline or sodium valproate (crossover studies were excluded from the review; therefore the Schrader et al. study was excluded). No recommendation was made for or against its use. A recommendation was made to state that if someone was already receiving an effective form of prophylaxis, it should not be stopped. Lisinopril and sodium valproate have

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						prescribe and the fact they are generic means further evidence on their efficacy is less likely to emerge. Topiramate studies were done while the drug was still patent and were commercially driven (page 209). We feel that Sodium Valproate remains a treatment option as head to head comparison has shown the drug to have efficacy equal to Topiramate (Page 183, 196). We are also concerned that Gabapentin is recommended on the basis of just one study (Page 186). We feel that amitriptyline remains the first line option in the prophylaxis of migraine. The withdrawal of this drug when it is better tolerated, used widely in practice and remains a cheaper option is difficult to understand. We agree that the evidence is much weaker than Topiramate but most of the evidence has come from fairly old studies and the fact that drug is so widely used any new evidence is highly unlikely to emerge in future (Chapter 14 Page 180 onwards). The recommendation for acupuncture for tension type headache as well as the strength of the recommendation in migraine	now been included as an example in the full guideline, amitriptyline is specifically mentioned in this recommendation. The GDG do not agree that gabapentin should be removed from the recommendation. The evidence for reduction in migraine frequency and intensity was of moderate quality and considered strong enough to include with the other recommended treatments. The recommendation for acupuncture for tension headache was based on three studies with a reduction in headache days as well as some evidence for improving responder rate, headache intensity and quality of life. The GDG agreed this was of sufficient quality to base a recommendation on. The developers decided that in the absence of evidence for any other treatment for the prophylaxis of tension headache, acupuncture should be recommended. The recommendation was worded as 'Consider' rather than 'Offer acupuncture' to reflect the low level of evidence. The evidence for acupuncture for migraine was compared with the pharmacological treatments in a network meta-analysis in which it was ranked joint second after topiramate (joint with propranolol and telmisartan) in reduction in migraine days. When the means and standard deviations are considered, acupuncture is ranked second. The direct comparisons demonstrated efficacy for improving responder rate, reducing

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						given as equivalent to other pharmacological options and remaining cost-effective is difficult to justify. Three low quality studies demonstrated some benefit from acupuncture compared to sham puncture although the net therapeutic gain was only 10%. Two reasonable sized study showed no difference and a small study indicated that sham acupuncture was better than verum acupuncture. We feel that acupuncture may be suitable and useful for some patients but feel that there is no strong reason to recommend the drug ahead of some pharmaceutical agents such as amitriptyline. Butterbur has been recommended inspite of a serious warning issued by the Medicine and Healthcare Regulatory Agency (MHRA) in January 2012 that the drug may cause liver failure. We feel that an unregulated herbal product should not be recommended.	migraine frequency, improving quality of life and reducing acute medication use. An economic study based on a RCT conducted in the UK showed that acupuncture is cost-effective when compared to no treatment in people with migraine or tension type headache. Although people suffering of tension type headache represented only 5% of the trial population (the remaining 95% were people suffering of migraine), the GDG considered the findings to be applicable to the overall population included in the RCT. The model developed for this guideline was in agreement with the results of the RCT (acupuncture could be cost-effective when the number of sessions is 10 or fewer) but this was based on a population of people with migraine. The GDG agreed the clinical and economic evidence was sufficient to base a recommendation on. We understand the issues you raise in relation to evidence for older, generic drugs such as amitriptyline, but the GDG considered it is possible to do a study of these drugs and have made a research recommendation to this effect. We agree that butterbur should not be recommended. We were not aware of the toxicity warning at the time of the consultation, but have no removed it from the recommendations.
SH	British Acupuncture Council	1	Full	232	15-22	In the absence of much understanding of acupuncture's mechanism of action there is no accepted definition of what comprises the	Thank you for your comments. The GDG considered these issues carefully. In any complex, therapist delivered, intervention it

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						specific effect. In traditional terms the specific and contextual effects are intertwined and inseparable, hence the distinction between verum and sham is blurred. Verum-sham comparisons provide fascinating data for researchers and for those interested in investigating different traditional theories, teachings and procedures but are inappropriate to inform clinical decision on the effectiveness of the therapy (as a whole) – for which one should look to comparative effectiveness trials. We can understand why NICE would feel more comfortable including the sham data but this should have happened in the context of all the RCT evidence, and bearing in mind current thinking on the evaluation of complex interventions.	can be difficult to disentangle the specific effects of the intervention and the non-specific effects of the therapeutic encounter. The GDG decided that for complex interventions, where a plausible sham control was possible, evidence from such trials should be used to inform judgements on clinical effectiveness. Several RCTs of acupuncture were identified with a plausible sham control. These data were, therefore used, to inform decision about its clinical effectiveness. The GDG agreed that these forms of sham were adequate to ensure blinding of the participant to the treatment, and therefore could be considered equivalent to a drug placebo in a RCT of a pharmacological intervention for the purposes of clinical analysis. They could therefore also be used appropriately in a network meta-analysis comparing acupuncture with prophylactic medication using drug trials that also had a placebo arm. This is the most rigorous approach to assessing the comparative effectiveness of acupuncture and pharmacological prophylaxis that reduces, as far as possible , risk of bias in making a decision about effectiveness. It was acknowledged that this may provide a conservative estimate of effect for acupuncture.
SH	British Acupuncture Council	2	Full	240	6	The excluded German study is the highest quality cost-effectiveness study to date on this subject. Given the paucity of economic evidence it seems strange to exclude it: are German conditions so different as to make their data not worthy of consideration?	Thank you for your comment. As explained in section 2.9.1.1 of the Full Guideline, we prioritise the economic evidence on the basis of their methodological quality and on their applicability to the UK setting. "If a high quality, directly applicable UK analysis was available other less relevant studies may not

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							have been included." In this case a good quality study conducted in the UK was available and its results would have been considered more useful compared to the German study for the purpose of this guideline. Therefore we still believe it is not necessary to include the German study.
SH	British Chiropractic Association	25.00	Full	258	13 & 14	We acknowledge the considered position of the Guideline Development Group (GDG) that based on the RCT evidence reviewed, there was not enough evidence to make a firm recommendation in any direction regarding the use manual therapies for patients with migraine or tension-type headache (TTH). We also acknowledge that there are relatively few RCT's available addressing the most useful questions and comparisons in this area. Of the relatively few studies available, there is significant heterogeneity in the studies (clinical and comparison type) and many are often considered to be of a relatively low quality when using a systematic grading method although a recent systematic review by Posadzki and Ernst (2012) graded the RCT evidence of spinal manipulation for TTH as 'mostly high' using the Jadad scale and Cochrane tool. We acknowledge that most of the quality problems with the headache studies surround issues of methodology, namely; methodological design limitations and/or a lack transparency or key omissions in methodology reporting. Some limitations do also involve the presentation of the results and possibly some positive reporting bias. However, although it does not mitigate against many of these study quality issues, even the best designed RCT's looking at the efficacy or effectiveness of a manual therapy	Thank you for your comment. The systematic review of spinal manipulations for tension type headaches by Posadzki and Ernst included three studies which did not meet our criteria for this review. Two of these studies were outside of the scope of this guideline as they were in people with cervicogenic headache. The third study was excluded as it reported outcomes at less than three months (Boline et al . 1995). The study by Carlsson et al. 1990 did show some benefit with physiotherapy as compared to acupuncture, but the evidence was for only one outcome (change in headache intensity) and was of very low quality. However, we do acknowledge the evidence and the text has been revised to read as suggested.

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						approach always score relatively poorly on a quality grading as it is very difficult to have an adequate placebo control treatment and is not possible to adequately blind the treatment providers and often the patients. As such, even without consideration of common other design and quality flaws together with reporting inadequacies, the evidence is generally considered to provide at best preliminary results and are or more commonly considered inconclusive. For migraine headache, as acknowledged by the GDG we feel that the current evidence may lend some preliminary support to use of manual therapies and as such could perhaps be reflected in the GDG statement. With respect to TTH, the GDG's considered opinion was consistent with most if not all the systematic reviews published up to and including 2011. However, none of these other reviews included the more recent study by Castien et al (2011). From a certain viewpoint, this is a very useful and pragmatic study with excellent external validity – it really reflects the real clinical world environment and the type of management that many manual therapy practitioners and GP's administer. On the face of it, the study demonstrates a large clinical benefit to using a manual therapy approach vs 'usual' GP care for several important outcomes. However, as with many more pragmatic trials, it suffers from many of the scientific limitations that are usually more tightly controlled for with less pragmatic RCT's. We do indeed acknowledge the scientific limitations highlighted in the full draft document and	

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						appendix and also some other possible limitations and issues that are apparent to us on detailed review of the study. Taken all together, some of these could raise a question of the specific vs non-specific effects of the comparison groups. Some of the limitations involve possible methodological flaws but several involve a lack of clarity or omissions in reporting in the methods description and could perhaps be clarified further with the authors. We also acknowledge that a proportion of the study participants were reported to have a migraine headache as co-morbity thus potentially limiting the directness of the study results to TTH. Interestingly, the authors did provide some secondary subgroup analysis which they felt showed that both pure TTH and TTH + migraine participants similar results to the primary outcomes. However we do acknowledge that these secondary analyses are 'unsafe' in terms of scientific validity particularly when as in this case, there was incomplete reporting of the data thus limiting the reviewers ability to make a more solid interpretation. A further discussion of the scientific interpretation of this study is beyond the scope of this comment section but we do feel the Castien et al study (2011) does provide some preliminary evidence that patients with TTH (or TTH + migraine) may benefit from seeing a manual therapy practitioner. As mentioned earlier, a more recent systematic review by Posadzki & Ernst (2012) covering TTH suggests that "*the evidence that spinal manipulation alleviates tension type headaches is encouraging, but inconclusive. The low quantity of the available data prevent firm*	

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						conclusion". They did include the Castien et al (2011) but have also included 3 studies not considered by the GDG. We note that acupuncture appears in the NICE document as a recommendation for the prophylactic treatment of TTH. It is interesting to note that the one study comparing acupuncture with a manual therapy approach (considered by the GDG) found similar improvements for both the manual therapy and acupuncture management (Carlsson et al. 1990). We do however acknowledge the quality issues with this study and particularly that the ranges of outcomes measured were limited. In view of all these comments, we would like to suggest that the GDG consider the following modification to the wording of the statement. **Suggestion for revision** '*Although there is some preliminary evidence to suggest that seeing a practitioner who utilises manual therapies may be of benefit*, the GDG decided there was not enough evidence to make a recommendation for or against the use of manual therapies for the prophylactic treatment of tension type headache or migraine'	
SH	British Chiropractic Association	1	Full	258	15 - 16	Our comment refers to the **first** recommendation in the Recommendations & Links to Evidence Table... *'The GDG agreed that responder rate was the most important outcomes for decision making'.* **Why was responder rate considered to be**	Thank you for your comment. Responder rate was rated as the most important outcome but the GDG did consider other outcomes such as change in headache days and headache intensity in decision making. We have now amended the text accordingly to reflect this.

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						<u>the most</u> important outcome for decision making in this section in isolation? Why were other outcomes such as headache frequency, intensity etc., not considered being equally important in the decision process? Although two other prophylactic management sections had responder rate highlighted as the most important outcome in isolation, for a number of the other sections, some variance was apparent in what were considered to be the most important outcomes for decision making. For several of these, more than one outcome was considered important. For instance in section 25 (prophylactic non-pharmacologic treatment of primary headache with exercise) a broad range of outcomes were considered as important for decision making with this section.... *'The GDG agreed that change in migraine days and responder rate were the most important outcomes, however change in patient reported migraine frequency and intensity were also important to consider'.* **Why was there an apparent inconsistency between different sections of the document and different treatment approaches as to the most important outcome/s for decision making?** Could this variance in emphasis on outcome for decision making introduce an element of bias between sections when the evidence for recommendations is considered?	
SH	British Chiropractic	2	Full	258	15 -	Our comment refers to the **<u>second</u>**	Thank you for your comment. We agree and

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	Association				16	recommendation in the Recommendations & Links to Evidence Table. This recommendation refers to the 'Trade off between clinical benefit and harms'. We feel that the phrasing of the recommendation statement could be improved to remove some imprecision, to be more complete in its breadth and more accurately reflect the current best evidence. We would like to suggest the following rewording of this section of the recommendations; '*There may be a risk of cervical artery dissection (CAD) and possible neurological compromise resulting in stroke associated with manual therapies of the neck. However, the evidence for this risk is based mainly on case reports and cases series which by design cannot determine causality. Many of the studies are of poor quality with high risk of reporting bias. However one high quality case control study found no evidence of excess risk of vertebro-basilar artery stroke associated with chiropractic care compared to primary (GP) care (Cassidy et al. 2008). Overall the evidence indicates that the risk of a major adverse event (such as stroke) is low to very low, although minor short-lived side effects (e.g. soreness) are relatively common. Practitioners are taught to be alert to the risk factors for CAD, the presenting features of CAD, and the need for appropriate and timely referral. The chiropractic profession in the UK have set up a reporting service for adverse events (www.cpirls.org).'*	the text has been amended accordingly.
SH	British Chiropractic	3	Full	258	15 -	Our comment refers to the **fifth**	Thank you for your comment. We agree and

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	Association				16	recommendation in the Recommendations & Links to Evidence Table. This recommendation refers to the 'Other considerations'. We again feel that the phrasing of the recommendation statement could be improved to remove some imprecision, to be more complete in its breadth and more accurately reflect the current best evidence. We would like to suggest the following rewording of this section of the recommendations; *'For migraine, there was one study showing some benefit. The GDG were concerned that the evidence reviewed was of low to very low quality with a lot of uncertainty in the effect estimates, and that rare adverse events may be severe when they do occur. It was agreed that better evidence was required to make a recommendation.'*	the text has been amended accordingly.
SH	British Chiropractic Association	4	Full	258	15 - 16	Our comment also refers to the **fifth** recommendation in the Recommendations & Links to Evidence table. This recommendation refers to the 'Other considerations'. The GDG state the following; *"For tension type headache the study states that the population was of chronic tension type headache, however the GDG considered that it was possible that many of these people actually had migraine rather than tension type headache and therefore these data may not be directly applicable to the headache type".*	Thank you for your comment. The study being referred to here is Castien et al. 2011. The GDG agreed that the diagnosis of chronic migraine and chronic tension type headache frequently overlap as per the diagnostic criteria in recommendation 1.2.1. This was the basis for the GDG's decision that the participants could probably have migraine.

