

Neuroimaging for the Evaluation of Chronic Headaches

An Evidence-Based Analysis

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List of Abbreviations

CI	Confidence interval(s)
MAS	Medical Advisory Secretariat
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SROC	Summary receiver operating characteristic

Executive Summary

Objective

The objectives of this evidence based review are:

- i) To determine the effectiveness of computed tomography (CT) and magnetic resonance imaging (MRI) scans in the evaluation of persons with a chronic headache and a normal neurological examination.
- ii) To determine the comparative effectiveness of CT and MRI scans for detecting significant intracranial abnormalities in persons with chronic headache and a normal neurological exam.
- iii) To determine the budget impact of CT and MRI scans for persons with a chronic headache and a normal neurological exam.

Clinical Need: Condition and Target Population

Headaches disorders are generally classified as either primary or secondary with further sub-classifications into specific headache types. Primary headaches are those not caused by a disease or medical condition and include i) tension-type headache, ii) migraine, iii) cluster headache and, iv) other primary headaches, such as hemicrania continua and new daily persistent headache. Secondary headaches include those headaches caused by an underlying medical condition. While primary headaches disorders are far more frequent than secondary headache disorders, there is an urge to carry out neuroimaging studies (CT and/or MRI scans) out of fear of missing uncommon secondary causes and often to relieve patient anxiety.

Tension type headaches are the most common primary headache disorder and migraines are the most common severe primary headache disorder. Cluster headaches are a type of trigeminal autonomic cephalalgia and are less common than migraines and tension type headaches. Chronic headaches are defined as headaches present for at least 3 months and lasting greater than or equal to 15 days per month. The International Classification of Headache Disorders states that for most secondary headaches the characteristics of the headache are poorly described in the literature and for those headache disorders where it is well described there are few diagnostically important features.

The global prevalence of headache in general in the adult population is estimated at 46%, for tension-type headache it is 42% and 11% for migraine headache. The estimated prevalence of cluster headaches is 0.1% or 1 in 1000 persons. The prevalence of chronic daily headache is estimated at 3%.

Neuroimaging

Computed Tomography

Computed tomography (CT) is a medical imaging technique used to aid diagnosis and to guide interventional and therapeutic procedures. It allows rapid acquisition of high-resolution three-dimensional images, providing radiologists and other physicians with cross-sectional views of a person's anatomy. CT scanning poses risk of radiation exposure. The radiation exposure from a conventional CT scanner may emit effective doses of 2-4mSv for a typical head CT.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a medical imaging technique used to aid diagnosis but unlike CT it

does not use ionizing radiation. Instead, it uses a strong magnetic field to image a person's anatomy. Compared to CT, MRI can provide increased contrast between the soft tissues of the body. Because of the persistent magnetic field, extra care is required in the magnetic resonance environment to ensure that injury or harm does not come to any personnel while in the environment.

Research Questions

1. What is the effectiveness of CT and MRI scanning in the evaluation of persons with a chronic headache and a normal neurological examination?
2. What is the comparative effectiveness of CT and MRI scanning for detecting significant intracranial abnormality in persons with chronic headache and a normal neurological exam?
3. What is the budget impact of CT and MRI scans for persons with a chronic headache and a normal neurological exam.

Research Methods

Literature Search

Search Strategy

A literature search was performed on February 18, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January, 2005 to February, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established.

Inclusion Criteria

- Systematic reviews, randomized controlled trials, observational studies
- Outpatient adult population with chronic headache and normal neurological exam
- Studies reporting likelihood ratio of clinical variables for a significant intracranial abnormality
- English language studies
- 2005-present

Exclusion Criteria

- Studies which report outcomes for persons with seizures, focal symptoms, recent/new onset headache, change in presentation, thunderclap headache, and headache due to trauma
- Persons with abnormal neurological examination
- Case reports

Outcomes of Interest

Primary Outcome

- Probability for intracranial abnormality

Secondary Outcome

- Patient relief from anxiety
- System service use
- System costs
- Detection rates for significant abnormalities in MRI and CT scans

Summary of Findings

Effectiveness

One systematic review, 1 small RCT, and 1 observational study met the inclusion and exclusion criteria. The systematic review completed by Detsky, et al. reported the likelihood ratios of specific clinical variables to predict significant intracranial abnormalities. The RCT completed by Howard et al., evaluated whether neuroimaging persons with chronic headache increased or reduced patient anxiety. The prospective observational study by Sempere et al., provided evidence for the pre-test probability of intracranial abnormalities in persons with chronic headache as well as minimal data on the comparative effectiveness of CT and MRI to detect intracranial abnormalities.

Outcome 1: Pre-test Probability.

The pre-test probability is usually related to the prevalence of the disease and can be adjusted depending on the characteristics of the population. The study by Sempere et al. determined the pre-test probability (prevalence) of significant intracranial abnormalities in persons with chronic headaches defined as headache experienced for at least a 4 week duration with a normal neurological exam. There is a pre-test probability of 0.9% (95% CI 0.5, 1.4) in persons with chronic headache and normal neurological exam. The highest pre-test probability of 5 found in persons with cluster headaches. The second highest, that of 3.7, was reported in persons with indeterminate type headache. There was a 0.75% rate of incidental findings.

Likelihood ratios for detecting a significant abnormality

Clinical findings from the history and physical may be used as screening test to predict abnormalities on neuroimaging. The extent to which the clinical variable may be a good predictive variable can be captured by reporting its likelihood ratio. The likelihood ratio provides an estimate of how much a test result will change the odds of having a disease or condition. The positive likelihood ratio (LR+) tells you how much the odds of having the disease increases when a test is positive. The negative likelihood ratio (LR-) tells you how much the odds of having the disease decreases when the test is negative.

Detsky et al., determined the likelihood ratio for specific clinical variable from 11 studies. There were 4 clinical variables with both statistically significant positive and negative likelihood ratios. These included: abnormal neurological exam (LR+ 5.3, LR- 0.72), undefined headache (LR+ 3.8, LR- 0.66), headache aggravated by exertion or valsalva (LR+ 2.3, LR- 0.70), and headache with vomiting (LR+ 1.8, and LR- 0.47). There were two clinical variables with a statistically significant positive likelihood ratio and non significant negative likelihood ratio. These included: cluster-type headache (LR+ 11, LR- 0.95), and headache with aura (LR+ 12.9, LR- 0.52). Finally, there were 8 clinical variables with both statistically non significant positive and negative likelihood ratios. These included: headache with focal symptoms, new onset headache, quick onset headache, worsening headache, male gender, headache with nausea, increased headache severity, and migraine type headache.

Outcome 2: Relief from Anxiety

Howard et al. completed an RCT of 150 persons to determine if neuroimaging for headaches was anxiolytic or anxiogenic. Persons were randomized to receiving either an MRI scan or no scan for investigation of their headache. The study population was stratified into those persons with a Hospital Anxiety and Depression scale (HADS) > 11 (the high anxiety and depression group) and those < 11 (the low anxiety and depression) so that there were 4 groups:

Group 1: High anxiety and depression, no scan group

Group 2: High anxiety and depression, scan group

Group 3: Low anxiety and depression, no scan group

Group 4: Low anxiety and depression, scan group

Anxiety

There was no evidence for any overall reduction in anxiety at 1 year as measured by a visual analogue scale of 'level of worry' when analysed by whether the person received a scan or not. Similarly, there was no interaction between anxiety and depression status and whether a scan was offered or not on patient anxiety. Anxiety did not decrease at 1 year to any statistically significant degree in the high anxiety and depression group (HADS positive) compared with the low anxiety and depression group (HADS negative).

There are serious methodological limitations in this study design which may have contributed to these negative results. First, when considering the comparison of 'scan' vs. 'no scan' groups, 12 people (16%) in the 'no scan group' actually received a scan within the follow up year. If indeed scanning does reduce anxiety then this contamination of the 'no scan' group may have reduced the effect between the groups resulting in a non significant difference in anxiety scores between the 'scanned' and the 'no scan' group. Second, there was an inadequate sample size at 1 year follow up in each of the 4 groups which may have contributed to a Type II statistical error (missing a difference when one may exist) when comparing scan vs. no scan by anxiety and depression status. Therefore, based on the results and study limitations it is inconclusive as to whether scanning reduces anxiety.

Outcome 3: System Services

Howard et al., considered services used and system costs a secondary outcome. These were determined by examining primary care case notes at 1 year for consultation rates, symptoms, further investigations, and contact with secondary and tertiary care.

System Services

The authors report that the use of neurologist and psychiatrist services was significantly higher for those persons not offered a scan, regardless of their anxiety and depression status ($P < 0.001$ for neurologist, and $P = 0.033$ for psychiatrist)

Outcome 4: System Costs

System Costs

There was evidence of statistically significantly lower system costs if persons with high levels of anxiety and depression (Hospital Anxiety and Depression Scale score > 11) were provided with a scan ($P = 0.03$ including inpatient costs, and 0.047 excluding inpatient costs).

Comparative Effectiveness of CT and MRI Scans

One study reported the detection rate for significant intracranial abnormalities using CT and MRI. In a cohort of 1876 persons with a non acute headache defined as any type of headache that had begun at least 4 weeks before enrolment Sempere et al. reported that the detection rate was 19/1432 (1.3%) using CT and 4/444 (0.9%) using MRI. Of 119 normal CT scans 2 (1.7%) had significant intracranial abnormality on MRI. The 2 cases were a small meningioma, and an acoustic neurinoma.

Summary

The evidence presented can be summarized as follows:

Pre-test Probability

Based on the results by Sempere et al., there is a low pre-test probability for intracranial abnormalities in persons with chronic headaches and a normal neurological exam (defined as headaches experienced for a minimum of 4 weeks). The Grade quality of evidence supporting this outcome is very low.

Likelihood Ratios

Based on the systematic review by Detsky et al., there is a statistically significant positive and negative likelihood ratio for the following clinical variables: abnormal neurological exam, undefined headache, headache aggravated by exertion or valsalva, headache with vomiting. Grade quality of evidence supporting this outcome is very low.

Based on the systematic review by Detsky et al. there is a statistically significant positive likelihood ratio but non statistically significant negative likelihood ratio for the following clinical variables: cluster headache and headache with aura. The Grade quality of evidence supporting this outcome is very low.

Based on the systematic review by Detsky et al., there is a non significant positive and negative likelihood ratio for the following clinical variables: headache with focal symptoms, new onset headache, quick onset headache, worsening headache, male gender, headache with nausea, increased headache severity, migraine type headache. The Grade quality of evidence supporting this outcome is very low.

Relief from Anxiety

Based on the RCT by Howard et al., it is inconclusive whether neuroimaging scans in persons with a

chronic headache are anxiolytic. The Grade quality of evidence supporting this outcome is low.

System Services

Based on the RCT by Howard et al. scanning persons with chronic headache regardless of their anxiety and/or depression level reduces service use. The Grade quality of evidence is low.

System Costs

Based on the RCT by Howard et al., scanning persons with a score greater than 11 on the High Anxiety and Depression Scale reduces system costs. The Grade quality of evidence is moderate.

Comparative Effectiveness of CT and MRI Scans

There is sparse evidence to determine the relative effectiveness of CT compared with MRI scanning for the detection of intracranial abnormalities. The Grade quality of evidence supporting this is very low.

Economic Analysis

Ontario Perspective

Volumes for neuroimaging of the head i.e. CT and MRI scans, from the Ontario Health Insurance Plan (OHIP) data set were used to investigate trends in the province for Fiscal Years (FY) 2004-2009.

Assumptions were made in order to investigate neuroimaging of the head for the indication of headache. From the literature, 27% of all CT and 13% of all MRI scans for the head were assumed to include an indication of headache. From that same retrospective chart review and personal communication with the author 16% of CT scans and 4% of MRI scans for the head were for the sole indication of headache. From the Ministry of Health and Long-Term Care (MOHLTC) wait times data, 73% of all CT and 93% of all MRI scans in the province, irrespective of indication were outpatient procedures.

The expenditure for each FY reflects the volume for that year and since volumes have increased in the past 6 FYs, the expenditure has also increased with a pay-out reaching 3.0M and 2.8M for CT and MRI services of the head respectively for the indication of headache and a pay-out reaching 1.8M and 0.9M for CT and MRI services of the head respectively for the indication of headache only in FY 08/09.

Cost per Abnormal Finding

The yield of abnormal finding for a CT and MRI scan of the head for the indication of headache only is 2% and 5% respectively. Based on these yield a high-level estimate of the cost per abnormal finding with neuroimaging of the head for headache only can be calculated for each FY. In FY 08/09 there were 37,434 CT and 16,197 MRI scans of the head for headache only. These volumes would generate a yield of abnormal finding of 749 and 910 with a CT scan and MRI scan respectively. The expenditure for FY 08/09 was 1.8M and 0.9M for CT and MRI services respectively. Therefore the cost per abnormal finding would be \$2,409 for CT and \$957 for MRI. These cost per abnormal finding estimates were limited because they did not factor in comparators or the consequences associated with an abnormal reading or FNs. The estimates only consider the cost of the neuroimaging procedure and the yield of abnormal finding with the respective procedure.

Background

Objective of Analysis

The following are the main objectives of this analysis:

- iv) To determine the effectiveness of computed tomography (CT) and magnetic resonance imaging (MRI) scans in the evaluation of persons with a chronic headache and a normal neurological examination.
- v) To determine the comparative effectiveness of CT and MRI scans for detecting significant intracranial abnormalities in persons with chronic headache and a normal neurological exam.
- vi) To determine the budget impact of CT and MRI scans for persons with a chronic headache and a normal neurological exam.

Clinical Need and Target Population

Description of Chronic Headaches

Headache disorders are generally classified as either primary or secondary disorders with further sub-classifications into specific headache types.(1) Primary headache disorders include i) tension-type headache, ii) migraine, iii) cluster headache, and iv) other primary headaches, such as hemicrania continua and new daily persistent headache.(2) Unlike primary headache disorders, secondary headache disorders are attributed to an underlying medical condition.(1) While primary headache disorders are far more frequent than secondary headache disorders, there is an urge to carry out neuroimaging studies (CT and/or MRI scans) out of fear of missing uncommon secondary causes (3) and often to relieve patient anxiety.

Tension type headaches are the most common primary headache disorder. They are characterized by a bilateral pressing or tightening pain of mild to moderate intensity. Persons with tension type headache also may experience sensitivity to noise.(1)

Migraines are the most common severe primary headache disorder. They are recurrent manifesting in attacks lasting 4-72 hours in duration. They are characterized by a unilateral pulsating pain that builds up over time and is of moderate to severe intensity. It can be accompanied by nausea and/or vomiting, and/or sensitivity to light, and/or sound.(1)

Cluster headaches are a type of trigeminal autonomic cephalalgia. Cluster headaches are less common than tension type or migraine headaches and are characterized by severe attacks of unilateral pain in the trigeminal area of the head. The pain is often experienced in one or a combination of areas including orbital, supraorbital, or temporal regions. The attacks start and end abruptly lasting 15 minutes to 3 hours. Persons experiencing cluster headaches may experience background headaches between attacks which may have migraine-like features.(1)

Chronic headaches are defined as headaches present for at least 3 months and lasting greater than or equal to 15 days per month.(2) The chronic nature of the headache happens over a period of time and as such many persons may at one time receive a neuroimaging scan to rule out a secondary headache disorder (personal communication, clinical expert, March 29-2010).

The International Classification of Headache Disorders (ICHD) states that for most secondary headaches the characteristics of the headache are poorly described in the literature and for those headache disorders where it is well described there are few diagnostically important features.(2) The ICHD gives the following criteria for secondary headaches:

- A. Headache with one (or more) of the following characteristics and fulfilling criteria C and D.
- B. Another disorder known to be able to cause headache has been demonstrated
- C. Headache occurs in close temporal relation to the other disorder and/or there is other evidence of a causal relationship
- D. Headache is greatly reduced or resolves within 3 months (may be shorter for some disorders) after successful treatment or spontaneous remission of causative disorder.

The characteristics noted in point A above are not listed in the ICHD document.

Secondary Headaches are attributed to the following causes:

- i) head and/or neck trauma
- ii) cranial or cervical vascular disorder
- iii) non vascular intracranial disorder
- iv) substance or its withdrawal
- v) infection
- vi) disorder of homeostasis,
- vii) Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinus, teeth, mouth or other facial or cranial structures
- viii) psychiatric disorder

Neuroimaging is used to detect secondary headaches attributed to intracranial abnormalities including ii) cranial or cervical vascular disorders or iii) non vascular intracranial disorders.

Burden of Illness

The global prevalence of headache in general in the adult population is estimated at 46%, for tension-type headaches it is 42%, and 11% for migraine headache.(4) The estimated prevalence of cluster headaches is 0.1% or 1 in 1000 persons. (1) The prevalence of chronic daily headache is estimated at 3%. (4)

System Impact

You et al, (5)determined the indications for computed tomography and magnetic resonance imaging in Ontario. They studied 11,824 CT and 11,867 MRI scans from a random sample of 40 hospitals in Ontario. Hospital sampling was stratified by region and hospital teaching status. The publication reports that of the 11,824 CT scans completed, 3930 (33%) were of the head and 1055 (26.8%) of these were for the indication of headache. Because the CT scans were done for more than one indication the actual proportion of CT scans done solely for the purpose of headache was 16% (unpublished data, personal correspondence with the author, April 29, 2010). Similarly, 4038 (34%) of all MRI scans were head scans of which 523 (13%) were for the indication of headache. However, similar to CT scans, the MRI scans were requested for multiple indications and the actual proportion of MRI scans done solely for the purpose of headache was estimated to be 4%. (unpublished data, personal communication with author, April 29, 2010).

Of the neurimaging scans done of the head less than 2% of CT scans and up to 5% of MRI scans done solely for the indication of headache revealed a treatable intracranial abnormality. You et al. (5) suggest that while negative scans are valuable for ruling out disease, persons with a very low pretest probability

for an intracranial abnormality could be reassured by their healthcare provider without performing a CT or MRI scan.

Neuroimaging

In this report neuroimaging will refer solely to CT or MRI scanning.

Computed Tomography

Computed tomography (CT) is a medical imaging technique used to aid diagnosis and to guide interventional and therapeutic procedures.(6) It uses ionizing radiation to produce high-resolution three-dimensional images of a person's anatomy. CT examinations are non-invasive although an intravenous contrast agent is sometimes required to enhance the images. (6) Radiation exposure occurs with every CT scan and the amount of radiation depends on which part of the body is being scanned. For a typical head CT, a CT scanner may emit radiation doses of 2-4 millisieverts (mSv). (6)

Ionizing radiation is a part of Canada's environment (7). The amount of natural background radiation that each Canadian receives each year is between 2 and 4 MSv. (8)

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a medical imaging technique used to aid diagnosis but unlike CT it does not use ionizing radiation. Instead, it uses a strong magnetic field to image a person's anatomy. Compared to CT, MRI can provide increased contrast between the soft tissues of the body. MRI scanners are classified as high field strength (with magnetic fields greater than 1.0Tesla (T)) or mid/low field strength (with magnetic fields less than 1.0T). Because of the persistent magnetic field, extra care is required in the magnetic resonance environment to ensure that injury or harm does not come to any personnel while in the MRI environment.(9)

Previous Research

Three systematic reviews have been completed on neuroimaging for the evaluation of headache (see Table 1).(1;10;11) Each systematic review determined the pre-test probability (prevalence) of detecting a treatable intracranial abnormality in persons with headache disorders. Similar pre-test probabilities were reported across all three systematic reviews.

Table 1: Systematic reviews on neuroimaging for the evaluation of headache

Author	Search Dates	Studies	Pre-test Probability of detecting a treatable intracranial abnormality.
Frishberg, 1994(10)	1974-1991	13 prospective 4 retrospective	Migraine-0.4% (4/897) Any Headache-2.4% (43/1825) §Any Headache-0.4% (3/725)
US Headache Consortium 2000(11)	1966-1998	6 prospective 22 retrospective	Migraine-0.2% Tension- 0% Unspecified with normal neurological exam-0%-6.7%
Scottish Intercollegiate Guidelines Network, 2008(1)	2000-2007	*1 systematic review †1 RCT ‡1 prospective 2 retrospective	Migraine-0.4% Tension-0.8% Cluster-5% Undefined-3.7%

* Systematic review by US Head Consortium., 2000, (11)

†RCT by Howard et al. (12)

‡Observational study by Sempere et al. (13)

§ Estimate determined without results from 2 studies.

Frishberg

The systematic review completed by Frishberg (10) searched the medical literature from 1974-1991 and included data from 13 prospective and 4 retrospective studies. The systematic review answered the following question: What is the usefulness of neuroimaging in evaluating headache patients?

The authors determined the probability of detecting an intracranial abnormality in two headache categories, i) migraine and ii) any headache. Nine studies (7 prospective and 2 retrospective) providing a sample size of 897 persons contributed data to the probability estimate for migraine headache disorder. Sixty-four per cent (64%) of the sample size for this estimate was derived from 2 retrospective studies. Four intracranial abnormalities (0.4%), 3 tumours and 1 arterio-venous malformation, were detected among the 897 persons with migraine headache disorder. The authors noted that of these 4 intracranial abnormalities, 2 persons had a history of seizures, 1 person had an untreatable tumour, and 1 tumour was most likely incidental to the migraine because the classical migraine persisted after the tumour was removed.

Eight studies (5 prospective, 2 retrospective, and 1 mixed design) providing a sample size of 1825 contributed data to the probability estimate for the category of 'any headache'. Thirty per cent (30%) of the sample size for this estimate was derived from 2 retrospective studies. Of the 1825 persons, 43 intracranial abnormalities (2.4%) were detected. In their analysis, the authors eliminated 2 large studies, one prospective study by Laffey et al., (14) (n=595) and one retrospective study by Baker et al., (15) (n=505), which were found to have a 500% higher rate of significant pathological findings when compared with 2 moderately larger prospective studies that by Weingarten et al., (16) and Mitchell et al. (17). In doing so, the case finding rate dropped from 43/1824 (2.4%) to 3/725 (0.4%) for persons with 'any headache'.

Frishberg (10) points out several limitations to the studies included in this systematic review including: small sample size, neuroimaging was done without contrast agent, studies were designed to look at brain changes in persons with migraine and not to look for intracranial pathology, studies used first generation CT scanners which the author suggested would lead to a higher false negative rate of intracranial abnormalities, and the studies were done in tertiary care facilities on persons referred by a neurologist and/or a neurosurgeon which may skew the frequency of intracranial abnormalities upwards. Finally, all

types of headaches were included in the study populations including those in which the medical history gave a suspicion for an intracranial abnormality.

Based on the results of this systematic review, Frishberg (10) concluded that:

- i) The routine use of neuroimaging is not warranted in adult patients with recurrent headaches defined as migraine, including those with visual aura, no recent change in headache pattern, no history of seizures, and no other focal neurological signs or symptoms.
- ii) CT or MRI may be indicated in persons with atypical headache patterns, a history of seizures, or focal neurological signs or symptoms.
- iii) The role of CT and MRI in the evaluation of persons with headaches that are not consistent with migraine cannot be defined due to insufficient evidence.

U.S. Headache Consortium

The systematic review completed by The United States (U.S.) Headache Consortium (11) searched the medical database from 1966-1998 and included 6 prospective and 22 retrospective studies. This systematic review answered 3 questions:

- i) What findings in the history and physical examination are helpful in identifying which patients have significant intracranial abnormalities?
- ii) What is the frequency of significant secondary causes of non-acute headache as detected by CT or MRI in persons with non-acute headache and a normal neurological examination?
- iii) What is the relative ability of CT and MRI to detect significant intracranial lesions among persons with non-acute headache?

The authors obtained 28 studies from their literature search. Based on the levels of evidence reported by Holleman and Simel (11), all studies received a grade IV level of evidence, defined as studies which did not meet the criteria for level III evidence. Level III evidence was defined as studies with an independent, blind comparison with a 'gold standard' among non-consecutive patients suspected of having the target condition.

Likelihood ratios for signs and symptoms found on history and physical examination were determined from the data obtained from 8 studies (see Table 2). Of these, both the positive and negative likelihood ratios for abnormal neurological exam (3.0, 95% CI 2.3-4.0; 0.70, 95% CI 0.52, 0.93 respectively) and any neurological sign or symptom (1.1, 95% CI 1.05, 1.2; 0.47, 95% CI 0.25, 0.89 respectively) were significant. Regarding the likelihood ratios for neurological symptoms (see Table 2) some symptoms had statistically significant positive likelihood ratios but not negative ratios while the converse was true for other symptoms. This made it difficult to use with confidence some symptoms as a predictor of an intracranial abnormality as absence or presence of the symptom could not always rule out or rule in the probability of an intracranial abnormality.