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						We are not certain what 'the study' was so cannot offer a solid comment on this statement. We are assuming this was the study by Castien et al (2011). Assuming this to be the case, we are unsure how the GDG arrived at the conclusion that '*many'* of the participants in the study had migraine and *'not'* TTH. The study mentioned in the results section of a subgroup of participants with co-morbid migraine but as stated above in comment 1, did not provide any data on the number of participants with this multiple headache diagnosis.	
SH	British Chiropractic Association	5	NICE Version	18 - 22		**When you look at section 4 (Research Recommendations), there is no recommendation for further research looking at the role of manual therapies in the management migraine and TTH. Why is this?** Manual therapies are generally widely used by the UK population and are a commonly considered treatment approach when the management of migraine and TTH is under review and guidelines are being formulated. There is certainly sufficient baseline evidence to justify further specific research and a clear need to obtain better quality data so more solid conclusions can be drawn. Indeed in the Full version, the GDG stated that for manual therapies.... '*It was agreed that better evidence was*	Thank you for your comment. We agree and a research recommendation for the role of manual therapies in management of migraine and tension type headache has been added. (Please see section 4 of the NICE guideline and Appendix M of the full guideline.) Other sources of evidence are used for evaluation of interventions if it is not possible to make a recommendation on the basis of using RCT evidence alone. The GDG considered that since they were able to make a recommendation for pharmacological interventions and acupuncture for tension type headache and migraine, other levels of evidence were not appropriate in this case.

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						required to make a recommendation'. (stated in the Recommendations & Links to Evidence table in section 22.4 (page 258) of the Full version) We would therefore like to request that the GDG consider the possibility of making a recommendation for well designed, high quality and comprehensive research looking at the use of manual therapies in the management of patients with migraine or TTH. With respect to a recommendation on the study designs we would like to perhaps rather boldly suggest that NICE consider adopting a new method of assessing the evidence regarding the use of manual therapies without a reliance on the RCT as **sole** provider of evidence for decision making. This possible change in viewpoint and approach has been suggested by a number of scientists and clinicians. It is interesting to note that the Chairman of NICE, Professor Sir Michael Rawlins in the Harverian Oration to the Royal College of Physicians (2008) argued a similar point (although manual therapy research was not the focus of his address). He and others have made a number of excellent points that perhaps could be considered further in framing recommendations for the gathering of evidence relating to the use manual therapies.	

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SH	British Society of Neuroradiologists	1	Full	General		I agree with the recommendations regarding imaging in primary headache	Thank you for your comment.
SH	College of Optometrists	1	Full	326	n/a	We believe the definition of glaucoma should include both the chronic (which has no symptoms in the early stages) and acute (which does have symptoms) forms. It may be helpful if the symptoms of acute glaucoma are described. These are a painful red eye with misty vision which may cause the patient to see haloes around lights. The patient may also feel unwell or be sick. The symptoms may be more noticeable at night or in dim conditions, when the pupil is dilated.	Thank you for your comment. The guideline now only mentions acute glaucoma. The definition in the glossary has been amended to clarify this.
SH	College of Optometrists	1	NICE	8	22	We would recommend that the symptoms of acute glaucoma be described. These are a painful red eye with misty vision which may cause the patient to see haloes around lights. The patient may also feel unwell or be sick. The symptoms may be more noticeable at night or in dim conditions, when the pupil is dilated.	Thank you for your comment. In order to be consistent with other conditions listed, further detail has been given in the glossary of the full guideline rather than in the recommendation.
SH	College of Optometrists	2	NICE	10	2	The symptoms of cluster headache include 'red and/or watery eye' and 'constricted pupil and/or drooping eyelid'. We feel it is important to distinguish this from the symptoms of acute glaucoma. These are a painful red eye with misty vision which may cause the patient to see haloes around lights. The patient may also feel unwell or be sick. The symptoms may be more noticeable at night or in dim conditions, when the pupil is dilated. In acute glaucoma the pupil is more likely to be semi-dilated than constricted, so this may be a useful distinguishing sign.	Thank you for your comment. The GDG agreed that with further information added to the glossary definition of glaucoma, and the other factors required for a diagnosis of cluster headache (pain location, intensity, duration and frequency), that no further detail was needed in this table.

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SH	College of Optometrists	3	Full	49	1	We would suggest prefacing 'glaucoma' with 'acute', as the chronic form is unlikely to cause headaches.	Thank you for your comment. This table indicates the starting point for this review and reflects the symptoms and signs as they were listed in other guidance. We have qualified as acute glaucoma in our recommendation (1.1.1).
SH	Department of Health	1				Thank you for the opportunity to comment on the draft for the above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.
SH	Elcena Jeffers Foundation	1				No comment	Thank you for your comment.
SH	Faculty of Pain Medicine of the Royal College of Anaesthetists	1	NICE version	General		Good comprehensive overview	Thank you for your comment.
SH	Faculty of Pain Medicine of the Royal College of Anaesthetists	2	NICE version	General		Good introduction on general principles including consent, capacity and signposting to key documents and websites	Thank you for your comment.
SH	Faculty of Pain Medicine of the Royal College of Anaesthetists	3	NICE version	General		It would be useful to comment that this guideline does not cover facial pain nor occipital neuralgia.	Thank you for your comment. A statement has now been included in the introduction to state this (p13).
SH	Faculty of Pain Medicine of the Royal College of Anaesthetists	4	NICE version	3	27	There is a British Pain Society publication on 'The use of drugs beyond licence in palliative care and pain management (2005)' which could be referenced here. http://www.britishpainsociety.org/pub_professional.htm	Thank you for your comment. We have added this reference to the full guideline section 2.10.
SH	Faculty of Pain Medicine of the Royal College of Anaesthetists	5	NICE version	7	6	Acute migraine 'Offer an intravenous … preparation of metoclopramide, chlorpromazine or prochlorperazine. I don't think many GPs would be happy to do this. Has the impact on	Thank you for your comment. This guidance is intended to be for all health care settings. We acknowledge that many people with headache attend emergency departments and the

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						Emergency Departments been fully considered? The full guidance page 162 points out that the evidence for these drugs is low and very low quality and that intravenous chlorpromazine and prochloperazine are not available in the UK.	recommendations are also directed at this setting. An accident and emergency medicine consultant was recruited to the guideline development group to ensure that perspective informed guideline development. The GDG agreed that a recommendation for treatment options were required for people who could not take oral medication. After further consideration, the GDG agreed to remove chlorpromazine from the recommendation as it is not widely used in the UK. Additional information has been added to the full guideline to detail the reasons for this decision. The recommendation has been reworded so as not to indicate the type of non-oral preparation that should be used. The GDG noted that it is available as an intramuscular preparation and therefore remain in the recommendation, and that availability may change with time.
SH	Faculty of Pain Medicine of the Royal College of Anaesthetists	6	NICE version	8	11	'Sudden onset headache' . Many headaches are sudden onset; I think from reading the full guidelines that what is meant is new-onset headache with risk factors	Thank you for your comment. After consideration this has been reworded to clarify, as 'Sudden onset headache reaching maximum intensity within 5 minutes'.
SH	Faculty of Pain Medicine of the Royal College of Anaesthetists	7	NICE version	10	1	This clinical classification of primary headache is useful and in particular more useful than the 'vascular, muscle contraction, traction and inflammatory' classification system one often sees (e.g. American National Institute of Neurological Disorders and Stroke)	Thank you for your comment.
SH	Faculty of Pain Medicine of the Royal College of Anaesthetists	8	NICE version	17	11	The issue of abrupt v gradual withdrawal. The guideline recommends abrupt withdrawal. This is contrary to the common management of inappropriate medication for any other painful	Thank you for your comment. The GDG acknowledged that this may depend on the individual, but their experience was that abrupt withdrawal was preferred and most

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						condition. The full guidance itself (page 305) says 'Patient experience suggested that gradual withdrawal is preferred', that 'this should be decided on a case by case basis' and that 'gradual withdrawal could be managed in the community'.	people could do this providing they were informed that symptoms would initially get worse and support was provided.
SH	Faculty of Pain Medicine of the Royal College of Anaesthetists	9	Full version		304-305	As above	Thank you for your comment. After careful consideration of the evidence and the GDG's clinical experience we do not think this recommendation needs to be changed. The GDG agreed that abrupt withdrawal is the preferred option, which is supported by the evidence. People can be supported through this, but the full guideline acknowledges that this should be decided on a case by case basis as for some people it won't be suitable.
SH	Faculty of Pain Medicine of the Royal College of Anaesthetists	10	NICE version	18	14	Clear and useful research recommendations	Thank you for your comment.
SH	Faculty of Pain Medicine of the Royal College of Anaesthetists	11	NICE version	24	1	The Guideline Group would have been strengthened by including members from the Faculty of pain Medicine and the British Pain Society	We advertised specifically for a pain specialist and received no responses directly for this position. One of the members of the GDG was subsequently nominated by the British Pain Society (Dr Sam Chong). Dr Chong was an active member throughout the guideline development process.
SH	Headache Clinics UK	1	Full		General	There are many inconsistencies in the development of recommendations in this document The recommendations are at times based on tentative evidence at best whilst other equally strong/weak evidence is ignored.	Thank you for your comment. For the development of the guideline we have followed the same process for all reviews. This involved, searching for the evidence according to the agreed protocol. Where evidence was identified, the developers considered the quality of the evidence (according to the GRADE profile) to form recommendations, using the highest quality evidence available in each review question. In

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							some areas, if no higher quality evidence was available, this may mean that a recommendation is based on 'low' quality evidence. Where no recommendation is made, this does not indicate a recommendation not to use the treatment. It is an indication of where there is not enough evidence for or against that treatment.
SH	Headache Clinics UK	2	Full		General	At the moment this draft fails to take into account other more 'rounded' guidelines and ignores the NHS 2008 pathway for headaches. It does not reflect the current and well accepted theory that headaches/migraine are best approached using a multidisciplinary approach. There seems to be an over emphasis on pharmacological approaches, despite many sufferers wishing to try other approaches, where there is evidence of any level.	Thank you for your comments. The areas covered by the guideline were defined by the scope. This was informed by stakeholder comments at a workshop held in July 2010 open to public consultation in August 2010 – September 2010, and amended accordingly. Non-pharmacological approaches including acupuncture, manual therapies, psychological therapies, dietary supplements, herbal remedies, exercise and education and self-management were all reviewed for tension type headache and migraine. Recommendations were made for acupuncture for tension type headache and migraine (recommendations 1.3.9 and 1.3.18) and dietary supplements for migraine (recommendation 1.3.21). In other areas, there was not sufficient evidence for the GDG to make a recommendation, however research recommendations were made for manual therapies, exercise and psychological therapies.
SH	Headache Clinics UK	3	Full	47	6	Although the GDG cannot make a	Thank you for your comment. We agree and a

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						recommendation on Manual Therapy but equally cannot say it doesn't work it does not feel able to suggest that further research is undertaken yet it does for Behavioural Therapies although the findings in recommendations are weaker than for Manual Therapy? Another inconsistency.	research recommendation for the role of manual therapies in management of migraine and tension type headache has been added. (Please see section 4 of the NICE guideline.)
SH	Headache Clinics UK	4	Full	61	4	A GDG consensus suggests that questionnaires should not be used - but in statements evidence is up to moderate quality and they are more sensitive in headache or neuro clinics. Surely it is not that the instruments are unhelpful but about educating those in primary care – especially as headaches are only defined by characteristics. An example of relatively good evidence (comparative to total evidence base) where GDG use consensus rather than evidence	Thank you for your comment. The evidence reviewed was of low to moderate quality, but did not support the use of questionnaires, such as the ID migraine, as the sensitivity and specificity were not adequate in a primary care /unselected population. The ideal questionnaire would have high sensitivity and specificity and would be applicable in a primary care setting for an undiagnosed population. Sensitivity would be expected to be higher in headache and neurology clinics where the incidence of migraine in the population studied is higher, and a diagnosis of migraine has already been assigned. This does not indicate an effective questionnaire.
SH	Headache Clinics UK	5	Full	66	1	GDG used 'informal' (what is that?) consensus here with lower quality evidence and came to a positive decision but not with questionnaires above? Inconsistent?	Thank you for your comment. Informal consensus is defined in the methods of the guideline (page 38-39). More detail has now been added to the glossary definition. The evidence reviewed for questionnaires did not support their use for diagnosis, which is why their use was not recommended. For headache diaries, the evidence was of low quality, but did indicate that these can be of use. The developers considered this evidence and their expert opinion to form the recommendation applying the same methodology for decision making as with all other recommendations.

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SH	Headache Clinics UK	6	Full	100	31	Statements such as 'TTH has migranous features therefore probably migraine' are inconsistent and illogical. How is this statement justified? If the logic is followed then all headaches are likely to be migraine.	Thank you for your comment. The GDG agreed that chronic tension type headache frequently overlaps with chronic migraine. Chronic tension type headache can be diagnosed when migrainous features are present (as stated in recommendation 1.2.1). The statements in the full guideline have been checked for consistency and the GDG do not agree they need to be changed.
SH	Headache Clinics UK	7	Full	103	12	Use of term 'suggested' is common throughout summaries of evidence reports but I cannot see a definition for 'suggested' it either is or it isn't- within a degree of confidence?	Thank you for your comment. The explanations of how suggested and showed are used in evidence statements is described on page 34 in the methods. This is consistent with methodology used across the NCGC at the time this guideline was developed.
SH	Headache Clinics UK	8	Full	112	19	Recommendations offer Aspirin NSAIDSs etc. This is based on very low evidence quality and in case of Aspirin 1 study with reported equivocal results. A recommendation seemingly based on what is 'thought' or 'done' rather than evidence. Yet same rules do not apply to other interventions throughout.	Thank you for your comment. For the development of the guideline we have followed the same process for all reviews. This involved, searching for the evidence according to the agreed protocol. Where evidence was identified, the developers considered the quality of the evidence (according to the GRADE profile) to form recommendations, using the highest quality evidence available in each review question. In some areas, if no higher quality evidence was available, this may mean that a recommendation is based on 'low' quality evidence. The wording of the recommendation has been changed from 'Offer' to 'Consider' to reflect that this is based on low quality evidence.
SH	Headache Clinics UK	9	Full	159	2	Recommendation based on low and very low evidence	Thank you for your comment. For the development of the guideline we have followed the same process for all reviews. This involved, searching for the evidence according to the agreed protocol. Where

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							evidence was identified, the developers considered the quality of the evidence (according to the GRADE profile) to form recommendations, using the highest quality evidence available in each review question. In some areas, if no higher quality evidence was available, this may mean that a recommendation is based on 'low' or 'very low' quality evidence. In this case, the GDG were aware that although the evidence supported the use of combination treatments in preference to monotherapy, there was a need to have a recommendation for people who prefer to take only one treatment.
SH	Headache Clinics UK	10	Full	209	1	How can this recommendation be valid? The evidence listed in the document in the main says there is little difference in most studies between topiramate and other medications and even placebo yet the potential adverse affects are large.	Thank you for your comment. After careful consideration, the GDG have decided to amend the recommendation to state: 'Offer topiramate or propranolol (recommendation 1.3.17). The new recommendation takes into account the limitations of the economic analysis such as the exclusion of adverse events and tolerability in the analysis and recognises the uncertainty over the superior cost-effectiveness of topiramate compared to propranolol. A statement has also been added stating according to patient preference, comorbidities and risk of adverse events. The economic analysis takes into account the mean effect and the uncertainty around the mean. The overall uncertainty is reflected in the strength of the recommendation. A summary of the results of the NMA for the clinical evidence are now also provided in the form of evidence statements in both the full