Table 2: Likelihood ratios for signs and symptoms from history and physical examination

Findings	Number of Studies	n	LR + (95 % CI)	LR- (95% CI)
Abnormal neurological exam	5	568	3.0 (2.3-4.0)	0.70 (0.52-0.93)
Any neurological sign or symptom	2	1461	1.1 (1.05, 1.2)	0.47 (0.25, 0.89)
			6.0 (4.7-7.8)	0 (0-7.9)
Neurological Symptoms				
Rapidly increasing headache frequency	1	350	12 (3.1, 48)	0.73 (0.46, 1.2)
History of headache causing awakening from sleep	2	450	98 (10-960)	0.72 (0.45, 1.1)
			1.7 (0.81-3.7)	0.78 (0.51, 1.2)
History of dizziness or lack of coordination	1	350	49 (3.4, 710)	0.86 (0.64, 1.2)
History of subjective numbness or tingling	1	350	49 (3.4, 710)	0.86 (0.64-1.2)
Headache worse with valsalva manoeuvre	1	100	2.3 (1.1, 4.6)	0.67 (0.42, 1.1)

Frequency of Intracranial Abnormalities

The frequency of significant intracranial abnormalities in persons with migraine, tension type, and unspecified headache with normal neurological exam was reported. Eleven studies contributed to the estimate for migraine headaches. The estimate was 0.2% with an upper 95% confidence interval of 0.6% and a range of 0% to 3.1%. Two studies contributed to the estimate for tension type headache which was 0%. No frequency estimate was determined for unspecified headache because the rates reported in the studies were too heterogeneous. Instead a range estimate of 0%-6.7% derived from ten studies was reported.

Based on 3 studies of fewer than 100 persons/study in which a small fraction of persons were imaged by both CT and MRI and in which no significant abnormalities were detected the relative effectiveness of MRI and CT could not be determined. The authors concluded that there was insufficient evidence to make recommendations regarding the relative sensitivity of MRI compared with CT in the evaluation of migraine or other non acute headache disorders.

The US Headache Consortium made evidence-based recommendations which were graded on a scale of A to C. No grade A recommendations were made. One Grade B recommendation was made. A Grade B recommendation is supported by evidence from randomized controlled trials which due to study limitations (e.g. few studies, inconsistency in studies, or studies not relevant to the recommendation) are considered sub-optimal scientific support. Most of the recommendations were grade C recommendations denoting consensus based recommendations because of the absence of relevant randomized controlled trials.

The following recommendations were made by the US Headache Consortium (11):

- i) Neuroimaging should be considered in patients with nonacute headache and an unexplained abnormal finding on the neurological exam.(Grade B)
- ii) Evidence is insufficient to make specific recommendations regarding neuroimaging in the presence or absence of neurological symptoms. (Grade C)

- iii) Neuroimaging is not usually warranted for persons with migraine and normal neurological exam. For persons with atypical headache features or who do not fulfill the strict definition of migraine, a lower threshold for neuroimaging may be applied. (Grade C)
- iv) Data were insufficient to make an evidence-based recommendation regarding the use of neuroimaging for tension type headache. (Grade C)
- v) Data were insufficient to make any evidence based recommendations regarding the relative sensitivity of MRI compared with CT in the evaluation of migraine or other non acute headache. (Grade C)

Scottish Intercollegiate Guidelines Network

The systematic review completed by The Scottish Intercollegiate Guidelines Network (SIGN) (1) searched the medical literature from 2000-2007 and included 1 systematic review, that by the U.S. Headache Consortium previously described, 1 RCT, 1 prospective study, and 2 retrospective studies. This systematic review answered the research question: when is neuroimaging required?

The SIGN reported that the frequency of intracranial abnormalities based on one prospective study of 1876 persons with chronic headaches presenting at a neurology clinic in Spain was 0.4% for persons with a migraine headache, 0.8% for persons with a tension type headache, 5% for persons with a cluster headache, and 3.7% for persons with an undefined headache (neither migraine, tension type, nor cluster headache) (1).

The SIGN reported that based on 2 retrospective reviews (18;19) neuroimaging in patients with headache and an abnormal neurological examination is significantly more likely to reveal an underlying cause.

The rate of incidental findings on brain MRI ranged between 6.55% in 2,536 healthy young males and 13.5% in a prospective cohort of 2000 volunteers aged between 45 and 96 years and a mean age of 63 years. (20;21)

The SIGN also reported the results of an RCT by Howard et al.(12), which determined whether neuroimaging for chronic headache was anxiolytic or axiogenic. Results of this RCT indicated that a reduction in anxiety was not seen at 1 year follow up in persons that received a neuroimaging scan compared with those that did not. However, persons who were anxious and/or depressed and not scanned had significantly higher health service costs overall due to a greater use of healthcare resources such as psychiatric consults compared to those who were anxious and/or depressed and were scanned.

The SIGN used the evidence base reported by the U.S. Headache Consortium previously discussed to conclude that MRI is more sensitive than CT in identifying white matter lesions and developmental venous anomalies.(1)

Based on the systematic review by The SIGN the following recommendations were made:

- i) Neuroimaging is not indicated in patients with a clear history of migraine, without red flag features for potential secondary headache, and a normal neurological examination.
- ii) MRI and CT can identify incidental neurological abnormalities which may result in patient anxiety as well as practical and ethical dilemmas with regard to management.
- iii) Brain CT should be performed in patients with headache who have unexplained abnormal neurological signs unless the clinical history suggests MRI is indicated.

These recommendations were graded as D meaning they are based on non-analytic studies such as case reports, or case series, or on expert opinion, or evidence which is extrapolated from well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.

Based on these 3 systematic reviews, the evidence up to 2007 which examines the effectiveness of neuroimaging in persons with chronic headache and a normal neurological exam is of low quality.

Evidence-Based Analysis

Research Question(s)

What is the effectiveness of CT and MRI scanning in the evaluation of persons with a chronic headache and a normal neurological examination?

What is the comparative effectiveness of CT and MRI scanning for detecting significant intracranial abnormalities in persons with chronic headache and a normal neurological exam?

What is the budget impact of CT and MRI scans for persons with a chronic headache and a normal neurological exam?

Research Methods

Literature Search

Search Strategy

A literature search was performed on February 18, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January, 2005 to February, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established.

Inclusion Criteria

- Systematic reviews, randomized controlled trials, observational studies
- Outpatient adult population with chronic headache and a normal neurological exam
- Studies reporting the likelihood ratio of clinical variables for a significant intracranial abnormality
- English language studies
- 2005-present

Exclusion Criteria

- Studies which report outcomes for persons with seizures, focal symptoms, sudden/new onset headache, change in presentation, thunderclap headache, and headache due to trauma
- Persons with abnormal neurological examination
- Case reports

Outcomes of Interest

Primary Outcome

- i) Pre-test probability of intracranial abnormality

Secondary Outcome

- i) Patient relief from anxiety
- ii) Health system service use
- iii) Health system costs
- iv) Detection rates for significant intracranial abnormalities in MRI and CT scans

Quality of Evidence

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (22) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the populations, interventions, and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

One systematic review, 1 small RCT, and 1 observational study met the inclusion and exclusion criteria. The systematic review completed by Detsky et al.,(23) reported the likelihood ratios of specific clinical variables to predict significant intracranial abnormalities. The RCT completed by Howard et al.,(12) evaluated whether offering neuroimaging scans to persons with chronic headache increased or reduced their anxiety. The prospective observational study by Sempere et al.,(13) provided evidence for the pre-test probability of intracranial abnormalities in persons with chronic headache and a normal neurological exam as well as minimal data on the comparative effectiveness of CT and MRI to detect intracranial abnormalities. The study by Sempere et al., (13) was incorporated into the systematic review by Detsky et al.(23). Therefore the systematic review by Detsky et al. (23)represents the most current systematic review on neuroimaging for the evaluation of headache for determining likelihood ratios for clinical variables.

Table 3: Level of evidence of included studies (24)

Study Design	Level of Evidence†	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	1
Large RCT unpublished but reported to an international scientific meeting	1(g)	
Small RCT	2	1
Small RCT unpublished but reported to an international scientific meeting	2(g)	
Non-RCT with contemporaneous controls	3a	
Non-RCT with historical controls	3b	
Non-RCT presented at international conference	3(g)	
Surveillance (database or register)	4a	
Case series (multisite)	4b	
Case series (single site)	4c	1
Retrospective review, modelling	4d	
Case series presented at international conference	4(g)	
	Total	3

RCT refers to randomized controlled trial;

Study Characteristics

Three studies including 1 systematic review by Detsky et al., (23) 1 randomized controlled trial by Howard et al.,(12) and 1 prospective observational study by Sempere et al., (13) comprise the evidence.

The characteristics of the systematic review by Detsky et al.,(23) are reported in table 4 and the studies included in that systematic review are reported in table 5. The purpose of the systematic review by Detsky et al., (23) in part was to determine the history and clinical features which may predict those persons with a higher probability of having a significant intracranial abnormality and who should therefore undergo neuroimaging. The systematic review was well conducted and adequately reported. Detsky et al.,(23) included 11 studies of varying methodology and populations (see Table 5). Using the Rational Clinical Examination Series quality of evidence scale, the author concluded that only 1 study, that by Sempere et al. (13) was a level 1 study denoting high quality. All other studies were level IV, denoting poor quality. Only 4 studies were completed in North America (in the U.S.), with one of those, that by Kahn et al. (25) being completed in part in Canada (Winnipeg). All but 2 studies that by Sempere et al., and Kahn et

al.,(25) had small sample sizes. Sempere et al., (13) completed a large prospective observational study which included 1876 persons while Kahn et al.,(25) completed a large retrospective study with a sample size of 1111 persons.

Table 4: Characteristics of systematic review by Detsky et al.

Author, Year, Country	Study Design	Inclusion Criteria	Exclusion Criteria	Population	Number of Studies (n)	Outcomes Measured	*Quality of Evidence
Detsky, 2006, Canada	Systematic Review 1966- 2005	Studies that assessed the usefulness of the history and physical examination in predicting the presence of significant intracranial pathology in adults with non-traumatic headache.	Studies that only assessed patients with a specific underlying chronic disease	Acute and chronic headache seen in outpatient, inpatient and emergency department settings	11	Likelihood ratios of findings on history and physical examination	The study by Sempere was rated as a level 1 All other studies were level IV

*The Rational Clinical Examination Series: Level 1, studies are independent, blinded comparisons of components of the clinical examination with a gold standard among 100 or more consecutive patients with headache. Level II studies have the same characteristics as level 1 studies but assess fewer patients (<100). Level III studies are independent, blinded comparisons of components of the clinical examination with a gold standard among nonconsecutive patients with headache. Level IV studies are those that do not meet the criteria for at least level III.

Table 5: Studies included in systematic review by Detsky et al.

Author	Year	Design	n	Country	Population
Sempere et al.(13)	2004	Prospective Consecutive Series	1876	Spain	Chronic headache, normal neurological exam, neurological clinic
Aygun and Bildki (18)	2003	Prospective Consecutive Series	70	Turkey	Adults with clinical warning criteria for secondary neurological headaches presenting in the emergency department
Landtblom et al.(26)	2002	Prospective Consecutive Series	137	Sweden	Persons presenting at emergency department with sudden onset headache defined as an onset time of < 10 seconds. Patients could be enrolled if they presented within 10 days after onset of headache
Linn et al. (27)	1998	Prospective Consecutive Series	102	Netherlands	Persons presenting in the emergency room with a sudden onset of headache suggestive of an aneurysmal subarachnoid haemorrhage and absence of focal deficits.
Duarte et al. (28)	1996	Prospective Consecutive Series	100	Spain	Headaches of recent onset defined as that which appeared for the first time ever in the last 12 months. Patients with past headache excluded unless there was a change in characteristic of the headache. Study population was obtained from a neurology clinic
Kahn et al. (25)	1993	Retrospective review of all CT	1111	U.S., Canada	Population included persons with an acute headache or migraine

Author	Year	Design	n	Country	Population
		scans between 1988-1991			
Cull (29)	1995	Prospective	69	Scotland	Neurology outpatient clinic between 1988-1994 Persons with first attacks of migraine with or without aura after the age of 40 were included
Larson et al. (30)	1980	Before and after cohort analysis 3 retrospective cohorts of consecutive patients.	40	U.S.	All persons with initial complaint of headache
Weingarten et al.(16)	1992	Retrospective review of CT	89	U.S.	Persons with headache as an isolated major complaint and normal neurological exam Persons with headache as well as one or more associated symptoms such as dizziness, episodic weakness, unusual sensations, normal neurological exam Persons with headache and a definite abnormality.
Carrera et al. (31)	1977	Retrospective Case Series	85	U.S.	Persons with headache as chief complaint were divided into three classifications: Headache as the isolated major complaint Headache and normal neurological exam. Headache and abnormal neurological exam.
Cala and Mastaglia(32)	1976	Prospective Case series	46	Australia	Persons with recurrent migraine for up to 18 years examined on CT scanner because of a change in headache pattern.

The characteristics of the prospective study by Sempere et al.,(13) and the RCT by Howard et al.,(12) are described in table 6. The limitations to the study by Sempere et al.,(13) include that it was completed in Spain and included persons attending a neurology clinic. These characteristics may make the results of this study less generalizable to Ontario and a primary care population. The limitations of the RCT by Howard et al., (12) include an inadequate sample size to achieve significance for the primary outcome (worry on a visual analogue scale), and contamination of the intervention group (one third of persons in the ‘no scan’ group received a scan within the 1 year follow up). These limitations and how they affect the outcomes of each study will be discussed in detail in this report. They have also been taken into consideration for the Grade quality of evidence evaluation.