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							guideline (sections 14.3) and appendix K to clarify the evidence the recommendation was based on.
SH	Headache Clinics UK	11	Full	209	1	Why is acupuncture included here? It is a non pharamacological approach? The study listed didn't actually come out strongly for acupuncture.	Thank you for your comment. Acupuncture was included within the network meta-analysis (NMA) for prophylactic treatment of migraine as there were double blind RCTs available. After careful consideration of the evidence from the direct comparisons and NMA, the GDG agreed there was sufficient evidence to recommend acupuncture as a treatment option as it was shown to be both clinically and cost effective.
SH	Headache Clinics UK	12	Full	209	1	Propanolol has no greater benefit than the other medications listed when you look at the studies.	A summary of the results of the NMA for the clinical evidence are now also provided in the form of evidence statements in both the full guideline (sections 14.3) and appendix K to clarify the evidence the recommendation was based on. This demonstrates that propranolol was ranked as joint second best treatment (with acupuncture and telmisartan).The reduction in migraine days was considered good enough to form a recommendation on, consistent with the criteria applied throughout the guideline. The economic analysis takes into account the mean effect and the uncertainty around the mean. When a distribution around the effectiveness of propranolol was used, the certainty around the cost-effectiveness of this treatment was still reasonable.
SH	Headache Clinics UK	13	Full	212	1	Recommendation for amitriptyline despite it not having a license for headache or migraine and based on consensus and not research evidence. In this case the GDG decided that they could	Thank you for your comment. We have not made a recommendation for the initiation of amitriptyline for people with migraine. The GDG were aware that amitriptyline is commonly used and

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						include it based on "**absence of evidence, not evidence that such treatments are ineffective' Why is this valid here but not in other areas such as Physical therapy or Behavioural approaches?** Another example of inconsistencies in developing recommendations.	recognised the practical implications of the recommendation to use medicines other than amitriptyline. The GDG considered that a person who is well controlled on amitriptyline or other drug should be able to continue to use that drug. The GDG considered that physical therapy and behavioural approaches are not standard methods of treating migraine and therefore provision was not required for people currently using these treatments for migraine. A consistent approach has been taken - research recommendations have been made for further research in all these areas and absence of evidence has not been presumed to be evidence of no benefit. Convincing evidence of no benefit would have resulted in a recommendation not to use a treatment for treatment of people with migraine.
SH	Headache Clinics UK	14	Full	218	13	Another recommendation based on 2 studies of very low quality with an 'expert advisor (not GDG?) and not selected in same way. Inconsistent approach to making recommendation and recommendation based on poor evidence	Thank you for your comment. For the development of the guideline we have followed the same process for all reviews. This involved, searching for the evidence according to the agreed protocol. Where evidence was identified, the developers considered the quality of the evidence (according to the GRADE profile) to form recommendations, using the highest quality evidence available in each review question. In some areas, if no higher quality evidence was available, this may mean that a recommendation is based on 'low' quality evidence.

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							GDG informal consensus was used in areas where evidence was lacking but expert opinion agreed that a recommendation was important. Absence of evidence does not indicate evidence of an absence of effect. In areas where the GDG did not contain sufficient expertise, expert advisors were invited to attend sections of the meeting and provide advice. These experts were not involved in the discussion of recommendations.
SH	Headache Clinics UK	15	Full	243	1	Recommendation based on all studies of which only one says acupuncture is better than sham and then only just. 10 sessions at 2 per week (based on what evidence?) - 1 study and an admitted 'guesstimate' on costs. Inconsistent approach to recommendation.	Thank you for your comment. The recommendations are based on a standard approach of evidence review, grading of quality of evidence review and GDG discussion. After careful review of the evidence it was agreed in development of this guideline that the evidence for acupuncture for tension headache, which was based on three studies with a greater effect size for reduction in headache days without uncertainty (also low quality) as well as some evidence for improving responder rate, headache intensity and quality of life was of sufficient quality to base a recommendation on. The developers agreed that in the absence of evidence for any other treatment for the prophylaxis of tension headache it was important to make this recommendation. The recommendation was worded as 'Consider' rather than 'Offer acupuncture' to reflect the low level of evidence. A suggested frequency of acupuncture sessions has been added to the recommendation, based on the evidence reviewed. The evidence for acupuncture for migraine

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							was compared with the pharmacological treatments in a network meta-analysis in which it was ranked second after topiramate (joint with propranolol and telmisartan) in reduction in migraine days. When the means and standard deviations are considered, acupuncture is ranked second. The direct comparisons demonstrated efficacy for improving responder rate, reducing migraine frequency, improving quality of life and reducing acute medication use. An economic study based on a RCT conducted in the UK showed that acupuncture is cost-effective when compared to no treatment in people with migraine or tension type headache. Although people suffering of tension type headache represented only 5% of the trial population (the remaining 95% were people suffering from migraine), the GDG considered the findings to be applicable to the overall population included in the RCT. The model developed for this guideline was in agreement with the results of the RCT (acupuncture could be cost-effective when the number of sessions is 10 or fewer) but this was based on a population of people with migraine. The GDG agreed the clinical and economic evidence was sufficient to base a recommendation on.
SH	Headache Clinics UK	16	Full	258	15	Why is such a play made of the risks and training practitioners undertake. It is inappropriate, unnecessary as not said of any other practitioners and could be taken as a bias.	Thank you for your comment. We agree and the text has been reworded accordingly to reflect this.
SH	Headache Clinics UK	17	Full	258	15	The GDG says cannot make a recommendation on Manual Therapy despite the fact that the evidence presented was of a similar level to that	Thank you for your comment. **An expert advisor did inform the developers on this area during guideline development. The**

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						for most other treatments and especially acupuncture. They state there is not enough evidence for or against and didn't feel the need to gain further expert opinion as they had with menstrual migraine or suggest as with some medications that patients should be given a full explanation explaining the positives and negatives. The study Manual Therapy and amitriptyline was accepted as valid study and showed Manual Therapy was as good but despite this the GDG feels able to recommend amitriptyline in 13 above but not make a recommendation on Manual Therapy. Another inconsistent approach to developing recommendations	**expert was involved in development of the protocol, confirming inclusion and exclusion of studies for the review, and attended the GDG meeting to talk to the GDG and answer their questions, in the same way as co-opted experts for acupuncture, psychological therapies and menstrual migraine. This is stated in section 22.1.1.** The evidence for manual therapy was not of a similar level to other treatments recommended. . Evidence from intervention reviews throughout the guideline was quality assessed according to the GRADE profile, in which participant blinding is a key factor. The GDG were in agreement that this approach should be applied, and where an active control was possible, this should be considered as the highest level of evidence. The majority of evidence for manual therapies was single blind, with the outcome assessor only blinded, where as the evidence for acupuncture (for example) was based on sham controlled trials (therefore participant blinded). The study comparing manual therapy and amitriptyline (Nelson et al. 1998) was an open label study. The participant numbers were larger in the meta-analysis of the acupuncture studies and there was moderate quality evidence showing benefit. We have not made a recommendation for the initiation of amitriptyline for people with migraine. The GDG were aware that amitriptyline is commonly used and recognised the practical implications of the

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							recommendation to use medicines other than amitriptyline. The GDG considered that a person who is well controlled on amitriptyline or other drug should be able to continue to use that drug. The GDG considered that physical therapy is not a standard method of treating migraine and therefore provision was not required for people currently using these treatments for migraine. A consistent approach has been taken - research recommendations have been made for further research in all these areas and absence of evidence has not been presumed to be evidence of no benefit. In that circumstance we would have considered a recommendation not to use the therapy for treatment of people with migraine.
SH	Headache Clinics UK	18	Full	258	15/16	The TTH study states that the subjects were chronic TTH but the GDG (on an unknown basis) decided that they were probably migraine and thus reduced validity of findings. Yet earlier GDG took a 5% group and said it was probably okay to say this was representative of the whole group and valid. This indicates another inconsistent approach to the use of evidence when developing recommendations.	Thank you for your comment. The study being referred to here is Castien et al. 2011. The GDG agreed that the diagnosis of chronic migraine and chronic tension type headache frequently overlap as per the diagnostic criteria in recommendation 1.2.1. This was the basis for the GDG's decision that the participants could probably have migraine. We assume the 5% group you refer to is that from the Vickers et al. 2004 study which was used in the economic analysis for acupuncture. This study had a group of 95% migraine and 5% tension type headache. Again, the GDG agreed that there is considerable overlap between chronic tension type headache and chronic migraine, and therefore this paper could be extrapolated to

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							either headache type. Applying the same cost assumptions to both primary headache disorders, based on the population in this study, was agreed as appropriate by the GDG. This study was not included in the clinical evidence review.
SH	Headache Clinics UK	19	Full	General		The study also seems to have altered the review of spinal manipulations for tension type headaches (Posadzki and Ernst, 2012), The GDG seems to have different views to Posadski and Ernst (2012) The RCT of Castien (2009), reported significant improvements in frequency of headache and use of medication in favour of manual therapy compared to usual GP care. This was considered a high quality RCT with appropriate randomisation and blinding of outcome assessors. The GDG identified this study as open label (p248, line 25) but this is not accurate as the outcome assessors were blind. Given that many of the recommendations in this review are based on low and very low quality evidence and relatively small numbers this study adds to the quality of manual therapy and must be included,	Thank you for your comment. We agree that the study by Castien et al. 2011 had blinded outcome assessors and the footnote has been amended accordingly to state that this was a single blind study. However, since all outcome measures were patient reported outcome measures, this does not affect the overall quality of the study assessed according to the GRADE profile). The GDG consistently applied the same criteria to all reviews to assess studies, in that, if a form of placebo or active control was possible as a comparator, it should be the basis for making recommendations in preference to comparisons with no active controls. The systematic review of spinal manipulations for tension type headaches (Posadzki and Ernst, 2012) concludes that '*although the evidence for spinal manipulation as a treatment option of tension type headache is mostly positive, it is far from conclusive'.* We have revised the text to read *''Although there is some preliminary evidence to suggest that seeing a practitioner who utilises manual therapies may be of benefit, the GDG decided there was not enough evidence to make a recommendation for or against the use of manual therapies for the prophylactic treatment of tension type headache or migraine'*

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SH	Headache Clinics UK	20	Full	"280	19	Recommendations based on low and very low evidence and one study with confounding factors highlighted in all studies. Another example of an inconsistent approach to developing recommendations when compared to Manual Therapy	Thank you for your comment. For the development of the guideline we have followed the same process for all reviews. This involved, searching for the evidence according to the agreed protocol. Where evidence was identified, the developers considered the quality of the evidence (according to the GRADE profile) to form recommendations, using the highest quality evidence available in each review question. In some areas, if no higher quality evidence was available, this may mean that a recommendation is based on 'low' quality evidence. The recommendation for riboflavin was based on moderate quality evidence. Trimagnesium dicitrate was recommended based on low quality evidence for headache days and frequency. The effect sizes and quality were similar to those of the pharmaceutical treatments recommended. The GDG agreed that this is sufficient evidence to advise people that there may be benefit from these treatments.
SH	Merck Sharp & Dohme UK Ltd	1	NICE	7	4	We suggest that this should be changed as follows: from "For people in whom oral preparations for the acute treatment of migraine…." to "For people in whom oral **tablet** preparations for the acute treatment of migraine…." By including the word 'tablet', this would provide a distinction between this and the oral lyophilisate triptan formulation, which may be a suitable alternative in patients who are experiencing nausea and not tolerating an oral	Thank you for your comment. After careful consideration, the GDG agreed the recommendation should not be changed. The committee considered these to be an oral preparation because they are not absorbed bucally.

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						tablet preparation. This comment applies to text on pages 7 (line 4) and 14 (line 15) of the draft NICE clinical guideline.	
SH	Merck Sharp & Dohme UK Ltd	2	NICE	14	15	Same as above comment concerning text on page 7 (line 4) of the draft NICE clinical guideline.	Thank you for your comment. After careful consideration, the GDG agreed the recommendation should not be changed. The committee considered these to be an oral preparation because they are not absorbed bucally.
SH	Merck Sharp & Dohme UK Ltd	3	NICE	7	8	We suggest that an oral lyophilisate triptan should also be listed as an alternative, in addition to non-oral NSAID or triptan. An oral lyophilisate formulation triptan offers an advantage compared to a conventional tablet formulation in those patients who are experiencing nausea. We suggest it should therefore be listed as a potential alternative alongside non-oral NSAID or triptan (i.e. sub-cutaneous triptan). This comment applies to text on pages 7 (line 8) and 14 (line 19) of the draft NICE clinical guideline.	Thank you for your comment. After careful consideration, the GDG agreed the recommendation should not be changed. The committee considered these to be an oral preparation because they are not absorbed bucally.
SH	Merck Sharp & Dohme UK Ltd	4	NICE	14	19	Same as above comment concerning text on page 7 (line 8) of the draft NICE clinical guideline.	Thank you for your comment. After careful consideration, the GDG agreed the recommendation should not be changed. The committee considered these to be an oral preparation because they are not absorbed bucally.
SH	Merck Sharp & Dohme UK Ltd	5	Full	40	23	We suggest that this should be changed as follows: from "For people in whom oral	Thank you for your comment. After careful consideration, the GDG agreed the

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						preparations for the acute treatment of migraine…." to "For people in whom oral tablet preparations for the acute treatment of migraine…." By including the word 'tablet', this would provide a distinction between this and the oral lyophilisate triptan formulation, which may be a suitable alternative in patients who are experiencing nausea and not tolerating an oral tablet preparation. This comment applies to text on pages 40 (line 23) and 45 (line 10) of the draft Full clinical guideline.	recommendation should not be changed. The committee considered these to be an oral preparation because they are not absorbed bucally.
SH	Merck Sharp & Dohme UK Ltd	6	Full	45	10	Same as above comment concerning text on page 40 (line 23) of the draft Full clinical guideline. *[NCGC pasted:* We suggest that this should be changed as follows: from "For people in whom oral preparations for the acute treatment of migraine…." to "For people in whom oral tablet preparations for the acute treatment of migraine…." By including the word 'tablet', this would provide a distinction between this and the oral lyophilisate triptan formulation, which may be a suitable alternative in patients who are experiencing nausea and not tolerating an oral tablet preparation. This comment applies to text on pages 40 (line 23) and 45 (line 10) of the draft Full clinical guideline.]	Thank you for your comment. After careful consideration, the GDG agreed the recommendation should not be changed. The committee considered these to be an oral preparation because they are not absorbed bucally.

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SH	Merck Sharp & Dohme UK Ltd	7	Full	40	27	We suggest that an oral lyophilisate triptan should also be listed as an alternative, in addition to non-oral NSAID or triptan. An oral lyophilisate formulation triptan offers an advantage compared to a conventional tablet formulation in those patients who are experiencing nausea. We suggest it should therefore be listed as a potential alternative alongside non-oral NSAID or triptan (i.e. sub-cutaneous triptan) This comment applies to text on pages 40 (line 27) and 45 (line 14) of the draft Full clinical guideline.	Thank you for your comment. After careful consideration, the GDG agreed the recommendation should not be changed. The committee considered these to be an oral preparation because they are not absorbed bucally.
SH	Merck Sharp & Dohme UK Ltd	26.07	Full	45	14	Same as above comment concerning text on page 40 (line 27) of the draft Full clinical guideline *[NCGC pasted:* We suggest that an oral lyophilisate triptan should also be listed as an alternative, in addition to non-oral NSAID or triptan. An oral lyophilisate formulation triptan offers an advantage compared to a conventional tablet formulation in those patients who are experiencing nausea. We suggest it should therefore be listed as a potential alternative alongside non-oral NSAID or triptan (i.e. sub-cutaneous triptan) This comment applies to text on pages 40 (line 27) and 45 (line 14) of the draft Full clinical guideline.]	Thank you for your comment. After careful consideration, the GDG agreed the recommendation should not be changed. The committee considered these to be an oral preparation because they are not absorbed bucally.

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SH	Merck Sharp & Dohme UK Ltd	8	NICE	14	8	This section states that "For people who prefer to take only one drug, consider monotherapy with a triptan, an NSAID, aspirin (900 mg) or paracetamol for the acute treatment of migraine if these drugs have not already been tried as monotherapy." This sentence does not make it clear that in cases where one triptan has failed to provide adequate relief, an alternative triptan may be suitable. Evidence from a randomised, placebo-controlled double-blind study has demonstrated that rizatriptan ODT was superior to placebo at providing 2-hour pain free relief and 2-hour pain freedom in the treatment of acute migraine in people who did not respond to treatment with sumatriptan 100 mg. (Ref.1) When looking at the corresponding recommendations and link to evidence in the draft full clinical guideline, the following text is included (page 160, under the sub-section "Other considerations"): **"…failure to respond to a particular triptan may not be indicative that another triptan will also not work, therefore it may be worth considering an alternative triptan if there's no response to the first one".** For additional clarity, we suggest it would be beneficial to include this text in the corresponding section of the NICE clinical guideline (i.e. page 14, at the end of paragraph 1.4.10). Ref 1: Seeburger, J.L. et al (2010) Efficacy and tolerability of rizatriptan for the treatment of acute migraine in sumatriptan non-responders *Cephalalgia* 0(0) 1-11	Thank you for your comment. The GDG agree and we have added an additional recommendation to highlight this (recommendation 1.3.12).

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SH	Merck Sharp & Dohme UK Ltd	9	NICE	16	4	Under the sub-heading "Menstrual-related migraine" this section states that "For menstrual-related migraine that does not respond adequately to acute treatment, consider prophylactic treatment with frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) on the days migraine is expected". We suggest that the following wording which appears in the draft full clinical guideline (page 218, box "recommendations and link to evidence" under the sub-section "Other considerations") should be added to this section of the NICE guideline: "**This treatment is off licence and menstruation needs to be predictable to use this method".**	Thank you for your comment. We agree. The recommendation has been reworded to include that the menstrual related migraine has to be predictable, and a footnote has been added to indicate that this treatment regimen is off license.
SH	Merck Sharp & Dohme UK Ltd	10	Full & NICE	General		As per comment 5 above, page 160 of the full draft guideline acknowledges that response to different triptans may differ. Additionally page 114, line 27 of the full draft guideline states "There are currently seven drugs within this family licensed for alleviating migraine. They differ in their drug interaction, duration of action and side-effects". Nevertheless, both the full and NICE versions of the draft clinical guideline frequently refer to "triptans" as a general group. It may be helpful for both the full and NICE versions of the clinical guideline to make the distinctions between different triptans clearer, in order to reinforce the point that the pharmacokinetic and pharmacodynamics parameters between triptans differ, so non-response to a particular triptan does not necessarily preclude response to a different triptan.	Thank you for your comment. The GDG considered that triptans have a class effect, therefore all were grouped as a class for the review. However, it was acknowledged that response to triptans can differ between individuals and therefore a recommendation has been added to consider using one or more alternative triptans if one is consistently ineffective.
SH	Merck Sharp & Dohme	11	Full &	Gener		It may be helpful if the guideline provides some	Thank you for your comment. We think this is

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	UK Ltd		NICE	al		advice on the most appropriate treatment options in patients in whom triptans are contraindicated.	adequately covered by the alternative options provided in the acute treatment of migraine and acute treatment of cluster headache recommendations.
SH	Merck Sharp & Dohme UK Ltd	12	Full & NICE	General		It may be helpful if the guideline could clarify the criteria for determining whether a treatment should be considered as 'ineffective' or 'unsuitable'. Alternatively the guideline could make clear that that this is outside of the remit of the guideline.	Thank you for your comment. We do not wish to be so prescriptive and we think that it would be up to the healthcare professional to decide according to clinical judgement.
SH	MHRA	1	NICE guideline	13	25	The guidance introduction (p. 8, line 5) states that all 'recommendations apply to adults and young people aged over 12 years unless specifically stated otherwise'. In section 1.4.6 it should be made clear that aspirin should **not** be offered for tension-type headache in individuals aged under 16 years.	Thank you for your comment. A footnote has been added to all recommendations for aspirin to state that it should not be used for people aged under 16 years.
SH	MHRA	2	NICE guideline	14	9	Again, it should be made clear that aspirin is **not** suitable for individuals aged under 16 years for treating the acute pain of migraine	Thank you for your comment. A footnote has been added to all recommendations for aspirin to state that it should not be used for people aged under 16 years.
SH	MHRA	3	NICE guideline	14	16	Paragraph 1.4.13 suggests options if 'oral preparations for the acute treatment of migraine are ineffective or not tolerated'. In many cases neither of these apply; oral preparations are in fact unsuitable because of vomiting that can accompany migraine. Consider substituting 'ineffective' with 'unsuitable'.	Thank you for your comment. We discussed your suggestion with the GDG who considered that the current wording is more appropriate and that 'not tolerated' covers the patient who has excessive vomiting.
SH	MHRA	4	NICE guideline	14	17	The preamble at lines 15–16 makes it sound as if the options in the first bullet are 'for the acute treatment of migraine'. Please consider clarifying that the interventions in the first bullet	Thank you for your comment. The evidence reviewed demonstrated efficacy of these drugs for producing freedom from pain at 2 hours superior to NSAIDs, lidocaine and triptans (one study for each, moderate to very

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						are intended to deal with nausea and vomiting; they are unlikely to affect the acute pain of migraine.	low quality evidence) and freedom from pain at twenty four hours compared to subcutaneous triptans (one study, very low quality evidence), regardless of whether the individual has either nausea or vomiting. This is explained in the full guideline, p166.
SH	MHRA	5	NICE guideline	14	18	The draft guidance suggests 'non-oral preparation of …chlorpromazine'. Chlorpromazine injection is now rarely, if ever, used for the management of acute nausea and vomiting (in the non-palliative setting); chlorpromazine suppositories are also not prescribed in the primary care setting. Please consider removing mention of chlorpromazine so as not to encourage inappropriate use of this drug	Thank you for your comment. The GDG have agreed to remove chlorpromazine from the recommendation.
SH	MHRA	6	NICE guideline	14	18 and footnote 6	It might be incorrect to imply that prochlorperazine injection products do not have marketing authorisation for migraine. The licensed indications for Mercury Pharma's Prochlorperazine Injection include: 'used ... for nausea and vomiting from whatever cause including that associated with migraine ....'	Thank you for your comment. The recommendation for prochlorperazine is for pain relief independent of its effect on nausea and vomiting. As the evidence reviewed demonstrated efficacy of antiemetics for producing freedom from pain at 2 hours superior to NSAIDs, lidocaine and triptans (one study for each, moderate to very low quality evidence) and freedom from pain at twenty four hours compared to subcutaneous triptans (one study, very low quality evidence), regardless of whether the individual has either nausea or vomiting. This is explained in the full guideline, p166.The footnote has been amended to clarify this.
SH	MHRA	7	NICE guideline	14	19	Oral lyophilisates and orodispersible tablets, though oral, might be reasonable alternatives for people suffering from nausea. The text implies that only non-oral preparations should	Thank you for your comment. Lyophilisates and orodispersible tablets were considered as 'oral' in the development of this guideline. This is because they are absorbed through the

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						be used.	stomach and would not be expected to confer advantage in improved absorption when compare to other oral preparations. The wording has therefore not been amended.
SH	MHRA	8	NICE guideline	15	1	Topiramate appears to be recommended as the prophylactic drug of choice. The relevant licensed indication for topiramate states: 'Topiramate is indicated in **adults** for the prophylaxis of migraine headache **after** careful evaluation of possible alternative treatment options.' Topiramate is not indicated for children in the management of migraine.	Thank you for your comment. After careful consideration the GDG have reworded the recommendation to Offer topiramate or propranolol. A statement has also been added stating according to patient preference, comorbidities and risk of adverse events. The footnote states that topiramate is not licensed for those under 18 years.
SH	MHRA	9	NICE guideline	15	12	The MHRA has warned that the use of butterbur can result in serious liver damage and has advised anyone using products containing butterbur to stop their use immediately. No products containing butterbur are licensed in the UK (under the Traditional Herbal Registration scheme).	Thank you for your comment. We agree and were not aware of this at the time of submission, but have now removed butterbur from the recommendation.
SH	MHRA	10	NICE guideline	15	13	Please indicate the licensing status of trimagnesium dicitrate and of riboflavin in the context of migraine prophylaxis. If these interventions are to be retained, please indicate likely adverse effects (e.g. diarrhoea)	Thank you for your comment. At the time of submission trimagnesium dicitrate and riboflavin (400mg) did not have a medical license for migraine prophylaxis. Magnesium salts of citric acid and riboflavin are marketed in the UK as food supplements however the evidence reviewed was only for trimagnesium dicitrate and riboflavin (400mg) .Further details have been added to the section on linking evidence to recommendation.
SH	MHRA	11	NICE guideline	16	4	Neither frovatriptan nor zolmitriptan are licensed for prophylactic treatment in menstrual-related	Thank you for your comment. This recommendation is intended as pre-emptive treatment of menstrual related migraine rather

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						migraine, or in any prophylactic treatment, as stated in the SPC for all triptans. Please consider flagging this in the footnotes.	than conventional prophylactic treatment. The recommendation has been reworded to clarify this, and a footnote has been added to indicate that this treatment regimen is off label.
SH	MHRA	12	NICE guideline	16	16	Among the $5HT_1$ receptor agonists ('triptans') only sumatriptan injection ('Imigran Injection Subject') is licensed for use in cluster headache; the nasal spray does not have marketing authorisation for cluster headache.	Thank you for your comment. A footnote has been added to the recommendation to indicate the current marketing authorisation.
SH	MHRA	13	NICE guideline	17	18	The draft suggests considering 'prophylactic treatment as an adjunct … for people with medication overuse headache'. Please suggest suitable prophylaxis.	Thank you for your comment. The recommendation has been reworded to clarify that this will depend on the underlying headache disorder.
SH	MICPA	1	Full	28	6	This organisation is encouraged by the involvement by NICE in the clinical area of headache. We understand that high quality evidence is sparse and that the committee had great difficulty identifying such evidence to address the review questions. It is understood that the guidance only starts to cover the area and that some would argue that the starting point for optimizing diagnosis, investigation and management is not always well represented by the review questions.	Thank you for your comment. We are limited by the evidence available and have used the expertise of the guideline development group to augment the available evidence. The main focus of the guideline is the diagnosis and management of primary headache disorders which are a primarily clinical diagnosis. The remit for the guideline did not include diagnosis of other conditions causing headache and we have aimed to alert practitioners to symptoms and signs that are likely to merit further evaluation and/or investigation.
SH	MICPA	2	Full	53	3	We welcome the guidance that those with a positive diagnosis of tension type headache, migraine and established cluster do not require neuroimaging. The points in 1.1.1 might easily be divided into acute/emergency presentations (which are of less clinical difficulty to primary and secondary care) and those with more	Thank you for your comment. The recommendation has been reworded to clarify that the individual should be evaluated to determine whether referral or further investigation is required.

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						gradually changing symptoms and signs that might merit investigation (eg prolonged aura not specifically mentioned in the guidance but covered by substantial change in characteristics) . The list however appears extensive enough to allow a clinician to investigate whomever they wish. The expectation of a sinister finding will still be low and therefore it is a mute point if the imaging is to reassure or exclude a sinister cause.	
SH	MICPA	3	Full	54	1	As in 2	Thank you for your comment. The recommendation has been reworded to clarify that the individual should be evaluated to determine whether referral or further investigation is required.
SH	MICPA	4	Full	61	4	Diagnosis is relatively straightforward if following Int Headache Soc guidance and 1.2.1 table. IDMigraine is an exclusive questionnaire (identifies migraine) that leaves most headache sufferers without a diagnosis - including some of those with migraine. There are other tools developed to 'screen' and place the majority in a diagnostic group (not covered by the guidance) but we agree that taking a history is gold standard. It should be noted that clinicians develop their own diagnostic questioning method – many start from stems such as < 15 days per month or >15days per month/ chronic. Then subdivide (eg re chronic <4hrs trigeminal cephalalgias/cluster or > 4 hrs Hemicrania Continua, New Daily Persistent Headache, Chronic Migraine or Chronic Tension Type Headache).Confirmation is using symptom check list and questioning regarding with medication overuse to complete process.	Thank you for your comment. We agree that individual practitioners will use different heuristic approaches when taking a history. The table we have provided allows practitioners to do this.

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SH	MICPA	5	Full	66	1	We also agree that although not mandated, diaries can be useful.	Thank you for your comment.
SH	MICPA	6	Full	73	1	There may be diagnostic uncertainty with those suffering chronic tension type headache who do not have 8 days of migraine but are considered to have frequent migraine features. Might it be best to be consistent with International guidelines	Thank you for your comment. After careful consideration, the GDG agreed that the diagnosis of chronic migraine for this guideline should remain unchanged. The recommendation wording was intended to be more helpful to a generalist in a clinical setting, rather than using the original ICHD-II definitions which were developed with the intention of standardising diagnosis for use in clinical research an in practice.
SH	MICPA	7	Full	90	1 and 2	We welcome the guidance that those with a positive diagnosis of tension type headache, migraine and established cluster do not require neuroimaging. The points in 1.1.1 might easily be divided into acute/emergency presentations (which are of less clinical difficulty to primary and secondary care) and those with more gradually changing symptoms and signs that might merit investigation (eg prolonged aura not specifically mentioned in the guidance but covered by substantial change in characteristics) . The list however appears extensive enough to allow a clinician to investigate whomever they wish. The expectation of a sinister finding will still be low and therefore it is a mute point if the imaging is to reassure or exclude a sinister cause.	Thank you for your comment. The recommendation has been reworded to clarify that the individual should be evaluated to determine whether referral or further investigation is required.
SH	MICPA	8	Full	98	5	If 4% of all GP consulations are for headache is it realistic to expect distribution of written information? Direction to suitable information is reasonable.	Thank you for your comment. The GDG believes this is a local implementation issue. NICE will be publishing implementation tools shortly after the publication of this Guideline which we hope will help with this matter.
SH	MICPA	9	Full	100	3	Might we respectfully remind the committee that intermittent headache (especially migraine)	Thank you for your comment. We agree that the evidence is of low quality in many areas.