Table 6: Characteristics of studies by Sempere et al.,(13) and Howard et al.(12)

Author, Year, Country	Study Design	n	Population	Intervention	Follow up	Outcomes Measured
Sempere 2004 Spain(13)	Prospective Observational	1876	≥ 15 years of age Attending Neurology Clinic referred by family doctor. Non acute headache defined as any type of headache that	All persons received neuroimaging studies either CT or MRI. MRI- 1.5 Tesla	3 months	1. Frequency of significant intracranial lesions. Significant abnormalities included: Neoplastic disease,

Author, Year, Country	Study Design	n	Population	Intervention	Follow up	Outcomes Measured
			had begun at least 4 weeks before enrolment in study.	imagers Standard saggittal and axial T1-weighted and axial T2 weighted imaging with 6mm section thickness.		Hydrocephalus, Vascular malformations (aneurysms, arterio-venous malformations, dural fistula, cavernous angiomas) Chiari malformation, Large arachnoid cysts, Intracranial haemorrhage, Acute cerebral infarcts. 2. Clinical variable helpful in identifying patients with intracranial lesions.
Howard, 2005 UK(12)	RCT	150	English speaking population with chronic daily headache defined as 15 days per month of headache for more than 6 months. It can include tension type headache, migraine, and secondary headache due to extensive medication consumption. New patients at a headache clinic referred primarily from general practitioner and occasionally from neurologist.	Screening MRI scan	3months & 1 year using postal questionnaires of the outcome instruments.	Primary: Health anxiety Use of health resources Secondary: Illness perception Medical Outcome Study Short Form 36 Headache diary

Effectiveness

Question: What is the effectiveness of CT or MRI scanning in the evaluation of persons with a chronic headache and a normal neurological examination?

Outcome 1: Pre-test Probability.

The evidence for this outcome is based on the prospective observational study by Sempere et al. (13)

The pre-test probability is usually related to the prevalence of the disease and can be adjusted depending on the characteristics of the population. The study by Sempere et al.(13) determined the pre-test probability (prevalence) of significant intracranial abnormalities in persons with chronic headaches defined in the study as a headache experienced for a duration of at least 4 weeks, and with a normal neurological exam. The pre-test probability of significant intracranial abnormalities obtained by Sempere et al.(13) are reported in table 7. There is a pre-test probability of 0.9% (95% CI 0.5, 1.4) in persons with chronic headache and a normal neurological exam. The highest pre-test probability of 5.0 was reported in persons with cluster headaches. The second highest, that of 3.7, was reported in persons with indeterminate type headache. There was a 0.75% rate of incidental findings. These included 3 pineal cysts, 3 intracranial lipomas, and 8 arachnoid cysts.

The study population included persons attending a neurology clinic who were referred by a family physician and as such these pre-test probabilities may be greater than expected for a primary care practice.

Table 7: Pre-test probability of a significant intracranial abnormality

Diagnosis	Significant Abnormality	Pre-test Probability % Rate (95% CI)
Chronic headache and normal neurological exam	17/1876	0.9 (0.5, 1.4)
Migraine	4/920	0.4 (0.1, 1.4)
Tension-Type	5/665	0.8 (0.2, 1.7)
Cluster Headache	1/20	5.0 (0.1, 25)
Post traumatic	0/69	0 (0, 5.2)
Indeterminate	7/188	3.7 (1.5, 7.5)
Incidental findings	14/1876	0.75 (0.4, 1.1)

Likelihood ratios for detecting a significant abnormality.

This evidence is based on the systematic review by Detsky et al.(23)

Clinical findings from the history and physical can be used as a screening test to predict abnormalities on neuroimaging. The extent to which the clinical variable may be a good predictive variable can be captured by reporting its likelihood ratio. The likelihood ratio uses both the sensitivity and specificity of a test to provide an estimate of how much a test result will change the odds of having a disease or condition. The positive likelihood ratio (LR+) is calculated by dividing the sensitivity of the test by 1-specificity of the test and the negative likelihood ratio (LR-) is calculated by dividing the 1-sensitivity of the test by the specificity. The positive likelihood ratio (LR+) tells you how much the odds of having the disease increases when a test is positive. The negative likelihood ratio (LR-) tells you how much the odds of having the disease decrease when the test is negative.

Sempere et al.,(13) determined there was a significant likelihood ratio of 42 (95% CI 16, 113) for persons presenting with an abnormal neurological exam. A negative likelihood ratio for this clinical variable was not reported. This likelihood ratio was thirteen fold greater than that reported by the U.S. Head Consortium in their systematic review 2000 (see Table 2)

Detsky et al.,(23)determined the likelihood ratio for specific clinical variable from the 11 studies reported in table 5. Those clinical variables with both positive and negative statistically significant likelihood ratios are reported in Table 8. There were two clinical variables with a statistically significant positive likelihood ratio but a non statistically significant negative likelihood ratio (see Table 9). Finally 8 clinical variables had a non statistically significant positive and negative likelihood ratio (see Table 10).

Table 8: Clinical variables with statistically significant positive and negative likelihood ratios

Findings	Studies contributing to LR estimate	Number of Studies	n	LR + (95 % CI)	LR- (95% CI)
Abnormal neurological exam	Cala 1976(32) Carrera 1977(31) Cull 1995(29) Duarte 1996(28) Larson 1980(30) Sempere 2004(13)	6	2116	5.3 (2.4, 12)	0.71 (0.60, 0.85)
Undefined headache	Sempere 2004(13) Weingarten 1992(16)	2	1965	3.8 (2.0, 7.1)	0.66 (0.44, 0.97)
Headache aggravated by exertion or valsalva	Duarte 1996(28) Linn 1998(27)	2	202	2.3 (1.4, 3.8)	0.70 (0.56, 0.88)
Headache with vomiting	Linn 1998(27) Weingarten 1992(16)	2	191	1.8 (1.2, 2.6)	0.47 (0.29, 0.76)

Table 9: Clinical variables with statistically significant positive likelihood ratios and non statistically significant negative likelihood ratios.

Findings	Studies	Number of Studies	n	LR + (95 % CI)	LR- (95% CI)
Cluster-type headache	Sempere 2004(13) Weingarten 1992(16)	2	1965	11 (2.2-52)	0.95 (0.84-1.1)
Headache with aura	Cala 1976(32) Cull 1995(29) Weingarten 1992(16)	3	204	3.2 (1.6-6.6)	0.51 (0.24-1.1)

Table 10: Clinical variables with non statistically significant positive and negative likelihood ratios

Findings	Studies	Number of Studies	n	LR + (95 % CI)	LR- (95% CI)
Headache with focal symptoms	Aygun 2003(18) Linn 1998(27)	2	172	3.1 (0.37, 25)	0.78 (0.51, 1.2)
New onset headache	Sempere 2004(13) Weingarten 1992(16)	2	1965	1.2 (0.74, 2.0)	0.89 (0.63, 1.3)
Quick onset headache	Aygun 2003(18) Linn 1998(27)	2	172	1.3 (0.33, 5.1)	0.79 (0.14, 4.4)
Worsening headache	Aygun 2003(18) Sempere 2004(13)	2	1946	1.6 (0.23, 10)	1.0 (0.78, 1.2)
Male gender	Cull 1995(29) Linn 1998(27) Sempere 2004(13)	3	2047	1.3 (0.89, 1.8)	0.86 (0.68, 1.1)
Headache with nausea	Cull 1995(29) Duarte 1996(28) Linn 1998(27) Weingarten 1992(16)	4	306	1.1 (0.87, 1.3)	0.86 (0.63,1.2)
Increased headache severity	Duarte 1996(28) Sempere 2004(13)	2	1976	0.83 (0.54, 1.3)	1.2 (0.91, 1.4)
Migraine type headache	Kahn 1993(25) Sempere 2004(13) Weingarten 1992(16)	3	2976	0.55 (0.28, 1.1)	1.2 (0.84, 1.7)

Outcome 2: Relief from Anxiety

The evidence for this outcome is based on the randomized controlled trial by Howard et al. (12)

Howard et al.(12)completed an RCT to determine if neuroimaging for headaches was anxiolytic or anxiogenic. Persons were randomized to receive either an MRI scan or no MRI scan for investigation of

their chronic headache. The study population was stratified into those persons with a Hospital Anxiety and Depression scale (HADS) score > 11 (the high anxiety and depression group) and those < 11 (the low anxiety and depression). There were 4 groups (see Figure 1):

- Group 1: High anxiety and depression (HADS POS), no scan group;
- Group 2: High anxiety and depression (HADS POS), scan group;
- Group 3: Low anxiety and depression (HADS NEG), no scan group;
- Group 4: Low anxiety and depression (HADS NEG), scan group;

The sample size calculation was predicated on detecting a difference of 9 points on a 100 point visual analogue scale (VAS) of ‘worry about health’. Sample size calculations indicated 30 patients in each of the 4 groups for a power of 90% using a significance level of 0.05. Patient outcomes were analyzed on an intention-to-treat basis.

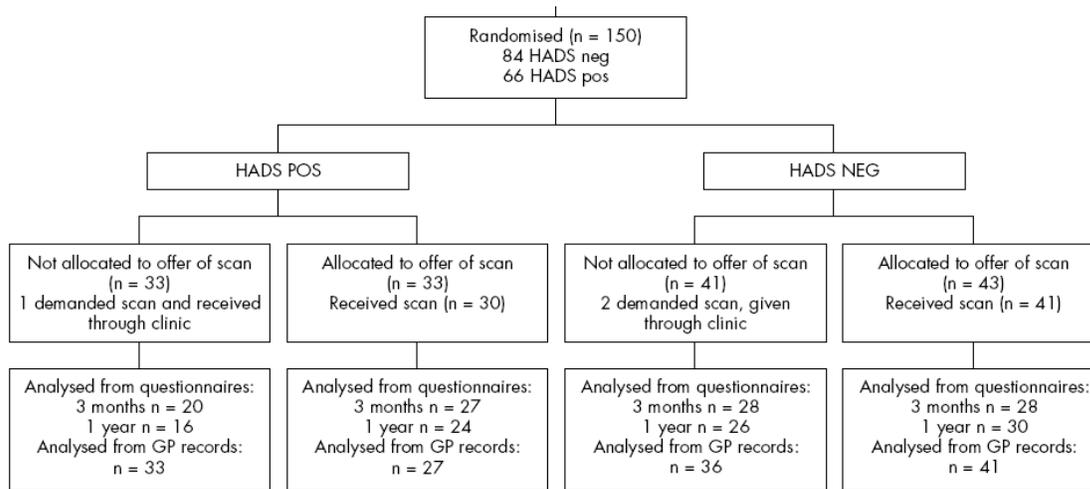


Figure 1: Flow diagram of RCT

Reproduced from: Are investigations anxiolytic or anxiogenic? A randomized controlled trial of neuroimaging to provide reassurance in chronic daily headache, Howard L., Wessely S., Leese M., Page L., McCrone P., Husain K., Tong J., Dowson A., 76, 1558-1564, 2005 with permission from BMJ Publishing Group Ltd.

One hundred and fifty persons were randomized, 66 in the high anxiety and depression (HADS positive) group, and 84 in the low anxiety and depression (HADS negative) group. The baseline characteristics of the study population are reported in table 11.

Table 11: Baseline characteristics

Variable	Scanned	Not Scanned
Gender, male n(%)	57 (77)	59 (78)
Age, mean (SD)	40 (13.2)	37 (11.4)
HADS score, mean (SD)	15.8 (7.2)	15.4 (7.6)
Headache index	35.9 (42.1)	33.3 (42.0)

The study limitations included the following: 11 persons in the high anxiety and depression (HADS positive) ‘no scan’ group received scans within the follow up year and 3 persons (1 in the HADS positive

'no scan' group and 2 in the HADS negative 'no scan' group) also received scans during the follow up period. Therefore 12 persons (36%) in the HADS positive 'no scan' group actually received scans within the follow up year. Five persons (6.6%) in the 'scanned' group (1 in the HADS positive group and 4 in the HADS negative group) could not receive MRI scans.

Anxiety

There was no evidence for any overall reduction in anxiety at 1 year as measured by the VAS scale of 'worry about health' or on the Hospital Anxiety Scale (a 21 question scale with four subscales: health, worry and preoccupation; fear of illness and death; reassurance seeking behaviour; and extent to which symptoms interfere with a persons life) when analysed by whether the person received a scan or not (Table 12). Similarly, there was no interaction between anxiety and depression status (HADS status) and whether a scan was offered or not on anxiety level. Anxiety did not decrease at 1 year to any statistically significant degree in the HADS positive group compared with the HADS negative group (Table 13).