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						management is driven by patients seeking better efficacy but tolerability is much more important to matters concerning prevention, especially in chronic headache. Furthermore, clinicians recognise that disability and quality of life are not only improved by less headache days or hours. Reduced severity and duration of headache as well as reduced comordid symptoms can be equally important. Rationalisation of preventative medications and changing to simpler analgesic rescue and using less doses might be the key parameter for some sufferers. It is probably fair to say that the general conclusion is that evidence is poor across all the treatment sections - tension, migraine and cluster.	We agree that the use of treatment options has to be directed by patient needs with a balance between prophylactic and acute treatment choices. The guideline provides recommendations on which treatments have evidence for benefit.
SH	MICPA	10	Full	78	1	Highlighting opiate, often unsuspectingly used in escalating frequency, as one route to analgesic dependant headache is valuable. We also acknowledge other rescue drugs can lead to same problem	Thank you for your comment.
SH	MICPA	11	Full	159 to 160	1,2 and 1	It is interesting that the committee can advise use of triptan with NSAID when there is only limited supporting evidence for sumatriptan, almotriptan and rizatriptan and with limited NSAIDs. Furthurmore, the use of additional antiemetic is recognised as practically important but mode of administration and activity on gastric stasis is not addressed. Clinically important issues for general migraine management such as staging care, timing of doses and modes of administration are not covered by the guidance. Practical differences between triptans are not addressed although it	Thank you for your comment. This recommendation to use triptan with NSAID was based on the evidence from direct comparisons of treatment, and network meta analysis for four outcomes comparing all treatments to each other. The results showed that these combinations of treatments were more clinically and cost effective than taking one drug alone. There are two recommendations in the guideline for the use of anti-emetic 1.3.13 and 1.3.15. These recommend consideration of an

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						is suggested several are tried which may at least in part address the point. It should be remembered that individualising care over a number of attacks and evolving strategy is likely to result in best outcomes.	oral or non-oral antiemetic even in the absence of nausea and vomiting because of the effect of anti-emetic on headache itself. The GDG considered that use of anti-emetics in people with significant nausea and vomiting was part of good medical practice but did not consider that routine addition of anti-emetic was required because of concern about gastric stasis. NICE recommendations do not usually discuss how treatment works or instructions for use that are contained in SPC unless the GDG consider there are issues that need to be highlighted. The issues included in the guideline were decided by the GDG based on the guideline scope. Treatment according to 'stages' was not identified as an issue either at scoping or during guideline development. The GDG however considered that a number of mono- and dual therapies are available; many individuals will already have tried adequate doses of analgesia when they consult and the evidence review indicated superiority of dual therapy over mono-therapy. We agree that individualising care is required and that the treatment strategy will need to be agreed by healthcare professional and patient. A recommendation has been added to consider using one or more alternative triptans if one is consistently ineffective (recommendation 1.3.12).
SH	MICPA	12	Full	173	1	Within acute cluster treatment there were also	Thank you for your comment and for this

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						some controversies. A study re oxygen flow rates is ongoing and will better inform about use of oxygen saturation machines and ambulatory cylinders. It should be remembered that some with cluster also have migraine and open access to unlimited triptans may lead to analgesic dependant complications. There must therefore be an index of suspicion particularly if the symptoms become atypical for such patients.	information.
SH	MICPA	13	Full	179	1	The reality is that frequent pure tension type headache rarely presents even to primary care. Probing is likely to uncover coexisting migraine symptomatology with a possible diagnosis of chronic migraine (note Int Headache Society diagnosis requires minimum of 8 migraine days per month or more).	Thank you for your comment. This detail has been added to the 'other considerations' section of the recommendation.
SH	MICPA	14	Full	208 to 212	1	In chronic migraine clinical practice tolerability drives adherence in sufferers and tricyclics are the most used prescribed drugs for chronic headache and propranolol in episodic migraine (herbs and supplements are commonly used by patients). ARBs have just one small study supporting their use and are not in common usage. Topiramate is notable for its potential for tolerability issues but is said not to induce estradiol metabolism unless at doses of 200mg or more (most are using 100-200mg in clinical practice, why then 1.4.15 suggesting a need to change contraceptive advice in all? In clinical practice Lamotigine is seen as useful in those with troublesome aura. There is no mention in recommendations of SNRI which can be helpful and SSRI which are usually not - both are commonly used to treat comorbid anxiety. The technology appraisal for Botox is due to be	Thank you for your comment. The recommendations for prophylactic treatment of migraine were based on evidence from direct treatment comparisons and a network meta-analysis comparing all treatments to each other. The statement regarding topiramate's effect on hormonal contraception is in agreement with the BNF. We do not have evidence for the dose-dependence of this effect and therefore do not agree the recommendation should be amended. No evidence relevant to the review was identified for lamotrigine, SNRIs or SSRIs therefore no recommendation was made for or against their use. At the time of going out to consultation on the clinical guideline the Final Appraisal Determination for the technology appraisal (TA) of BOTOX had not been issued and

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						finalised within the next few weeks. It seems strange that this, the only licenced agent for chronic migraine, is excluded from this guidance.	therefore was not included within the guideline. Since the publication of the TA we will now cross reference the TA in both the full and NICE versions of the guideline. The TA will also be included as a relevant treatment option within the Headaches pathway of recommendations. This will be available on the NICE website when the clinical guideline is published.
SH	MICPA	15	Full	218	13	The use of frovatriptan and zolmitriptan pedictively to prevent a menstrual migraine is interesting as neither drug has a licence for such use anywhere in the world and the supporting studies required dosing over 6 days. Also menstrually related migraine is defined as migraine starting day -2 to +3. For those starting migraine predictably +2 and +3 they would not have to have regular periods as specified in 15.3.of the guidance.	Thank you for your comment. This recommendation is intended as pre-emptive treatment of menstrual related migraine rather than conventional prophylactic treatment. The recommendation has been reworded to clarify this. Extra detail has been added to the recommendation to clarify the population that this is appropriate for and footnotes have been added to indicate the off license use.
SH	MICPA	16	Full	243	1	It seems strange that consideration for acupuncture is singled out for tension type headache, especially when those with mixed headache are to be labelled chronic migraine and subject to a different management strategy! Note, according to Int HS chronic migraine is defined as more than 15 days per month headache with more than 8 days per month migraine and with no analgesic dependence.	Thank you for your comment. There was evidence that acupuncture may be effective for the prophylactic treatment of tension type headache. After careful consideration of this evidence, and the lack of any other option for tension type headache, the developers agreed that a recommendation should be made for acupuncture for those people with pure tension type headache who did require prophylaxis. The studies included in this review excluded people who had migraine symptoms (for more than one day a month). Acupuncture is also included within the recommendation as an option to consider for

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							people with migraine requiring prophylaxis. Therefore should there be an overlap with migraine in these people, this would remain an effective treatment option.
SH	MICPA	17	Full	243 and 270	1 and 13	Acupuncture and physical therapy may be difficult to study because of a lack of realistic sham. Many studies have been reported over the years and no overall consensus has been reached, often because of methodological issues. As tension type headache rarely presents to primary care – either episodic or chronic, it seems that the target population for acupuncture may not be accessing care. If such patients are seen and reclassified as migraine acupuncture is again not recommended. In practice physical therapies and acupuncture appear to help a cohort of sufferers – at least as part of an integrated package of care. Similarly psychological approaches appear helpful, especially in those with mood and sleep comorbidity.	Thank you for your comment. We acknowledge the issues you raise. We have recommended acupuncture for both tension type headache and migraine based on the evidence reviewed. We agree there is some evidence that indicates psychological and manual therapies could be beneficial for some people, however the evidence reviewed was not strong enough to form a recommendation at this stage. We have therefore made research recommendations for both of these therapies.
SH	MICPA	18	Full	304-6	1	Medication overuse is the elephant in the room for headache in the UK. 'Bridges' used to facilitate abrupt withdrawal with inpatient stays was not for routine recommendation however no consideration was made of outpatient strategies and follow up at 4-8 weeks is likely to be inadequate. These patients need a lot of support in the short term but by 3-4 weeks may have achieved the withdrawal.	Thank you for your comment. The GDG considered the evidence and their own experience of management of medication overuse headache. We agree that these patients may need a lot of support in short term and this is reflected in the wording of the recommendation.
SH	MICPA	19	Full	313-5	1	The committee has considered triptans in pregnancy and must advise. Either we must offer the same acute treatment or not to pregnant ladies. The triptans (sumatriptan has the most evidence but rizatriptan also has a	Thank you for your comment. After careful consideration we have revised this recommendation to be more specific about recommendation of paracetamol as first line treatment and NSAIDS and triptans as second

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						good database) specifically need to be recommended or not.	line treatment (recommendation 1.3.24).
SH	MICPA	20	Full	319	1	The advice on combined contraception and migraine is confusing. Aura has been regarded as an independent risk factor for stroke in younger women. The Int Headache Society had defined migraine with aura as having 3 auras ever. Are the committee are now suggesting that migraine with and without aura should be regarded as an independent risk factor for all women (the exception being women without aura under 35)? Individuals having had 5 migraine headaches ever will now be regarded as having risk factor for stroke. Clearly migraine will be a risk factor considered within the context of the individual's other risk factors. This position does not represent the International consensus and with diagnostic uncertainties for primary care diagnosis of headache could potentially have medicolegal ramifications.  Response to NICE Headache Clinical Gui	Thank you for your comment. We acknowledge that our recommendations in the draft guideline could have been interpreted in a different way than we intended and we have revised our recommendations in this area. We have removed the recommendation on migraine without aura. We have checked the IHCD 11 criteria and it suggests 2 episodes of aura for diagnosis.
SH	Migraine Action	1	Full	General		Our comments are as follows. Migraine Action, wish to advise that in their opinion, in general the clinical evidence referred to in the guidelines is not of particularly high scientific quality. However we do recognise that the guidelines have been developed in order to support patients when in primary care settings with the intention of ensuring that GP's will be able to	Thank you for your comment. The process used for the development of NICE guidelines requires a comprehensive review of the evidence available. We agree that in many areas the evidence available is of low quality and the GRADE approach allows us to be transparent about the quality of the evidence available. The guidelines are directed to all NHS setting where headache is treated but will be more

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						provide an accurate assessment of the patient's headaches. Following that assessment the guidelines are meant to encourage doctors to hold a proper dialogue with patients. Migraine Action believes there needs to be a stronger recommendation made that further scientific data needs to be collected to inform these guidelines in the future with particular reference to the patients voice with regard to primary care setting experiences. There is little attention given in these guidelines to delivering a multi –disciplinary approach to managing migraine. In the opinion of our members and new patients accessing our helpline the guidelines fall some way short of being able to influence primary care practitioners to help patients to manage their symptoms and take better control of their migraine. Whilst Migraine Action acknowledge that these guidelines are aimed at primary care practitioners the reality is that many patients with serious headache do not attend their GP surgery but present in A and E departments initially. As always the patient with serious headache is seeking reassurance that they do not have a brain tumour. However, Migraine Action have real concerns that unless additional training in headache as well as the guidelines are offered at primary care level worried patients will continue to keep returning back to primary care or A and E departments until they are referred for a brain scan. Patients then will continue as they have, to	relevant to the generalist in all settings. We have made a number of research recommendations (see Appendix M) and included patient centred outcomes in all of these. Multidisciplinary care for people with headache was not an issue identified for review during scoping phase of the guideline. NICE guideline recommendations do not generally specify who will deliver care but in the case of headache it is expected that general practitioners, general practitioners with specialist interest , neurologists and specialist nurses will be involved. The guideline also recommends use of acupuncture. We acknowledge that many people with headache attend accident and emergency departments and the recommendations are also directed at this setting. We have specifically included evidence reviews and recommendations for severe headache and when people are unable to tolerate oral medication. An accident and emergency medicine consultant was recruited to the guideline development group to ensure that perspective informed guideline development. We agree that guidelines alone will not

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						manage their migraines themselves with over the counter medication, perhaps never seeing a health professional which can lead to medication overuse leading to chronic daily headache. We are keen to welcome these guidelines initially although we believe further work is required to make them meaningful. Hopefully, one of the outcomes of these guidelines will be that headache will be seen by GP's as a real condition and be given the correct attention.	change the experience of patients and that guidelines need to be supported by implementation measures and health practitioner training. NICE implementation team will support the implementation of the guideline.
SH	Migraine Trust	13.00				The Migraine Trust does not wish to submit any comments at this stage.	Thank you.
SH	RCGP	20.00	NICE	General		The main issues that GPs are faced, with which are covered in these guidelines, which are to check for red flag symptoms, distinguishing between migraines and tension headache, using the findings from headache diaries and management strategies including drug treatment. The use of neuroimaging is usually controlled by neurologists who usually are pretty good at deciding whether there is a need for CT/MRI. It's unlikely that many GPs will choose to prescribe off label drugs in this setting unless supporting evidence is strong and I suspect will continue to refer even if symptoms are suggestive of tension headaches. I am not sure how widely available acupuncture is? Please note one of the RCGP affiliated societies(migraine in primary care advisors) have also responded.	Thank you for your comment. The GDG hope that the guidelines will increase confidence of GPs in making a positive diagnosis of primary headaches so that referral is appropriate. We are required to be specific about the licensing of medicines. Recommendations for use of unlicensed medicines can only be made if there is evidence of benefit. The GDG considered that use of unlicensed medicines does occur but is often not recognised as such e.g. the use of amitriptyline for neuropathic pain and migraine are both unlicensed indications which many GPs are happy to advise.
SH	Royal College of Nursing	21.00	General	General		The Royal College of Nursing welcomes this guideline. It is informative.	Thank you for your comment.
SH	Royal College of Nursing	21.01	General	Gener		The NICE version of the guidelines is easy to	Thank you for your comment.

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				al		follow, useful and will make a good reference guide for healthcare professionals.	
SH	Royal College of Paediatrics and Child Health	23.00				Thank you for inviting the Royal College of Paediatrics and Child Health to comment on the draft guideline, *Headaches*. We have not received any comments for this draft guideline.	Thank you for your comment.
SH	Royal College of Radiologists & British society of neuroradiologists	14.00				The RCR has produced guidelines on imaging in headache. These are included in *iRefer: Making the best use of clinical radiology*. London: The Royal College of Radiologists, 2012. www.irefer.org.uk. The relevant guidelines are N05: Headache: sudden onset, severe; subarachnoid haemorrhage, N06: Headache: chronic and P14: Headache in children (see copy attached). We suggest that the NICE clinical guideline on headaches should be consistent with the iRefer guidelines.	Thank you for your comment. The guideline remit is for the management of primary headache disorders. The GDG considered that these are disorders diagnosed using clinical history and have not made recommendations about routine imaging. The recommendations advise against imaging in primary headache disorders and recommend discussion with a specialist before considering imaging in a patient with first bout of cluster headache.
SH	Salford Primary Care Trust	12.00		general		Although there are various guidelines available which take account of the evidence base for management of migraine and other headache disorders (SIGN, BASH, American Academy of Neurology) the new NICE guidelines are the first to combine the evidence-base for efficacy and diagnosis with an analysis of the economics of various management strategies. This evidence-based National Gold Standard for headache management will help to bring this important group of disorders to the fore, highlighting their importance to commissioners. The new guidelines, however, give advice differing from previous standard practice. Some of this advice, we believe, is based upon opinion rather than evidence of efficacy (acupuncture),	Thank you for your comment. The development of NICE guidance follows a rigorous process to ensure recommendations are based on best evidence. This process, in particular the addition of health economics, may mean that recommendations differ from standard practice. The development of the guideline follows standard NICE processes for all reviews. This involves, searching for the evidence according to the agreed protocol, reviewing the evidence and considering the quality of the evidence (according to the GRADE profile) to form recommendations. The highest quality evidence available in each review question is used to inform the

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						whilst other advice is based on a rather mechanistic dispassionate review of the available data without taking account of the practicalities and sensitivities of clinical management (recommendation of topiramate as first-line treatment for migraine).	recommendation and the strength of the recommendation. . The GDG then use their professional experience and expertise to discuss the evidence review and consider aspects such as practicalities and the reality of clinical practice.
SH	Salford Primary Care Trust	12.01	NICE Guideline	15	1	The recommendation to use Topiramate first line in Migraine treatment The evidence for efficacy is clearly strongest for topiramate, which can, in part, be explained by the number of industry-funded high quality studies which are less numerous for the other older, patent-expired, accepted treatments. Current practice is to use a beta-blocker (usually propranolol) or amitriptyline as first-line agents. Apart from its poor tolerability, topiramate is teratogenic and inhibits the efficacy of oral contraceptives. In a group of patients who are more likely to be young women of childbearing age, this is an issue which has not been included in the economic assessment, although one appreciates the lack of evidence to guide such an assessment. In summary, we believe that the side effect profile of topiramate is such that it should be recommended as a 2nd line treatment. There are, of course, situations when one would choose to use topiramate as 1st line, for example in patients with medication-overuse or in asthmatics with an excessively high BMI. These examples might be expressed as footnotes to avoid complicating the core guidance.	Thank you for your comment. All recommendations were made based on a standard process of reviewing the available evidence and then discussion by the GDG. The GDG discussed at length the issues associated with topiramate, and were aware of concerns. All of these factors were taken into account alongside the effectiveness demonstrated by the clinical and economic evidence and the GDG agreed that it should be recommended first line. The GDG have decided to amend t he recommendation, following concerns raised by stakeholders, to offer topiramate or propranolol as first line options (recommendation 1.3.17). The new recommendation takes into account the limitations of the economic analysis such as the exclusion of adverse events and tolerability in the analysis and recognises the uncertainty over the superior cost-effectiveness of topiramate compared to propranolol. The teratogenic risk and interaction with oral contraceptives is addressed directly in the recommendation.
SH	Salford Primary Care Trust	12.02	NICE Guideli	15	1	The withdrawal of the use of amitriptyline as a preventative agent for migraine and tension type	Thank you for your comment. The GDG have not made a recommendation

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			ne			headache and promotion of gabapentin to a 3rd line agent We do not understand the rationale for withdrawing amitriptyline from mainstream use as a first or second-line agent. Of course, the evidence-base is weaker than for topiramate. However, it tends to be tolerated better than topiramate, has once-daily dosing (resulting in better adherence) and is cheap. Furthermore, the recent AAN recommendation (1) classes it as 'probably effective' with at least 2 class II studies. This is ahead of gabapentin, classified as having inadequate or conflicting data. Our opinion is that amitriptyline should remain as an alternative first-line agent for those in whom propranolol is contraindicated. ref Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012; 17:1337-45.	to withdraw amitriptyline as a preventative agent. There were no RCTs for amitriptyline relevant to the review protocol for the prophylactic treatment of tension type headache or migraine., The GDG were aware that amitriptyline is commonly used and recognised the practical implications of the recommendation to use medicines other than amitriptyline. They decided therefore not to make a recommendation for or against its use. The GDG considered that a person who is well controlled on amitriptyline or other drug should be able to continue to use that drug and a consensus recommendation was made to reflect this for migraine. A research recommendation was also made with the intention of informing future guidance. The GDG agreed the evidence for gabapentin was adequate to recommend as a possible second line agent as there was moderate quality evidence showing efficacy for reduction of migraine frequency and intensity compared to placebo.
SH	Salford Primary Care Trust	12.03	Nice guideline	14	6	Dispersible aspirin 600-900mg is omitted from the recommendations for acute treatment of migraine in combination with a triptan.	Thank you for your comment. There was no available evidence for dispersible aspirin in combination with a triptan for this review, therefore no recommendation was made for or against it's use.
SH	Salford Primary Care Trust	12.04	Nice guidelin	7	1	Domperidone is omitted from the list on non-oral anti-emetics. Domperidone can be given as a	Thank you for your comment. The recommendation includes the treatments for

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			e			suppository. Furthermore, it has a much lower risk of extrapyramidal effects than metoclopramide or phenothiazines.	which evidence was identified and reviewed. The GDG acknowledge that there may be other non-oral antiemetics which may be effective, but without evidence, no recommendation has been made for or against their use.
SH	Salford Primary Care Trust	12.05	Nice guideline	14	3	Acupuncture is recommended without any robust evidence of efficacy for tension type headache. Furthermore, the strength of recommendation for migraine is equivalent to that of other pharmacological treatments which have greater evidence of efficacy. The evidence, at best, appears of low quality, the recommendation appearing to be made on the basis of economic evidence. We wondered whether this was a recommendation to pay for a placebo without stating it as such, certainly for tension type headache. Clearly, this might be useful for some patients, but we did not feel that it was a strong-enough reason to recommend it ahead of amitriptyline, particularly when implementation would be difficult without the commissioning of new services to deliver acupuncture.	Thank you for your comment. The GDG considered that the evidence for treatment of tension headache with acupuncture, was of sufficient quality to base a recommendation on. The evidence was from three studies, each with a sham control, and found a greater effect size for reduction in headache days without uncertainty (also low quality, but no uncertainty in the treatment effect) as well as some evidence for improving responder rate, headache intensity and quality of life. The developers decided that in the absence of evidence for any other treatment for the prophylaxis of tension headache, acupuncture should be recommended. The recommendation was worded as 'Consider' rather than 'Offer acupuncture' to reflect the low level of evidence. The evidence for acupuncture for migraine was compared with the pharmacological treatments in a network meta-analysis in which it was ranked joint second after topiramate (joint with propranolol and telmisartan) in reduction in migraine days. When the means and standard deviations are considered, acupuncture is ranked second. The direct comparisons demonstrated efficacy for improving responder rate, reducing migraine frequency, improving quality of life

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							and reducing acute medication use. An economic study based on a RCT conducted in the UK showed that acupuncture is cost-effective when compared to no treatment in people with migraine or tension type headache. Although people suffering of tension type headache represented only 5% of the trial population (the remaining 95% were people suffering from migraine), the GDG considered the findings to be applicable to the overall population included in the RCT. The model developed for this guideline was in agreement with the results of the RCT (acupuncture could be cost-effective when the number of sessions is 10 or fewer) but this was based on a population of people with migraine. The GDG agreed the clinical and economic evidence was sufficient on which to base a recommendation.
SH	Salford Primary Care Trust	12.06	Nice guideline	15	8	Acupuncture is recommended without any robust evidence of efficacy for tension type headache. Furthermore, the strength of recommendation for migraine is equivalent to that of other pharmacological treatments which have greater evidence of efficacy. The evidence, at best, appears of low quality, the recommendation appearing to be made on the basis of economic evidence. We wondered whether this was a recommendation to pay for a placebo without stating it as such, certainly for tension type headache. Clearly, this might be useful for some patients, but we did not feel that it was a strong-enough reason to recommend it ahead of amitriptyline, particularly when implementation would be difficult without the commissioning of new services to deliver	Thank you for your comment. The GDG considered that the evidence for treatment of tension headache with acupuncture, was of sufficient quality to base a recommendation on. The evidence was from three studies, each with a sham control, and found a greater effect size for reduction in headache days without uncertainty (also low quality, but no uncertainty in the treatment effect) as well as some evidence for improving responder rate, headache intensity and quality of life. The developers decided that in the absence of evidence for any other treatment for the prophylaxis of tension headache, acupuncture should be recommended. The recommendation was worded as 'Consider'

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						acupuncture.	rather than 'Offer acupuncture' to reflect the low level of evidence. The evidence for acupuncture for migraine was compared with the pharmacological treatments in a network meta-analysis in which it was ranked joint second after topiramate (joint with propranolol and telmisartan) in reduction in migraine days. When the means and standard deviations are considered, acupuncture is ranked second. The direct comparisons demonstrated efficacy for improving responder rate, reducing migraine frequency, improving quality of life and reducing acute medication use. An economic study based on a RCT conducted in the UK showed that acupuncture is cost-effective when compared to no treatment in people with migraine or tension type headache. Although people suffering of tension type headache represented only 5% of the trial population (the remaining 95% were people suffering from migraine), the GDG considered the findings to be applicable to the overall population included in the RCT. The model developed for this guideline was in agreement with the results of the RCT (acupuncture could be cost-effective when the number of sessions is 10 or fewer) but this was based on a population of people with migraine. The GDG agreed the clinical and economic evidence was sufficient on which to base a recommendation.
SH	Salford Primary Care Trust	12.07	Full guideline	232-243		Prophylactic Non-pharmacological Management of Primary Headaches with Acupuncture (Ch 21	Thank you for your comment. We acknowledge that the lay out of these two chapters may cause some confusion.

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						p232-243) The layout in the full guideline is confusing: The table of recommendations at the end of this chapter, which follows the section on migraine, only concerns tension type headache, whilst the recommendation for acupuncture in migraine is within the chapter concerning the pharmacological treatment	Acupuncture was reviewed for the prophylactic treatment of migraine therefore is relevant to both of these chapters. Cross references to the alternate chapter were provided to direct readers to the other relevant sections.
SH	Salford Primary Care Trust	12.08	Nice guideline	15	12	Butterbur is recommended, but is currently an unregulated herbal product about which the MHRA issued a serious warning in January 2012(2). Pyrrolizidine alkaloids found in the butterbur root extract can cause liver failure. Until there is a regulatory body giving advice about which preparations are safe, this should not be recommended. Ref http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Herbalmedicines/Herbalsafetyupdates/Allherbalsafetyupdates/CON140849	Thank you for your comment. We agree and were not aware of this at the time of submission, but have now removed butterbur from the recommendation.
SH	Salford Primary Care Trust	12.09				Telmisartan is recommended ahead of Lisinopril. There is one randomised double-blind study of Lisinopril in the treatment of migraine, which demonstratedefficacy(3). Given the significantly higher cost of 28 days' treatment with a drug which is still under patent (£17 for telmisartan 80mg; £1.11 forLisinopril 20mg) andhas a black triangle status in the BNF (V63, March 2012), we don't see how the recommendation is justified.	Thank you for your comment. We agree. Telmisartan has now been removed from the recommendation. No evidence relevant to the review protocol was identified for Lisinopril (crossover studies were excluded from the review, therefore the Schrader et al. study was excluded). No recommendation was made for or against it's use. A recommendation was made to state that if someone was already receiving an effective form of prophylaxis, it should not be stopped. Lisinopril has now been included as an example in the full guideline.

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						Ref Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ. 2001;322(7277):19-22.	
SH	Salford Primary Care Trust	12.10	Nice guideline	7	2	The use of an initial triptan at lowest acquisition cost is not discussed at all in the document. There is a big price difference between the generic triptans and branded and yet this does not seem to have been considered.	Thank you for your comment. After careful consideration the GDG decided to amend the recommendation to take into account the cost of different triptans (recommendation 1.3.12)
SH	Salford Primary Care Trust	12.11				We hope that our comments will be taken into account and should be very pleased to hear any comments from the GDG in response.	Thank you for your comment.
SH	Salford Primary Care Trust	12.12	Full	General		Our comments are as follows: The new NICE guidelines are the first to combine the evidence-base for efficacy and diagnosis with an analysis of the economics of various management strategies. This evidence-based National Gold Standard for headache management will help to bring this important group of disorders to the fore, highlighting their importance to commissioners.	Thank you for your comment.
SH	Salford Primary Care Trust	12.13	Full	General		Our comments are as follows: The new guidelines, give advice differing from previous standard practice. Some of this advice appears to be based upon opinion rather than evidence of efficacy e.g. acupuncture, whilst other advice is based on a rather mechanistic dispassionate review of the available data without taking account of the practicalities and sensitivities of clinical management e.g. recommendation of topiramate as first-line	Thank you for your comment. A consistent approach has been taken to developing recommendations in all areas - all recommendations were made based on a standard process of reviewing the available evidence and then discussion by the GDG. The recommendations for acupuncture were made on the basis of clinical evidence of effectiveness of moderate quality supported

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						treatment for migraine.	by the economic evidence. The GDG discussed at length the issues associated with topiramate, and were aware of potential concerns about its use.. All of these factors were taken into account alongside the effectiveness demonstrated by the clinical and economic evidence and the GDG agreed that it should be recommended first line. The recommendation has been amended following concerns raised by stakeholders to offer topiramate or propranolol.
SH	Salford Primary Care Trust	12.14	Full	44	35-36	Our comments are as follows with regard to point 1.4.8: Acupuncture is recommended without any robust evidence of efficacy for tension type headache. Furthermore, the strength of the recommendation for acupuncture in migraine is portrayed as equivalent to that of other pharmacological treatments which have greater evidence of efficacy. The evidence, at best, appears of low quality, the recommendation appearing to be made on the basis of economic evidence. We wondered whether this was a recommendation to pay for a placebo without stating it as such, certainly for tension type headache. Clearly, this might be useful for some patients, but we did not feel that it was a strong-enough reason to recommend it ahead of amitriptyline, particularly when implementation would be difficult without commissioning new services to deliver acupuncture.	Thank you for your comment. After careful review of the evidence it was agreed in development of this guideline that the evidence for acupuncture for tension headache, which was based on three studies with a greater effect size for reduction in headache days without uncertainty (also low quality) as well as some evidence for improving responder rate, headache intensity and quality of life was of sufficient quality to base a recommendation on. The developers agreed that in the absence of evidence for any other treatment for the prophylaxis of tension headache, this was important to include. The recommendation was worded as 'Consider' rather than 'Offer acupuncture' to reflect the low level of evidence. The evidence for acupuncture for migraine was compared with the pharmacological treatments in a network meta-analysis in which it was ranked joint second after topiramate (joint with propranolol and telmisartan) in reduction in migraine days. When the means and standard deviations are