The authors concluded that the provision of a scan, made little difference to overall levels of anxiety regardless of the level of anxiety or depression and therefore most patients do not benefit from neuroimaging where anxiety relief is concerned. However, there are serious methodological limitations which may have contributed to these negative results. First, when considering the comparison of 'scan' vs. 'no scan' groups, 12 people (16%) in the 'no scan group' actually received a scan within the follow up year. If indeed scanning does reduce anxiety then this contamination of the 'no scan' group may have reduced the effect between the group results resulting in a non significant difference in anxiety scores between the 'scanned' and the 'no scan' group. Second, there was an inadequate sample size at 1 year follow up in each of the 4 groups which may have contributed to a Type II statistical error (missing a difference when one may exist) when comparing scan vs. no scan by anxiety and depression status. Therefore, based on the results and study limitations it is inconclusive as to whether scanning reduces anxiety. Finally, 36% of persons in the HADS positive no scan group received a scan. If scanning does relieve anxiety this confounding may have reduced the VAS scores in this group contributing to a statistically non significant difference between groups.

Table 12: Results of primary outcome for anxiety by scan offered (Yes or No)

Primary clinical outcomes	Scan offered		n	1 year mean	p-value
	Yes (Y)	No (N)			
VAS worry	N		42	42.9	0.41
	Y		54	42.8	
HAQ health, worry and preoccupation	N		34	6.47	0.77
	Y		48	6.04	
HAQ fear of illness	N		33	4.67	0.60
	Y		50	4.46	
HAQ reassurance seeking behaviour	N		35	2.26	0.16
	Y		50	1.78	
HAQ life interference	N		33	2.91	0.66
	Y		51	2.73	

Source: Are investigations anxiolytic or anxiogenic? A randomized controlled trial of neuroimaging to provide reassurance in chronic daily headache, Howard L., Wessely S., Leese M., Page L., McCrone P., Husain K., Tong J., Dowson A., 76, 1558-1564, 2005

Table 13: Results of primary outcome for anxiety by HADS status and scan offered

Primary clinical outcomes	HADS Status	Scan offered		n	1 year mean	p-value (interaction scan x HADS status)
		Yes (Y)	No (N)			
VAS worry	Negative	N		26	38.7	0.80
		Y		30	40.1	
	Positive	N		16	49.6	
		Y		24	46.1	
HAQ health, worry and preoccupation	Negative	N		NR	5.33	0.61
		Y		NR	4.62	
	Positive	N		NR	8.31	
		Y		NR	7.73	
HAQ fear of illness	Negative	N		NR	4.25	0.52
		Y		NR	3.39	
	Positive	N		NR	5.31	
		Y		NR	5.82	
HAQ reassurance seeking behaviour	Negative	N		NR	2.05	0.78
		Y		NR	1.64	
	Positive	N		NR	2.57	
		Y		NR	1.95	
HAQ life interference	Negative	N		NR	2.70	0.27
		Y		NR	2.17	
	Positive	N		NR	3.23	
		Y		NR	3.45	

Source: Are investigations anxiolytic or anxiogenic? A randomized controlled trial of neuroimaging to provide reassurance in chronic daily headache, Howard L., Wessely S., Leese M., Page L., McCrone P., Husain K., Tong J., Dowson A., 76, 1558-1564, 2005

Outcome 3: System Services

The evidence for this outcome is based on the randomized controlled trial by Howard et al.(12)

Data for this outcome was obtained by examining primary care case notes at 1 year for consultation rates, symptoms, further investigations, and contact with secondary and tertiary care.

Health Services

The authors reported that the use of neurologist and psychiatrist services were significantly greater for those persons not offered a scan, regardless of their anxiety and depression status compared to those who were offered a scan ($P < 0.001$ for neurologist, and $P = 0.033$ for psychiatrist) (see Table 14). There was also a significant interaction effect between scanning and HAD status such that persons who were HADS positive and not scanned reported statistically significantly more neurologist and psychiatrist visits than those who were HADS positive and scanned.

Table 14: Health services used

	HADS negative		HADS positive		p*	
	Not offered (n=41)	Offered (n=43)	Not offered (n=33)	Offered (n=33)	Scan offered	(Interaction scan×HAD status)
Intervention (scan)	2 (5)	41 (95)	1 (3)	30 (91)		
GP	33 (92)	40 (98)	33 (100)	27 (100)	0.619	0.200
Neurologist	7 (19)	1 (2)	10 (30)	0 (0)	<0.001	<0.001
Psychiatrist/therapist	2 (6)	1 (2)	6 (18)	0 (0)	0.033	0.023
Out patient	16 (44)	19 (46)	16 (48)	11 (41)	0.864	0.949
Other imaging	12 (33)	8 (20)	9 (27)	5 (19)	0.166	0.466
Tests	16 (44)	9 (22)	13 (39)	12 (44)	0.215	0.122
In patient care	4 (11)	4 (10)	6 (18)	1 (4)	0.274	0.374
Other services	5 (14)	5 (12)	1 (3)	1 (4)	1	0.305
Sick notes	4 (11)	2 (5)	3 (9)	4 (15)	1	0.544

*Fisher's exact tests for two and four groups for main effect (scan offered) and interaction effect, respectively.

Reproduced from *Are investigations anxiolytic or anxiogenic? A randomized controlled trial of neuroimaging to provide reassurance in chronic daily headache*, Howard L., Wessely S., Leese M., Page L., McCrone P., Husain K., Tong J., Dowson A., 76, 1558-1564, 2005 with permission from BMJ Publishing Group Ltd.

Outcome 4: System Costs

Health System Costs

There was evidence of statistically significant lower system costs in persons with high levels of anxiety and/or depression (Hospital Anxiety and Depression Scale (HADS) score >11) who were scanned compared to those who were not (306£ vs. 771£, $p = 0.03$ respectively, including inpatient costs and 297£ vs. 419£, $p = 0.047$ respectively, excluding inpatient costs) (see Table 15).

Table 15: Health system costs

	HADS negative		HADS positive		p*	
	Not offered (n = 41)	Offered (n = 43)	Not offered (n = 33)	Offered (n = 33)	Scan offered	(Interaction scan × HAD status)
Intervention	6 (26)	113 (25)	4 (21)	108 (35)		
GP	148 (147)	117 (83)	150 (114)	135 (91)	0.212	0.691
Neurologist	33 (77)	3 (17)	46 (82)	0 (0)	<0.001	0.423
Psychiatrist/therapist	5 (24)	3 (20)	93 (242)	0 (0)	0.029	0.034
Out patient	80 (103)	90 (193)	81 (125)	40 (55)	0.592	0.228
Other	6 (19)	7 (25)	1 (4)	2 (12)	0.648	0.945
Imaging	11 (23)	8 (24)	41 (87)	4 (8)	0.017	0.036
Test	8 (22)	5 (17)	3 (4)	6 (10)	0.745	0.230
In patient care	61 (177)	118 (643)	352 (1121)	9 (47)	0.265	0.073
Total service cost†						
Including inpatient costs	352 (363)	464 (713)	771 (1314)	306 (162)	0.267	0.030
Excluding inpatient costs	292 (257)	346 (220)	419 (367)	297 (137)	0.605	0.047

Values are mean (SD) in £.

*Based on robust standard errors in linear regressions; †excluding costs of lost employment.

Reproduced from: *Are investigations anxiolytic or anxiogenic? A randomized controlled trial of neuroimaging to provide reassurance in chronic daily headache*, Howard L., Wessely S., Leese M., Page L., McCrone P., Husain K., Tong J., Dowson A., 76, 1558-1564, 2005 with permission from BMJ Publishing Group Ltd.

Of note, there were 12 persons (36%) in the HADS positive no scan group who actually received a scan. We might have expected this to reduce the effect difference between this group and the HADS positive scanned group, however it did not. As well, if we assume the converse, that this scanning did reduce the absolute costs in the HADS positive no scan group then the results reported in Table 15 represent a conservative estimate and the actual costs in the HADS positive no scan group may in fact be even greater.

Summary of Effectiveness of Neuroimaging for the Evaluation of Chronic Headaches

The evidence can be summarized as follows:

Pre-test Probability

Based on the results by Sempere et al., (13) there is a pre-test probability of 0.9% for intracranial abnormalities in persons with chronic headaches and a normal neurological exam (defined in the study as headaches experienced for a minimum of 4 weeks). The Grade quality of evidence supporting this outcome is very low (See Appendix 2).

Likelihood Ratios

Based on the systematic review by Detsky et al.,(23) there is a statistically significant positive and negative likelihood ratio for the following clinical variables: abnormal neurological exam, undefined headache, headache aggravated by exertion or valsalva, and headache with vomiting. Grade quality of evidence supporting this outcome is very low (See Appendix 2).

Based on the systematic review by Detsky et al.(23) there is a statistically significant positive likelihood ratio but non statistically significant negative likelihood ratio for the following clinical variables: cluster headache and headache with aura. The Grade quality of evidence supporting this outcome is very low (See Appendix 2).

Based on the systematic review by Detsky et al.,(23) there is a non significant positive and negative likelihood ratio for the following clinical variables: headache with focal symptoms, new onset headache, quick onset headache, worsening headache, male gender, headache with nausea, increased headache severity, and migraine type headache. The Grade quality of evidence supporting this outcome is very low (See Appendix 2).

Relief from Anxiety

Based on the RCT by Howard et al.,(12) it is inconclusive whether neuroimaging scans in persons with a chronic headache are anxiolytic. The Grade quality of evidence supporting this outcome is low (See Appendix 2).

Health Services

Based on the RCT by Howard et al.,(12) scanning persons with chronic headache regardless of their anxiety and/or depression level reduces health service use (psychiatrist and neurologist visits). The Grade quality of evidence is low (see Appendix 2).

System Costs

Based on the RCT by Howard et al.,(12) scanning persons with a score greater than 11 on the High Anxiety and Depression Scale reduces system costs. The Grade quality of evidence is moderate (see Appendix 2).

Comparative Effectiveness of CT and MRI Scans

Question 2: What is the comparative effectiveness of CT and MRI for detecting significant intracranial abnormalities in persons with chronic headache and a normal neurological exam?

Sempere et al., (13) reported the detection rate for significant intracranial abnormalities using CT and MRI. In a cohort of 1876 persons with a non acute headache defined as any type of headache experienced for at least 4 weeks, the rate of detection was 19/1432 (1.3%) using CT and 4/444 (0.9%) using MRI. Of 119 normal CT scans 2 (1.7%) had significant intracranial abnormality on MRI. The 2 cases were a small meningioma and an acoustic neurinoma.

Summary of Comparative Effectiveness of CT and MRI Scans

There is sparse evidence to determine the relative effectiveness of CT compared with MRI scanning for the detection of intracranial abnormalities. The Grade quality of evidence supporting this is very low (see Appendix 2).

Existing Guidelines for Neuroimaging for the Evaluation of Chronic Headaches

Guidelines

Several guidelines exist which advise on the use of neuroimaging for the evaluation of headache.

Canadian

The guidelines for the diagnosis and management of migraine in clinical practice published in 1997 stated that “neither CT scans nor MRI scans are warranted in adult patients whose headaches fit a broad definition of recurrent migraine and who have not demonstrated the following: any recent substantial change in headache pattern, a history of seizures or the presence of focal neurological symptoms.” Furthermore, “there is insufficient evidence to define the role of CT and MRI in the evaluation of patients with headache that is not consistent with migraine.” (33)

US Head Consortium

Consensus based general principles:

- i) Testing should be avoided if it will not lead to a change in management.
- ii) Testing is not recommended if the individual is not significantly more likely than anyone else in the general population to have a significant abnormality.
- iii) Testing that normally may not be recommended as a population policy may make sense at an individual level resources notwithstanding. For example exceptions can be considered for patients who are disabled by their fear of serious pathology, or for whom the provider is suspicious even in the absence of known predictors of abnormalities on neuroimaging studies (red flags).

Evidence-Based Guidelines:

- iv) Neuroimaging should be considered in patients with non-acute headache and an unexplained abnormal finding on the neurological exam.
- v) Evidence is insufficient to make specific recommendations regarding neuroimaging in the presence or absence of neurological symptoms.
- vi) Data were insufficient to make an evidence-based recommendation regarding the use of neuroimaging for tension-type headache.
- vii) Data were insufficient to make any evidence-based recommendations regarding the relative sensitivity of MRI compared with CT in the evaluation of migraine or other non acute headache.

Scottish Intercollegiate Guidelines Network

- i) Neuroimaging is not indicated in patients with a clear history of migraine, without red flag features for potential secondary headache, and a normal neurological examination.
- ii) Clinicians requesting neuroimaging should be aware that both MRI and CT can identify incidental neurological abnormalities which may result in patient anxiety as well as practical and ethical dilemmas with regard to management.
- iii) Brain CT should be performed in patients with headache who have unexplained abnormal neurological signs, unless the clinical history suggests MRI is indicated.