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							considered, acupuncture is ranked second. The direct comparisons demonstrated efficacy for improving responder rate, reducing migraine frequency, improving quality of life and reducing acute medication use. An economic study based on a RCT conducted in the UK showed that acupuncture is cost-effective when compared to no treatment in people with migraine or tension type headache. Although people suffering of tension type headache represented only 5% of the trial population (the remaining 95% were people suffering of migraine), the GDG considered the findings to be applicable to the overall population included in the RCT. The model developed for this guideline was in agreement with the results of the RCT (acupuncture could be cost-effective when the number of sessions is 10 or fewer) but this was based on a population of migraine sufferers. The GDG agreed the clinical and economic evidence was sufficient to base a recommendation on.
SH	Salford Primary Care Trust	12.15	Full	45	2-3	Our comments are as follows with regard to point 1.4.9: Aspirin is omitted - dispersible aspirin 600-900mg is omitted from the recommendations for acute treatment of migraine in combination with a triptan.	Thank you for your comment. There was no available evidence for dispersible aspirin in combination with a triptan for this review, therefore no recommendation was made for or against its use.
SH	Salford Primary Care Trust	12.16	Full	45	12-13	Our comments are as follows with regard to point 1.4.13: Domperidone is omitted from the list on non-oral anti-emetics. Domperidone can be given as a suppository. Furthermore, it has a much lower risk of extrapyramidal effects than metoclopramide or phenothiazines.	Thank you for your comment. No evidence was identified relevant to this review for non-oral domperidone therefore no recommendation was made for or against its use. The GDG also considered that because domperidone acts peripherally, it would not

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							have the same anti-migraine effects (leading to pain relief) of metoclopramide and prochlorperazine which justified their recommendation.
SH	Salford Primary Care Trust	12.17	Full	45	19-22	Our comments are as follows with regard to point 1.4.15: The recommendation to use topiramate as a first line in migraine treatment - the evidence for efficacy is clearly strongest for topiramate, which can, in part, be explained by the number of industry-funded high quality studies which are less numerous for the other older, patent-expired, accepted treatments. Current practice is to use a beta-blocker (usually propranolol) or amitriptyline as first-line agents. Apart from its poor tolerability, topiramate is teratogenic and inhibits the efficacy of oral contraceptives. In a group of patients who are more likely to be young women of childbearing age, this is an issue which has not been included in the economic assessment, although one appreciates the lack of evidence to guide such an assessment. In summary, we believe that the side effect profile of topiramate is such that it should be recommended as a 2nd line treatment. There are, of course, situations when one would choose to use topiramate as 1st line, for example in patients with medication-overuse or in asthmatics with an excessively high BMI. These examples might be expressed as footnotes to avoid complicating the core guidance.	Thank you for your comment. After careful consideration, the GDG have decided to amend the recommendation to state: 'Offer topiramate or propranolol (recommendation 1.3.17). The new recommendation takes into account the limitations of the economic analysis such as the exclusion of adverse events and tolerability in the analysis and recognises the uncertainty over the superior cost-effectiveness of topiramate compared to propranolol.
SH	Salford Primary Care Trust	12.18	Full	45	25-27	Our comments are as follows with regard to point 1.4.17: The withdrawal of the use of amitriptyline as a preventative agent for migraine and tension type headache and promotion of gabapentin to a 3rd	Thank you for your comment. For the development of the guideline we have followed the same process for all reviews. This involved, searching for the evidence according to the agreed protocol. Where

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						line agent. The rationale for withdrawing amitriptyline from mainstream use as a first or second-line agent is unclear. The evidence-base is weaker than for topiramate but it tends to be tolerated better than topiramate, has once-daily dosing (resulting in better adherence) and is cheap. Furthermore, the recent AAN recommendation classes it as 'probably effective' with at least 2 class II studies. This is ahead of gabapentin, classified as having inadequate or conflicting data. Amitriptyline should remain as an alternative first-line agent for those in whom propranolol is contraindicated. Again acupuncture is recommended without any robust evidence of efficacy for tension type headache (see comment 3 above). Telmisartan is recommended ahead of lisinopril. There is one randomised double-blind study of lisinopril in the treatment of migraine, which demonstrated efficacy. The justification for the recommendation of telmisartan is unclear given the significantly higher cost of 28 days' treatment with a drug which is still under patent (£17 for telmisartan 80mg; £1.11 for Lisinopril 20mg) and has a black triangle status in the BNF (V63, March 2012).	evidence was identified, the developers considered the quality of the evidence (according to the GRADE profile) to form recommendations, using the highest quality evidence available in each review question. In some areas, if no higher quality evidence was available, this may mean that a recommendation is based on 'low' quality evidence. There were no RCTs for amitriptyline relevant to the review protocol for the prophylactic treatment of tension type headache or migraine, therefore the developers did not make a recommendation for or against its use. The GDG acknowledged that amitriptyline was widely used and considered to be effective, therefore a consensus recommendation was made to reflect this for migraine. The GDG agreed that the evidence for acupuncture for tension headache, which was based on three studies with a good effect size for reduction in headache days as well as some evidence for improving responder rate, headache intensity and quality of life was of sufficient quality to base a recommendation on. The developers agreed that in the absence of evidence for any other treatment for the prophylaxis of tension headache, this was important to include. The recommendation was worded as 'Consider' rather than 'Offer acupuncture' to reflect the low level of evidence. After careful consideration the GDG have agreed to remove telmisartan from the

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							recommendation.
SH	Salford Primary Care Trust	12.19	Full	45	28-30	Our comments are as follows with regard to point 1.4.17: Butterbur is recommended, but is currently an unregulated herbal product about which the MHRA issued a serious warning in January 2012. Pyrrolizidine alkaloids found in the butterbur root extract can cause liver failure. Until there is a regulatory body giving advice about which preparations are safe, this should not be recommended.	Thank you for your comment. We agree and were not aware of this at the time of submission, but have now removed butterbur from the recommendation.
SH	Salford Primary Care Trust	12.20	Full	232-243		Our comments are as follows with regard to Chapter 21, Prophylactic Non-pharmacological Management of Primary Headaches with Acupuncture: The layout of the chapter in the full guideline is confusing. The table of recommendations at the end of this chapter, which follows the section on migraine, only concerns tension type headache, whilst the recommendation for acupuncture in migraine is within the chapter concerning the pharmacological treatment.	Thank you for your comment. We acknowledge that the lay out of these two chapters may cause some confusion. Acupuncture was reviewed for the prophylactic treatment of migraine therefore is relevant to both of these chapters. Cross references to the alternate chapter were provided to direct readers to the other relevant sections.
SH	Samantha Dickinson Brain Tumour Trust	28.00	FULL	15	30	We note that the guidance includes young people from the age of 12 upwards. We notice that no specific coverage is given to dealing with young people in the guidance. As an organisation, we represent the interests of both adults and children, but in this context, we focus our response on young people aged 12-18, because of our work on symptoms in this age group. Our view is that young adults are a group which is poorly served when it comes to referral for suspected brain tumours. One study has shown that 59% of teenagers with brain tumours visited their GP four or more times with symptoms	Thank you for your comment and this information. The GDG considered this carefully and have made some changes to recommendations in light of this comment. The recommendation is not intended as a definitive list of the symptoms of brain tumour and other conditions but intended to alert healthcare practitioners when not to diagnose a primary headache disorder. We have added reference to Headsmart campaign and the NICE guideline on Referral for Suspected Cancer to the Full guideline; and also added a footnote to the recommendation to alert healthcare professionals to the Referral for Suspected cancer guideline.

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						before they were referred. Young people are typically inexperienced users of the healthcare system. They may lack confidence in attending their GP and in expressing their health concerns clearly. During adolescence, we are aware of brain tumour patients whose symptoms are attributed to exam stress or puberty. We feel that health care professionals should give particular attention to young people presenting with signs and symptoms that could indicate cancer, such as a headache. We would like to highlight three resources not referred to in the guidance, that relate to young people with possible symptoms of brain tumours, including headache. Firstly, an evidence-based clinical guideline, endorsed by RCPCH, accredited by NHS Evidence and produced with funding from ourselves: 'Diagnosis of brain tumours in Children', available online at: http://www.headsmart.org.uk/Additional-information-for-healthcare-professionals/guideline-and-implementation/. This makes recommendations about practice in relation to initial consultations, referral for imaging, imaging and feedback, aspects of which should, we suggest, be considered in your guideline. Secondly, the HeadSmart campaign, which is based on the above guideline, and promotes awareness of the signs and symptoms of brain tumours in children and young adults and is aimed at parents, young people and health	

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						professionals: www.headsmart.org.uk. This is led by a partnership between Samantha Dickson Brain Tumour Trust, Royal College of Paediatrics and Child Health, University of Nottingham and The Health Foundation. The website is designed to provide a decision support tool to doctors, guiding them about when to review, when to refer and when to reassure. The section on headache on persistent/recurrent headache is recommended and can be found here: http://www.headsmart.org.uk/Young-people/healthcare-professionals/Persistent-%7C-recurrent-headache/	
SH	Samantha Dickinson Brain Tumour Trust	28.01		41	12	Within recommendation 1.1.1, there are several other symptoms or features that we would suggest particular attention be paid where these present alongside a headache. This is based on the evidence based guideline 'Diagnosis of children with brain tumours' mentioned above and specifically relates to those aged 12-18, although in many cases we consider they will be relevant in adults also. These features or symptoms are as follows: Persistent headaches that wake the patient from sleep Persistent headaches that occur on waking Confusion or disorientation occurring with a headache An abnormal neurological examination Persistent / recurrent vomiting Abnormal balance / walking / co-ordination Abnormal eye movements Blurred or double vision Fits or seizures Behaviour change	Thank you for your comment. The GDG re-considered the recommendation taking your comment into account. The recommendation is not intended as a definitive list of the symptoms of brain tumour and other conditions but intended to alert healthcare practitioners when not to diagnose a primary headache disorder. We have added reference to the Headsmart campaign and the NICE guideline on Referral for Suspected cancer to the Full guideline; and also added a footnote to the recommendation to alert healthcare professionals to the Referral for Suspected cancer guideline.

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						Delayed or arrested puberty Diabetes insipidus Abnormal growth Further details about each of these can be found within the guideline (from www.headsmart.org.uk/Additional-information-for-healthcare-professionals/guideline-and-implementation/) or from the HeadSmart website homepage (www.headsmart.org.uk)	
SH	Samantha Dickinson Brain Tumour Trust	28.02		41	27	The 'Diagnosis of children with brain tumours' guideline notes that "Delayed diagnosis has been associated with failure to reassess a child [up to age 18] with migraine or tension headache when the headache character changes." We conclude that this point, made here in your guidance, is important.	Thank you for your comment.
SH	St Jude Medical UK Ltd	11.00	Full	General		It is noted that there is no mention of surgical therapies such as occipital nerve stimulation (ONS) or deep brain stimulation (DBS) that are indicated in a small percentage of carefully selected headache patients including chronic migraine & cluster headache. Both of these surgical neuromodulation therapies are currently offered by specialist select tertiary centres in the UK. Whilst this guideline's principle target audience may be directed at primary & secondary care St Jude Medical believe that surgical neuromodulation therapies should be included even if it is a very brief overview in the non-pharmacological section or as a dedicated surgical section. Inclusion would insure uniformity of comprehensive clinical knowledge and parity with previously published NICE guidelines that mention surgical options e.g. NICE MS Guideline	Thank you for your comment. The guidelines are directed to all NHS setting where headache is treated but will be more relevant to the generalist in all settings. Both of these treatments were also undergoing intervention procedure assessments when the Headaches guideline began development, therefore it was agreed that these treatments were outside of the remit of the guideline. The occipital nerve stimulation for intractable headache Interventional Procedure has been suspended pending devices receiving CE marking for intractable headache: http://guidance.nice.org.uk/IP/699 The IP for deep brain stimulation for intractable trigeminal autonomic cephalalgias has now been issued http://publications.nice.org.uk/deep-brain-

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							stimulation-for-intractable-trigeminal-autonomic-cephalalgias-ipg381 This has been added to the related NICE guidance in the full guideline (p17).
SH	The College of Chiropractors	22.00	Full	general		We wish to draw attention to a recent systematic review of spinal manipulations for tension type headaches (Posadzki and Ernst, 2012), the conclusions of which differed significantly from those of the Guideline Development Group (GDG). Posadski and Ernst (2012) found the RCT of Castien et al (2011), which reported significant improvements in frequency of headache and use of medication in favour of manual therapy compared to usual GP care, to be a high quality RCT which had appropriate randomisation and blinding of outcome assessors (Jadad score = 4). The lack of blinding of participants, not unexpected considering the nature of the treatments under comparison, was considered by Posadski and Ernst (2012) to constitute a low risk of bias in this study. We submit that the evidence in support of manual therapy is of significantly better quality than concluded by the GDG in its draft document and this issue should be reviewed. Furthermore, in its recommendations in relation to manual therapies (p258), the draft guideline reaches its conclusions with reference to risks being 'severe when they do occur'. We suggest it is inappropriate to consider this as a contributory factor in compiling the recommendation because the GDG presented no supporting evidence of severe risks in relation to manual therapy, nor did they consider the relative risks of manual therapy and NSAID	Thank you for your comment. We agree that the study by Castien et al. 2011 had blinded outcome assessors and the footnote has been amended accordingly to state that this was a single blind study. However, since all outcome measures were patient reported outcome measures, this does not affect the overall quality of the study (assessed according to the GRADE profile).The GDG consistently applied the same criteria to all reviews to assess studies, in that, if a form of placebo or active control was possible as a comparator, it should be the basis for making recommendations in preference to comparisons with no active controls. The systematic review of spinal manipulations for tension type headaches (Posadzki and Ernst, 2012) concludes that '*although the evidence for spinal manipulation as a treatment option of tension type headache is mostly positive, it is far from conclusive'.* We have revised the text to read *"Although there is some preliminary evidence to suggest that seeing a practitioner who utilises manual therapies may be of benefit, the GDG decided there was not enough evidence to make a recommendation for or against the use of manual therapies for the prophylactic treatment of tension type headache or migraine'*

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						use for example. Note that Castien et al (2011) stated that 'no adverse events were reported in both intervention groups.' On the basis that the evidence in support of manual therapy is of significantly better quality than concluded in the draft document and that the evidence of any risk was apparently not reviewed, we suggest the final guideline should recommend manual therapy delivered by a trained practitioner, such as a chiropractor, osteopath or physiotherapist, as a valid option for TTH care. **Refs:** Castien RF, van der Windt DAWM, Grooten A, Dekker J. Effectiveness of manual therapy for 12 chronic tension-type headache: a pragmatic, randomised, clinical trial. Cephalalgia. 2011; 13 31(2):133-143. *(Guideline Ref ID CASTIEN2011)* Posadzki P, Ernst E. Spinal manipulations for tension-type headaches: A systematic review of randomized controlled trials. Complementary Therapies in Medicine. 2012; 20:232-239.	
SH	UK Clinical Pharmacy Association	29.00		Tension type headache		Simple analgesics are the only pharmacological treatment listed for this condition. I note amitriptyline was considered but rejected but the GDG as they felt the risk outweighed the benefit. However, this decision seems to be based on one study alone and has not included other evidence for the use of this drug in this condition. As simple analgesics may be ineffective, contraindicated or not tolerated, and hence guidance on second line pharmacological treatments or next steps following acupuncture	Thank you for your comment. After careful review of the evidence it was agreed in development of this guideline that the only evidence for amitriptyline for prophylaxis of tension headache was from low quality evidence for reduction in headache days with considerable uncertainty from one study. This is weaker evidence than that for acupuncture which was based on three studies with a greater effect size for reduction in headache days without uncertainty (also low quality) as

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						are lacking in the guideline.	well as some evidence for improving responder rate, headache intensity and quality of life. The developers considered that pure tension type headache requiring prophylaxis is rare, and clinical examination is likely to uncover coexisting migraine and a possible diagnosis of chronic migraine and therefore use of prophylactic treatments for migraine. The evidence for acupuncture for prophylaxis of tension headache was stronger than that for amitriptyline, therefore this was recommended as an option for people with tension type headache who did require prophylaxis.
SH	UK Clinical Pharmacy Association	29.01		Treatment of migraine		The draft NICE guidance recommends where pharmacological therapy is indicated, that a combination of a triptan plus paracetamol/NSAID is offered as first line treatment. The GDG state the reason for this is because the combinations were superior in outcomes in clinical studies compared to either type of treatment used alone. This is different to guidance/evidence in other national guidance e.g. SIGN which states simple analgesics e.g. paracetamol/NSAIDs are first line, followed by a triptan if these have been ineffective at treating migraine. This is also the usual steps that would be followed in clinical practice/primary care as the primary steps in managing migraine, depending on what patients have self-treated with. Most GPs will start with optimised doses of simple analgesics before using a triptan as second line treatment. Providing a combination first line may be providing unnecessary treatment if migraine can be managed with optimised simple analgesics and can avoid patients being exposed to unnecessary drug	Thank you for your comment. This recommendation was based on the evidence from direct comparisons of treatment, and network meta analysis for four outcomes comparing all treatments to each other. The results showed that these combinations of treatments were more clinically and cost effective than taking one drug alone. The developers considered that some people may prefer to take one drug only and therefore a second recommendation was included to recommend options for these people.

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						treatment and potential side-effects if not required. NICE suggest that if oral treatment for acute migraine is not effective or tolerated iv/non-oral antiemetic should be considered. It should be made clear this is only where nausea and vomiting are severe enough to warrant this. If oral treatments are ineffective or not tolerated this may not be due to N+V. Administration by the IV route is not commonly available/practiced in primary care. SIGN recommend rectal as an option and this seems more appropriate than IV.	Thank you for your comment. The evidence reviewed suggested that antiemetics are effective for pain relief, regardless of whether the patient has either nausea or vomiting. This guideline is intended to cover all healthcare settings and will include accident and emergency settings where these preparations are used. Including the term 'or other non-oral preparation' would include rectal as a possible preparation.
SH	UK Clinical Pharmacy Association	29.02		Prophylaxis for migraine		Although both propranolol and topiramate are licensed for prophylaxis of migraine, propanalol is often used first line because it is marginally better tolerated than topiramate. I would also question the evidence for inclusion of gabapentin and telmisartan over conventional therapy (as well as stating unlicensed).	Thank you for your comment. After careful consideration, the GDG have decided to amend the recommendation to state: 'Offer topiramate or propranolol (recommendation 1.3.17). The new recommendation takes into account the limitations of the economic analysis such as the exclusion of adverse events and tolerability in the analysis and recognises the uncertainty over the superior cost-effectiveness of topiramate compared to propranolol. A statement has also been added stating according to patient preference, comorbidities and risk of adverse events. After careful consideration the GDG do not agree that gabapentin should be removed from the recommendation. The evidence for reduction in migraine frequency and intensity was of moderate quality and considered strong enough to include with the other recommended treatments. However, after

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							consideration, telmisartan has been removed from the recommendation.
SH	United Chiropractic Association	16.00	Full	General		As reported by the NICE guidelines, tension type headaches (TTH) is the most common form of headache (HA) in the general population. The three most common types of primary HA are migraine, TTH, and cervicogenic headache (CGH), (1). The HA continuum theory suggests that what had been thought to be separate types of HA many overlap – migraine could convert to chronic TTH, episodic TTH could convert to chronic HA. Movement abnormalities or dysfunctions in the cervical spine are significant contributing factors to primary HA's (2). In light of the above facts it seems that an investigation by the GDG into the effectiveness of manual therapy to be crucial for the NICE guidelines. In its current form the GDG have made some major omissions and therefore their conclusions are misrepresented. A systematic review from the Duke University Evidence Based Practice Centre in 2001 summarised the research evidence to that time concerning the safety and effectiveness of various physical and behavioural treatments for CGH and TTH. It found that, even on a narrow definition given by the I.H.S, CGH was one of the most common forms of HA, similar in prevalence to migraine, and that the one physical or behavioural treatment with proven effectiveness was manipulation. Manipulation had two distinct advantages over use of medication, first it targeted the source of the pain rather than control of symptoms, and	Thank you for your comment. Cervicogenic headache was outside of the scope of this guideline and, therefore these papers were excluded from the reviews. The study by Boline et al. 1995 was excluded because it did not match the inclusion criteria for the review as it reported outcomes at less than three months (see Appendix N, Excluded studies, section N. 1. 14.1, Pg 554).

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						second it was safe with fewer side effects. The GDG report, using MEDLINE, and Embase for the clinical literature search. The trials reported in this review in brief: • The trial on TTH concluded that manual therapy was clinically effective (3). • The trial on migraine concluded the SMT (spinal manipulative therapy) may be more clinically effective than placebo (4). • The trial between amytriptyline and combined treatment remained inconclusive, (5) • The study identified comparing spinal manipulation and soft tissue therapy with low power laser placebo for TTH; concluded no difference between SMT and placebo(6). The thrust of the usefulness of SMT is based on the above accounts with the conclusion that the evidence reviewed was of low to very low quality and that there was not enough evidence to form a recommendation for or against manual therapies for prophylaxis of TTH or migraine. No mention is made of CGH. However, some pertinent omissions have been made which would provide further evidence to support the effectiveness of manual therapy in the management of primary HA's. Most systematic reviews found evidence of the	

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						efficacy of SMT for the management of HA's, as reported in the Spine Journal 2011 (11)94-95 (7). 3 trials which were omitted from the guidelines include: • The study by Boline et al 1995, reported that chiropractic manipulation was superior to amytriptyline in reducing headache frequency and severity (8). • Jull et al 2002 – reported manipulative therapy and exercise can reduce the symptoms of CGH and the effects are maintained (9). • Haas et al 2010 – report on the latest trial on chiropractic spinal manipulative therapy, overall conclusions; Clinically important differences between the chiropractic treatment group and light massage group were observed for the CGH pain and disability (10). Also, the risk associated with manual therapy needs some clarification. The internal forces sustained by the vertebral artery during spinal manipulation therapy have been reviewed in a paper by Symons et al, (11). The conclusions were that the forces of a single	

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						typical (high-velocity, low-amplitude) SMT thrust are very unlikely to mechanically disrupt the V.A. Conservative estimates of the risk of a stroke associated with SMT are on the order of 1 per million (12). The latest high quality study on stroke risk reported no evidence of excess risk of VBA stroke associated with chiropractic care compared to primary care (13). **References:** **1.** Nilsson-Grunnet N Epidemiology of Headache. Eur J Chiro (2002) (49) : 33-35 **2.** David Chapman Smith. The Chiropractic Report, (2010) Vol 24 No 5. 3. Castien R.F et al. Effectiveness of Manual Therapy for chronic Tension type Headache: A pragmatic, randomised, clinical trial. Cephalalgia. 2011; 31 (2): 133-143 4. Tuchin P.J et al. A randomised control trial of chiropractic spinal manipulative therapy for migraine. JMPT. 2000; 23 (2): 91-95 5. Nelson.C.F et al. The Efficacy of spinal manipulation, amytriptyline and the combination of both therapies for the prophylaxis of migraine headaches.	

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						JMPT. 1998; 21(8): 511-519. 6. Bove.G, Nilsson.N. Spinal Manipulation in the treatment of episodic tension-type headache: A randomised controlled trial. JAMA. 1998; 280 (18): 1576-1579. 7. Haas. M. et al. Letters to the editor. Spine. 2011 (11): 94-95 8. Boline.P et al. Spinal Manipulation VS Amytriptyline for the treatment of chronic Tension Type Headaches. JMPT. 1995 (18): 148-154. 9. Jull et al. A Randomized controlled Trial of exercise and Manipulative Therapy for Cervicogenic Headache. Spine. 2002; 27(17): 1835-1843. 10. Haas.M et al. Dose Response and Efficacy of Spinal Manipulation of chronic Cervicogenic Headache: A pilot randomised controlled trial. Spine. 2010; (10): 117-128. 11. Symons. B.P et al Internal Forces Sustained by the Vertebral Artery Curing Spinal Manipulative Therapy: JMPT. 2001; (25) 504-510. 12. Hurwitz.E.L et al. Manipulation and mobilisation of the cervical spine: A	

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						systematic review of the literature. Spine. 1996: (21) 1746-1760. 13. Cassidy.J.D et al. Risk of Vertebro Basilar Stroke and Chiropractic Care: Results of a population based case control and case cross over study. Spine. 2008; (33): 176-183	

These organisations were approached but did not respond:

Action for ME
Air Products PLC
Airedale NHS Trust
Alder Hey Children's NHS Foundation Trust
Anglo European College of Chiropractic
Association of British Neurologists
Association of Clinical Pathologists
Association of Optometrists
BOC Healthcare
Bradford District Care Trust
Brain and Spine Foundation
British Association of Behavioural and Cognitive Psychotherapies
British Infection Association
British Medical Acupuncture Society
British Medical Association
British Medical Journal
British National Formulary
British Paediatric Mental Health Group
British Paediatric Neurology Association
British Pain Society
British Psychological Society
British Society for Stereotectic and Functional Neurosurgery
Cambridge University Hospitals NHS Foundation Trust
Camden Link
Capsulation PPS
Care Quality Commission (CQC)
Central & North West London NHS Foundation Trust

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Cerebra
Chartered Society of Physiotherapy
Children's Brain Tumour Research Centre
Citizens Commission on Human Rights
Cochrane Pain, Palliative Care and Supportive Care Group
Coeliac UK
College of Emergency Medicine
Commission for Social Care Inspection
Community District Nurses Association
Department for Communities and Local Government
Department of Health, Social Services and Public Safety Northern Ireland
Derriford Hospital
Dorset Primary Care Trust
East and North Hertfordshire NHS Trust
Equalities National Council
Faculty of Occupational Medicine
Faculty of Sport and Exercise Medicine
Federation of Ophthalmic and Dispensing Opticians
General Chiropractic Council
George Eliot Hospital NHS Trust
Gloucestershire Hospitals NHS Foundation Trust
Gloucestershire LINk
Great Western Hospitals NHS Foundation Trust
H & R Healthcare Limited
Hammersmith and Fulham Primary Care Trust
Health Protection Agency
Health Quality Improvement Partnership
Healthcare Improvement Scotland
Hindu Council UK
Hull and East Yorkshire Hospitals NHS Trust
Humber NHS Foundation Trust
Independent Healthcare Advisory Services
Integrity Care Services Ltd.
International Brain Tumour Alliance
International Neuromodulation Society
Joint Royal Colleges Ambulance Liaison Committee
KCARE
King's College London
Lambeth Community Health
Lancashire Care NHS Foundation Trust
Leeds Primary Care Trust (aka NHS Leeds)
Leeds Teaching Hospitals NHS Trust
Liverpool Community Health
Liverpool Primary Care Trust

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Lothian University Hospitals Trust
Luton and Dunstable Hospital NHS Trust
McTimoney Chiropractic Association
Medicines and Healthcare products Regulatory Agency
Medtronic
Medtronic International Trading Sarl
Menarini Pharma U.K. S.R.L.
Ministry of Defence
Musculoskeletal Association of Chartered Physiotherapists
National Clinical Guideline Centre
National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health
National Collaborating Centre for Women's and Children's Health
National Council for Osteopathic Research
National Hospital for Neurology & Neurosurgery
National Institute for Health Research Health Technology Assessment Programme
National Institute for Health Research
National Migraine Centre
National Patient Safety Agency
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
Neuromodulation Society of UK & Ireland
NHS Bournemouth and Poole
NHS Clinical Knowledge Summaries
NHS Connecting for Health
NHS Direct
NHS Pathways
NHS Plus
NHS Sheffield
NHS South of England
NHS Warwickshire Primary Care Trust
NHS Worcestershire
NICE TLOC GDG
Norfolk and Norwich University Hospital
North Midlands Regional Headache Clinic
North Tees and Hartlepool NHS Foundation Trust
Nottingham City Hospital
OUCH
Pain Concern
Pain UK
Paracetamol Information Centre
PERIGON Healthcare Ltd
Pfizer
Pharmametrics GmbH

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Public Health Wales NHS Trust
Roche Diagnostics
Royal Berkshire NHS Foundation Trust
Royal College of Anaesthetists
Royal College of General Practitioners in Wales
Royal College of Midwives
Royal College of Obstetricians and Gynaecologists
Royal College of Ophthalmologists
Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition
Royal College of Pathologists
Royal College of Physicians
Royal College of Psychiatrists
Royal College of Surgeons of England
Royal National Institute of Blind People
Royal Pharmaceutical Society
Royal Society of Medicine
SCHOOL AND PUBLIC HEALTH NURSES ASSOCIATION
Scottish Intercollegiate Guidelines Network
Sheffield Childrens Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Social Care Institute for Excellence
Social Exclusion Task Force
Society and College of Radiographers
Society for Acute Medicine
Society of British Neurological Surgeons
South Asian Health Foundation
South East Coast Ambulance Service
South West Yorkshire Partnership NHS Foundation Trust
Sussex Partnership NHS Foundation Trust
TACT
Teva UK
The Association for Clinical Biochemistry
The Rotherham NHS Foundation Trust
The Walton Centre for Neurology and Neurosurgery
University Hospital Birmingham NHS Foundation Trust
Welsh Government
Welsh Institute of Chiropractic
Welsh Scientific Advisory Committee
West Herts Hospitals NHS Trust
Western Cheshire Primary Care Trust
Western Health and Social Care Trust
Wirral University Teaching Hospital NHS Foundation Trust

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Wirrall Community NHS Trust
Worcestershire Acute Hospitals Trust
York Hospitals NHS Foundation Trust

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