- iv) Red flag features include:
- a. New onset or change in headache in patients who are aged over 50
 - b. Thunderclap: rapid time to peak headache intensity (seconds to 5 minutes)
 - c. Focal neurological symptoms (e.g. Limb weakness, aura < 5min or > 1hr)
 - d. Non focal neurological symptoms (e.g. Cognitive disturbance)
 - e. Change in headache frequency, characteristics, or associated symptoms
 - f. Abnormal neurological examination
 - g. Headache that changes with posture
 - h. Headache wakening the patient up (N.B. migraine is the most frequent cause of morning headache)
 - i. Headache precipitated by physical exertion or valsalva maneuver (eg. Coughing, laughing, straining)
 - j. Patients with risk factors for cerebral venous sinus thrombosis
 - k. Jaw claudication or visual disturbance
 - l. Neck stiffness
 - m. Fever
 - n. New onset headache in a patient with a history of human immunodeficiency virus (HIV) infection
 - o. New onset headache in a patient with a history of cancer.

American College of Radiology

Table 16: American College of Radiology ACR Appropriateness Criteria

Clinical Condition:

Headache

Variant 1:

Chronic headache. No new features.

Radiologic Procedure	Rating	Comments	<u>RRL*</u>
MRI head without and with contrast	4	See statement regarding contrast in text under "Anticipated Exceptions."	O
MRI head without contrast	4		O
CT head without contrast	4		☼☼☼
CT head without and with contrast	4		☼☼☼
MRA head with or without contrast	2		O
Arteriography cervicocerebral	2		☼☼☼
CTA head	2		☼☼☼
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

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Economic Analysis

DISCLAIMER: The Medical Advisory Secretariat uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

Downstream costs: All numbers reported are based on assumptions on population trends (i.e. incidence, prevalence and mortality rates), time horizon, resource utilization, patient compliance, healthcare patterns, market trends (i.e. rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents *an estimate only*, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

Economic Literature Review

A literature search was conducted on February 16th, 2010 and the following databases were searched:

- OVID MEDLINE
- MEDLINE In-Process and Other Non-Indexed Citations
- OVID EMBASE
- Wiley Cochrane
- CINAHL
- Centre for Reviews and Dissemination/International Agency for Health Technology Assessment
- EconLit

The search strategy is presented in Appendix 1. We reviewed published articles that fit the following inclusion criteria:

- full economic evaluations (cost-effectiveness analysis [CEA], cost-utility analysis [CUA], cost-benefit analysis [CBA])
- Economic evaluations reporting Incremental Cost-Effectiveness Ratios (ICER) i.e. cost per quality adjusted life year (QALY)/life years gained (LYG) or cost per event avoided
- studies in patients with chronic headaches
- studies reporting on outpatient neuroimaging testing of the head – including Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans
- studies in English
- 2005-present

No article was identified that fit the inclusion criteria.

Ontario Perspective

Volumes for neuroimaging of the head from the Ontario Health Insurance Plan (OHIP) data set were used to investigate trends in the province. The following OHIP codes from the Ontario Schedule of Benefits (OSB) (34) were used to obtain data for the Fiscal Years (FY) 2004-2009. Number of neuroimaging services of the head and the fee paid for these services are described in Appendix 3.

Table 17: OHIP codes associated with neuroimaging of the head

Head CT codes	Fee
X400 - without IV contrast	\$44.55
X401 - with IV contrast	\$66.90
X188 - with and without IV contrast	\$78.15
Head MRI codes	Fee
X421 – multi-slice sequence	\$71.50
X425 - repeat (another plane, different pulse sequence - to a maximum of 2 repeats)	\$35.85

Code reference: Ontario Schedule of Benefits – accessed April 2010.

Assumptions were made in order to investigate neuroimaging of the head for the indication of headache. You et al. (5) reported from a random sample of hospitals that 27% of all CT and 13% of all MRI scans for the head included an indication of headache on the medical chart. From that same retrospective chart review and personal communication with the author 16% of CT scans and 4% of MRI scans for the head were completed for the sole indication of headache.

From the Ministry of Health and Long-Term Care (MOHLTC) wait times data (35), 73% of all CT and 93% of all MRI scans in the province, irrespective of indication were outpatient procedures.

These assumptions are documented in table 18.

Table 18: Assumptions regarding neuroimaging of the head for the indication of headache

Parameter	Proportion	Reference
CT for Headache	27%	(5)
CT for Headache Only	16%	Personal communication, McMaster University, April 2010.
Outpatient CT Services*	73%	(35)
MRI for Headache	13%	(5)
MRI for Headache Only	4%	Personal communication, McMaster University, April 2010.
Outpatient MRI Services*	93%	(35)

*Assumed proportion of scan would be similar regardless of the type of scan (brain versus abdomen versus chest etc.)

Figure 2 and table 19 describe the outpatient neuroimaging services of the head for the indication of headache in Ontario for the past 6 FYs.

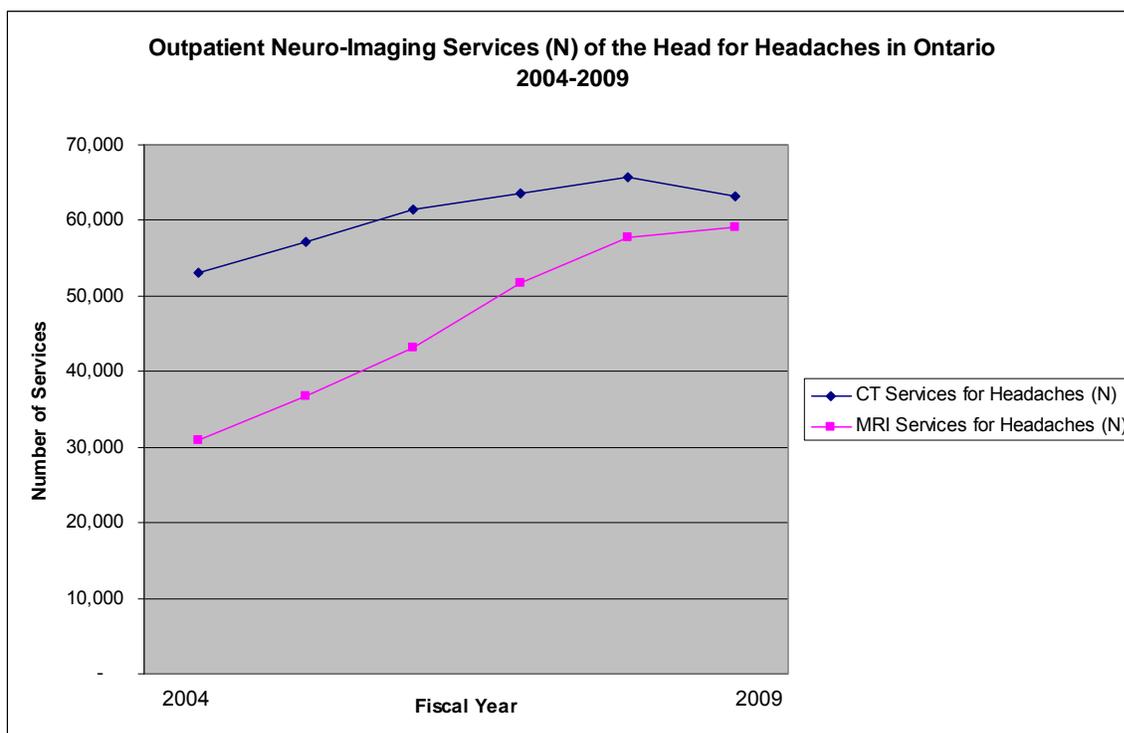


Figure 2: Number of outpatient neuroimaging services (N) of the head for headache in Ontario 2004-2009.

Table 19: Number of outpatient neuroimaging services of the head for headache in Ontario 2004-2009

Services	Fiscal Year					
	2004	2005	2006	2007	2008	2009
CT Services for Headaches	53,103	57,108	61,413	63,515	65,700	63,170
MRI Services for Headaches	30,944	36,673	43,202	51,631	57,730	59,142

The number of neuroimaging services of the head for the indication of headache has increased over the past 6 FYs. There was a small dip in CT services from FY 07/08 to FY 08/09 however the trend has been a consistent increase in services.

Figure 3 and table 20 describe the expenditure associated with these outpatient neuroimaging services of the head for the indication of headache in Ontario for the past 6 FYs.

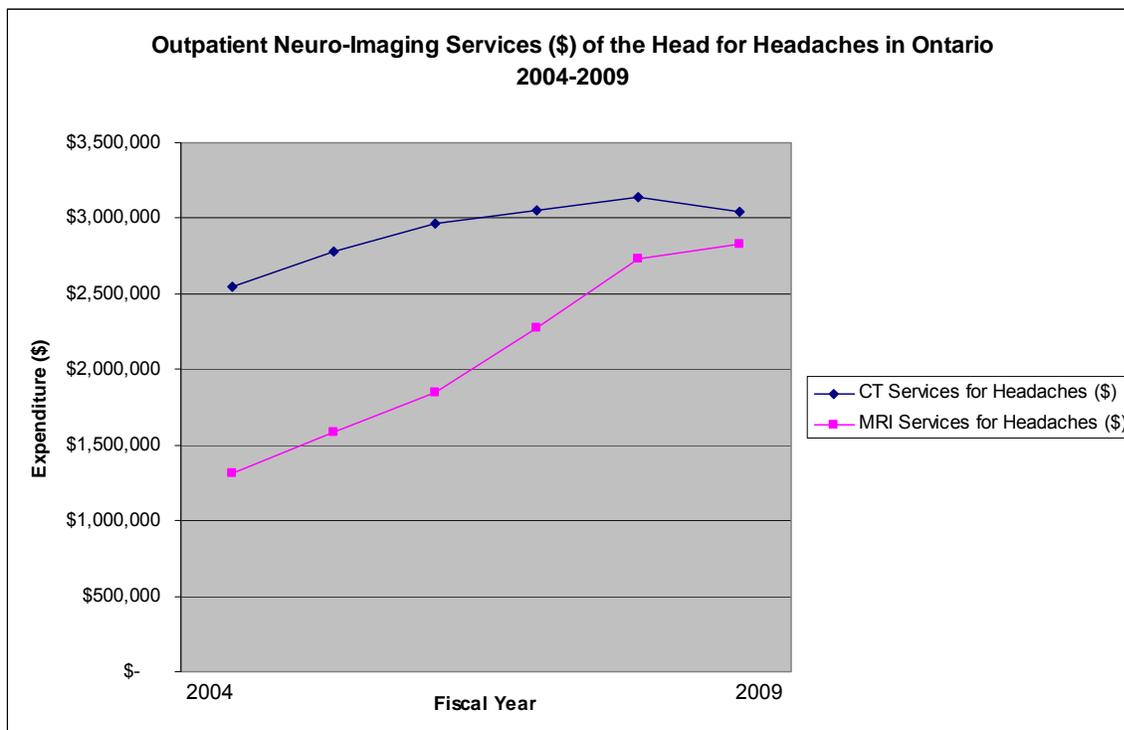


Figure 3: Outpatient neuroimaging expenditure (\$) of the head for headache in Ontario 2004-2009.

Table 20: Outpatient neuroimaging expenditure (\$) of the head for headache in Ontario 2004-2009

Services	Fiscal Year					
	2004	2005	2006	2007	2008	2009
CT Services for Headaches (\$)	\$2,551,241	\$2,777,455	\$2,966,982	\$3,050,614	\$3,141,298	\$3,044,961
MRI Services for Headaches (\$)	\$1,309,535	\$1,585,959	\$1,849,372	\$2,274,281	\$2,733,465	\$2,830,604

The expenditure for each FY reflects the volume for that year and since volumes have increased in the past 6 FYs, the expenditure has also increased with a pay-out reaching 3.0M and 2.8M for CT and MRI services of the head respectively for the indication of headache in FY 08/09.

Figure 4 and table 21 describe the outpatient neuroimaging services of the head for the indication of headache only in Ontario for the past 6 FYs.

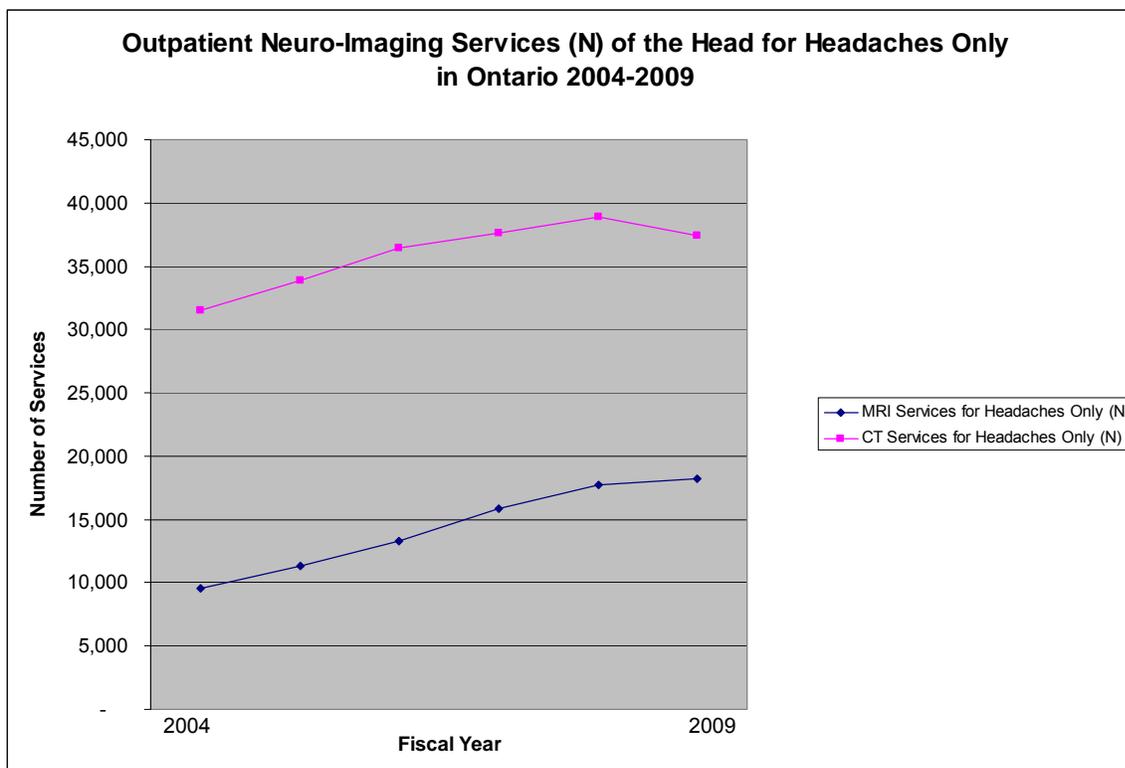


Figure 4: Outpatient neuroimaging services (N) of the head for headache only in Ontario 2004-2009.

Table 21: Number of outpatient neuroimaging services (N) of the head for headache only in Ontario 2004-2009

Services	Fiscal Year					
	2004	2005	2006	2007	2008	2009
CT Services for Headaches Only (N)	31,469	33,842	36,393	37,639	38,933	37,434
MRI Services for Headaches Only (N)	9,521	11,284	13,293	15,886	17,763	18,197

The number of neuroimaging services of the head for the indication of headache only has increased over the past 6 FYs as expected since neuroimaging services of the head in general have increased. There was a small dip in CT services from FY 07/08 to FY 08/09 however the trend has been a consistent increase in overall services.

Figure 5 and table 22 describe the expenditure associated with these outpatient neuroimaging services of the head for the indication of headache only in Ontario for the past 6 FYs.

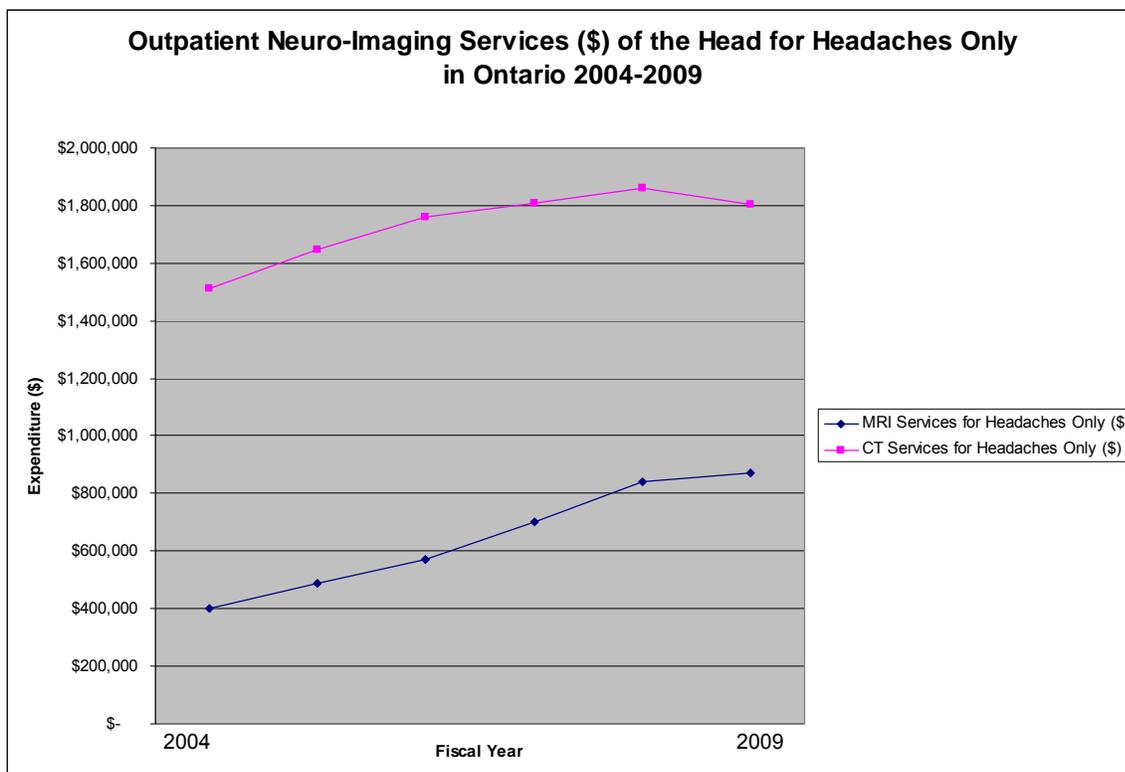


Figure 5: Outpatient neuroimaging expenditure (\$) of the head for headache only in Ontario 2004-2009.

Table 22: Outpatient neuroimaging expenditure (\$) of the head for headache only in Ontario 2004-2009

Services	Fiscal Year					
	2004	2005	2006	2007	2008	2009
CT Services for Headaches Only (\$)	\$1,511,846	\$1,645,899	\$1,758,211	\$1,807,771	\$1,861,510	\$1,804,421
MRI Services for Headaches Only (\$)	\$402,934	\$487,988	\$569,037	\$699,779	\$841,066	\$870,955

The expenditure for each FY reflects the volume for that year and since volumes have increased in the past 6 FYs, the expenditure has also increased with a pay-out reaching 1.8M and 0.9M for CT and MRI services of the head respectively for the indication of headache only in FY 08/09.

Cost per Abnormal Finding

The yield of abnormal finding for a CT and MRI scan of the head for the indication of headache only is 2% and 5% respectively (5). Based on these yields a high-level estimate of the cost per abnormal finding with neuroimaging of the head for headache only can be calculated for each FY. In FY 08/09 there were 37,434 CT and 16,197 MRI scans of the head for headache only. These volumes would generate a yield of abnormal finding of 749 and 910 with a CT scan and MRI scan respectively. The expenditure for FY 08/09 was 1.8M and 0.9M for CT and MRI services respectively. Therefore the cost per abnormal finding would be \$2,409 for CT and \$957 for MRI.

The following illustration describes this calculation. In FY 08/09:

- 37,434 CTs → yield 2% ~ 749
- 18,197 MRIs → yield 5% ~ 910
- \$1,804,421 for CTs → cost/abnormal finding = $1,804,421/749 \sim \$2,409$
- \$870,955 for MRIs → cost/abnormal finding = $870,955/910 \sim \$957$

These cost per abnormal finding estimates were limited because they did not factor in comparators or the consequences associated with an abnormal reading or false negatives. The estimates only consider the cost of the neuroimaging procedure and the yield of abnormal finding with the respective procedure.

Summary

Neuroimaging services of the head for the indication of headache are increasing in Ontario. Further economic analysis is required to calculate a more accurate cost per abnormal finding.

Expert Advisory Panel

At the request of the OHTAC an Expert Advisory Panel was convened to review this evidence-based analysis. The panel membership included representatives from the disciplines of neurology, family medicine, radiology and diagnostic imaging, internal medicine, epidemiology and from the Ministry of Health and Long-Term Care.

The purpose of the Advisory Panel was to:

1. Comment on the accuracy of evidence-based analysis and any omissions in its content.
2. Comment on the quality of the data reviewed and the generalizability of the evidence to Ontario.
3. Determine if there is sufficient evidence for OHTAC to pursue guideline development.

The Expert Advisory Panel found that the evidence-based analysis was accurate and comprehensive with respect to the research questions posed. The Panel found the evidence to date poor regarding the use of neuroimaging for chronic headaches and that there are no high quality studies determining the effectiveness of neuroimaging for chronic headaches in part because the definition of chronic headache differs among the studies. The Panel noted that since the term 'chronic headache' was either not defined in the evidence or the definition differed between studies, that there is a significant problem with the generalizability of this evidence and in using it to developing guidelines on imaging for chronic headaches. The Panel concluded from the evidence that the overall use of neuroimaging for headache evaluation in the province is not excessive but noted it would be useful to clinicians to better understand the patterns of scanning in Ontario including determining the types of headaches being scanned (acute, episodic, chronic).

Appendices

Appendix 1: Literature Search

Clinical Review

Search date: February 18, 2010

Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1996 to February Week 2 2010>

Search Strategy:

-
- 1 exp Headache/ or exp Headache Disorders/ (19454)
 - 2 (headache* or migraine* or cephalgia* or cephalalgia* or hemicrania continua).ti. (12618)
 - 3 1 or 2 (19624)
 - 4 exp Magnetic Resonance Imaging/ (177270)
 - 5 exp Tomography, X-Ray Computed/ (139631)
 - 6 (mri or magnetic resonance or mr).ti,ab. (165186)
 - 7 (ct or (comput* adj tomograph*) or cat scan*).ti,ab. (140047)
 - 8 (neuroimag* or neuro-imag*).ti,ab. (13762)
 - 9 or/4-8 (389576)
 - 10 3 and 9 (3359)
 - 11 limit 10 to (english language and humans and yr="2005 -Current") (1496)
 - 12 limit 11 to (case reports or comment or editorial or letter) (1023)
 - 13 11 not 12 (473)

Database: EMBASE <1980 to 2010 Week 06>

Search Strategy:

-
- 1 exp chronic daily headache/ or exp exertional headache/ or exp headache/ or exp hypnic headache/ or exp migraine/ or exp posttraumatic headache/ or exp postural headache/ or exp primary headache/ or exp secondary headache/ or exp sinus headache/ or exp stabbing headache/ or exp temporal arteritis/ or exp tension headache/ or exp thunderclap headache/ or exp trigeminal autonomic cephalalgia/ or exp trigeminal neuralgia/ or exp vascular headache/ (103167)
 - 2 (headache* or migraine* or cephalgia* or cephalalgia* or hemicrania continua).ti. (21206)
 - 3 1 or 2 (103816)
 - 4 exp nuclear magnetic resonance imaging/ (261960)
 - 5 exp computer assisted tomography/ (318202)
 - 6 (magnetic resonance or mr or mri).ti,ab. (211999)
 - 7 (ct or (comput* adj tomograph*) or cat scan*).ti,ab. (203923)
 - 8 (neuroimag* or neuro-imag*).ti,ab. (15977)
 - 9 or/4-8 (594945)
 - 10 3 and 9 (14863)
 - 11 limit 10 to (human and english language and yr="2005 -Current") (6743)
 - 12 limit 11 to (editorial or letter or note) (725)
 - 13 case report/ (1079114)
 - 14 11 not (12 or 13) (2147)

Economic Review

Search date: February 16, 2010

Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment, EconLit

Database: Ovid MEDLINE(R) <1996 to February Week 1 2010>

Search Strategy:

-
- 1 exp Headache/ or exp Headache Disorders/ (19445)
 - 2 (headache* or migraine* or cephalgia* or cephalalgia* or hemicrania continua).ti. (12614)
 - 3 1 or 2 (19615)
 - 4 exp Magnetic Resonance Imaging/ (177151)
 - 5 exp Tomography, X-Ray Computed/ (139570)
 - 6 (mri or magnetic resonance or mr).ti,ab. (165071)
 - 7 (ct or (comput* adj tomograph*) or cat scan*).ti,ab. (139972)
 - 8 (neuroimag* or neuro-imag*).ti,ab. (13749)
 - 9 or/4-8 (389354)
 - 10 3 and 9 (3358)
 - 11 limit 10 to (english language and humans and yr="2005 -Current") (1496)
 - 12 limit 11 to (case reports or comment or editorial or letter) (1023)
 - 13 11 not 12 (473)
 - 14 exp Economics/ (212291)
 - 15 exp Models, Economic/ (5862)
 - 16 exp Resource Allocation/ (7258)
 - 17 exp "Value of Life"/ or exp "Quality of Life"/ (66944)
 - 18 (econom\$ or cost\$ or budget\$ or pharmaco-economic\$ or pharmaco-economic\$ or valu\$).ti. (82493)
 - 19 ec.fs. (167059)
 - 20 ((cost\$ adj benefit\$) or costbenefit\$ or (cost adj effective\$) or costeffective\$ or econometric\$ or life value or quality-adjusted life year\$ or quality adjusted life year\$ or quality-adjusted life expectanc\$ or quality adjusted life expectanc\$ or sensitivity analys\$ or "value of life" or "willingness to pay").ti,ab. (46546)
 - 21 or/14-20 (384323)
 - 22 10 and 21 (51)
 - 23 limit 22 to (english language and yr="2005 -Current") (19)

Database: EMBASE <1980 to 2010 Week 06>

Search Strategy:

-
- 1 exp headache/ (80630)
 - 2 (headache* or migraine* or cephalgia* or cephalalgia* or hemicrania continua).ti. (21206)
 - 3 1 or 2 (91583)
 - 4 exp nuclear magnetic resonance imaging/ (261960)
 - 5 exp computer assisted tomography/ (318202)
 - 6 (magnetic resonance or mr or mri).ti,ab. (211999)
 - 7 (ct or (comput* adj tomograph*) or cat scan*).ti,ab. (203923)
 - 8 (neuroimag* or neuro-imag*).ti,ab. (15977)
 - 9 or/4-8 (594945)
 - 10 3 and 9 (12992)
 - 11 limit 10 to (human and english language and yr="2005 -Current") (5975)
 - 12 limit 11 to (editorial or letter or note) (605)

13 case report/ (1079114)
14 11 not (12 or 13) (1800)
15 exp "Health Care Cost"/ (114023)
16 exp Health Economics/ (250941)
17 exp Resource Management/ (15487)
18 exp Economic Aspect/ or exp Economics/ or exp Quality Adjusted Life Year/ or exp Socioeconomics/ or exp
Statistical Model/ or exp "Quality of Life"/ (527557)
19 (econom\$ or cost\$ or budget\$ or pharmacoeconomic\$ or pharmaco-economic\$ or valu\$).ti. (115434)
20 ((cost\$ adj benefit\$) or costbenefit\$ or (cost adj effective\$) or costeffective\$ or econometric\$ or life value or
quality-adjusted life year\$ or quality adjusted life year\$ or quality-adjusted life expectanc\$ or quality adjusted life
expectanc\$ or sensitivity analys\$ or "value of life" or "willingness to pay").ti,ab. (57326)
21 or/15-20 (604611)
22 10 and 21 (420)
23 limit 22 to (english language and yr="2005 -Current") (215)

Appendix 2: Grade Profile Table

Quality Assessment							No. of Patients		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Significant intracranial abnormality	No significant intracranial abnormality	Quality
Pre-test probability (frequency of significant intracranial abnormalities on CT and/or MRI)									
1	observational studies	no serious limitations	None	Some ¹	None	Sparse data	17/1876 (0.9%)	1859/1876 (99.1%)	VERY LOW
Likelihood ratio for abnormal neurological exam									
6	observational studies	serious ³	Important ²	Some ⁴	Some ⁵	None	N/A	N/A	VERY LOW
Likelihood ratio for undefined headache									
2	observational studies	serious ⁶	Important ⁷	None	None	None	N/A	N/A	VERY LOW
Likelihood ratio for headache aggravated by exertion or valsalva									
2	observational studies	serious ⁸	None	Some ⁹	None	None	N/A	N/A	VERY LOW
Likelihood ratio for headache with vomiting									
2	observational studies	serious ¹⁰	Important ¹¹	Some ¹²	None	None	N/A	N/A	VERY LOW
Likelihood ratio for cluster type headache									
2	observational studies	serious ⁶	Important ¹³	None	None	None	N/A	N/A	VERY LOW
Likelihood ratio for headache with aura									
3	observational studies	serious ¹⁵	no serious inconsistency	Some ¹⁴	Some ¹⁶	None	N/A	N/A	VERY LOW
Likelihood ratios for headache with focal symptoms or headache with quick onset headache									
2	observational studies	no serious limitations	Important ¹⁷	Some ¹⁸	None	None	N/A	N/A	VERY LOW
Likelihood ratio for new onset headache									
2	observational studies	serious ⁶	None	None	None	None	N/A	N/A	VERY LOW
Likelihood ratio for worsening headache									
2	observational studies	no serious limitations	None	Some ¹⁹	None	None	N/A	N/A	VERY LOW
Likelihood ratio for headache with nausea									
4	observational studies	no serious limitations	None	Some ²⁰	None	None	N/A	N/A	VERY LOW
Likelihood ratio for increased headache severity									
2	observational studies	no serious limitations	None	Some ²¹	None	None	N/A	N/A	VERY LOW
Likelihood ratio for migraine type headache									
3	observational studies	serious ²²	None	Some ²³	none	None	N/A	N/A	VERY LOW
Likelihood ratio for male gender									
3	observational studies	no serious limitations	None	Some ²⁴	None	None	N/A	N/A	VERY LOW
Relief from Anxiety (Patient)									
1	randomised trial	serious ²⁵	None	None	Some ²⁶	None	N/A	N/A	LOW
Health Services Used									
1	randomised trial	serious ²⁵	None	None	Some ²⁶	None	N/A	N/A	LOW
Health System Costs									
1	randomised trial	serious ²⁷	None	None	Some ²⁶	Increased effect ²⁹	N/A	N/A	MODERATE
Rates of Detection CT vs. MRI									
1	observational studies	no serious limitations	None	None	Some ²⁸	None	N/A	N/A	VERY LOW

¹ Study included persons attending a neurology clinic and may not represent those attending a primary care practice.

² Positive likelihood ratios range from 2.6 to 42. Highest quality study reports 42 (2.4-12)

³ Of the six studies, only that by Sempere et al. was considered high quality. The other studies had small sample sizes. In total, there are 4 prospective, 1 retrospective, and 1 before and after study in this body of evidence. The author of the systematic review rated the quality of evidence as a IV on the Rational Clinical Examination series scale. Level IV is poor quality.

⁴ Likelihood ratios determined from studies which included persons with a variety of headache types (eg. thunderclap, migraine, new/change in headache). One study, that by Sempere et al., included persons with chronic headache defined as persistent headache for 4 weeks before enrolment in study.

⁵ Positive likelihood ratio is wide and because of this may be consistent with conflicting recommendations depending on the pre-test probability.

⁶ Pooled likelihood ratio determined from the study by Sempere et al. which was a large prospective observational study, and from Weingarten et al., 1992, which was a small (n=89) retrospective study of CT scans.

⁷ Study by Sempere et al. reported statistically significant positive and negative likelihood ratios while that by Weingarten et al. reported non statistically significant positive and negative likelihood ratios. However, the summary positive and negative likelihood ratios were statistically significant

⁸ Studies considered low quality by author. Both studies prospective observational studies in populations with sudden onset headache

⁹ Indirectness exists if generalizing this to a population with chronic headache. Studies included persons with recent onset headache.

¹⁰ One prospective study (Linn n=102) and one retrospective study (Weingarten n=89). Total Sample size is small (n=191)

¹¹ Study by Linn et al., reported statistically significant positive and negative likelihood ratios. The study by Weingarten et al. reported non statistically significant positive and negative likelihood ratios. However, the summary statistics for both the positive and negative likelihood ratios were statistically significant.

¹² Two small studies. One study included persons with thunderclap headache and another was a retrospective study which included persons with normal neurological exam as well as persons with neurological symptoms. This may not be generalizable to persons with chronic headache and a normal neurological exam.

¹³ One large study with statistically significant positive and negative likelihood ratios and one small study with a statistically significant positive likelihood ratio but a non statistically significant negative likelihood ratio. As well, the positive likelihood ratio for the large study was 5.7 and was 30 for the smaller study. There were large confidence intervals for the positive likelihood ratios.

¹⁴ Populations in study are not generalizable to persons with chronic headaches. Evidence is comprised of 2 studies from 1995 and 1992 and 1 study from 1976. Because of the year the studies were completed they may not represent current neuroimaging technology

¹⁵ Evidence is from prospective and retrospective study designs. Variety of headache disorders in study population

¹⁶ Some imprecision in the positive likelihood ratios between studies. The positive likelihood ratio is statistically significant in 2 studies but not in the third study. The positive likelihood ratios ranges from 1.7-12.9. The negative likelihood ratios are non significant in all three studies, contributing to a non significant summary negative likelihood ratio.

¹⁷ There is inconsistency in the direction of significance for the positive likelihood ratios for both headache with focal symptoms and headache with quick onset.

¹⁸ Studies completed in Turkey and Netherlands may not be generalizable to Ontario.

¹⁹ Studies completed in Spain and Turkey and therefore may not be generalizable to Ontario

²⁰ Studies completed in Scotland, Spain, Netherlands and California and may not be generalizable to Ontario.

²¹ Both studies completed in Spain. May not be generalizable to Ontario

²² Two retrospective cohort studies contributing to 60% of data

²³ 40% of pooled study population from study completed in Spain. Other studies completed in California, Chicago and Winnipeg.

²⁴ Studies completed in Scotland, Netherlands, and Spain and therefore may not be generalizable to Ontario population.

²⁵ Inadequate power to detect difference in outcome. Contamination of treatment group (no scan group).

²⁶ One small randomized controlled trial with small sample sizes in 4 treatment groups.

²⁷ Study not powered to detect difference in this outcome. Retrospective data collection from primary care case notes at 1 year follow up.

²⁸ Sparse data, low event rate.

²⁹ All plausible confounders would have reduced the effect. Contamination of high anxiety/high depression (HADS positive) no scan group; 36% received a scan. This confounding might be expected to reduce costs in this group and eliminate a statistically significant effect. However, the effect difference (higher costs) between the high anxiety/high depression (HADS positive) no scan group and high anxiety/high depression (HADS positive) scan group is still statistically significantly different.

Appendix 3: Neuroimaging services (CT and MRI) of the head by fiscal year

Fiscal Year	FSC	CT Scan - Code Description	# Services	Fee Paid
2004	X188	CT of head with and without IV contrast	18,188	\$ 1,392,484
2004	X400	CT of head without IV contrast	223,762	\$ 9,766,889
2004	X401	CT of head with IV contrast	26,792	\$ 1,751,764
2005	X188	CT of head with and without IV contrast	18,195	\$ 1,420,913
2005	X400	CT of head without IV contrast	244,511	\$ 10,880,734
2005	X401	CT of head with IV contrast	26,303	\$ 1,754,301
2006	X188	CT of head with and without IV contrast	20,304	\$ 1,580,552
2006	X400	CT of head without IV contrast	264,599	\$ 11,710,464
2006	X401	CT of head with IV contrast	25,892	\$ 1,724,073
2007	X188	CT of head with and without IV contrast	19,077	\$ 1,483,501
2007	X400	CT of head without IV contrast	277,773	\$ 12,317,983
2007	X401	CT of head with IV contrast	24,584	\$ 1,636,846
2008	X188	CT of head with and without IV contrast	17,976	\$ 1,396,832
2008	X400	CT of head without IV contrast	289,948	\$ 12,864,116
2008	X401	CT of head with IV contrast	24,567	\$ 1,636,311
2009	X188	CT of head with and without IV contrast	17,347	\$ 1,366,216
2009	X400	CT of head without IV contrast	281,077	\$ 12,612,438
2009	X401	CT of head with IV contrast	21,262	\$ 1,431,067

Fiscal Year	FSC	MRI - Code Description	# Services	Fee Paid
2004	X421	MRI of head - multislice sequence	86,199	\$ 5,465,674
2004	X425	MRI of head - repeat (another plane, different pulse sequence - to a maximum of 2 repeats)	169,934	\$ 5,373,688
2005	X421	MRI of head - multislice sequence	102,183	\$ 6,607,614
2005	X425	MRI of head - repeat (another plane, different pulse sequence - to a maximum of 2 repeats)	201,373	\$ 6,519,785
2006	X421	MRI of head - multislice sequence	120,383	\$ 7,705,317
2006	X425	MRI of head - repeat (another plane, different pulse sequence - to a maximum of 2 repeats)	237,209	\$ 7,602,415
2007	X421	MRI of head - multislice sequence	143,415	\$ 9,464,209
2007	X425	MRI of head - repeat (another plane, different pulse sequence - to a maximum of 2 repeats)	283,948	\$ 9,360,606
2008	X421	MRI of head - multislice sequence	160,757	\$ 11,361,533
2008	X425	MRI of head - repeat (another plane, different pulse sequence - to a maximum of 2 repeats)	317,093	\$ 11,264,070
2009	X421	MRI of head - multislice sequence	164,749	\$ 11,778,797
2009	X425	MRI of head - repeat (another plane, different pulse sequence - to a maximum of 2 repeats)	324,781	\$ 11,650,853

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