University of Alberta

Practice Variation in the Treatment of Children with Migraine in the Emergency Department

by

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Abstract

This thesis presents the results of three studies examining the management of migraine in children. First we conducted a systematic review of all clinical trials conducted in children and adolescents of the acute migraine therapy. A meta-analysis of the 26 randomized controlled trials is presented. A single trial with a focus on Emergency Department (ED) management was identified. As such, we then examined current ED practice in two retrospective practice variation studies. The first compared four regional hospital EDs where practice patterns were significantly different between mixed population EDs (both adult and pediatric patients) and the tertiary pediatric ED. The second examined practice variation among ten tertiary pediatric EDs in Canada where significant differences were again observed. Factors that influenced the choice of medications included increasing patient age and the physician's diagnosis of migraine. Important areas of future investigation include: (1) the effectiveness of intravenous fluids alone; and (2) the use of combined medications.

Preface

This thesis is presented in a traditional format with the prefatory pages followed by the body of text and bibliography. The body of text comprises an introductory chapter, a systematic review of drugs for acute migraine therapy in children, a regional practice variation study of Emergency Department management of migraine, a related national practice variation study among ten tertiary pediatric centers, and summary chapter. Chapter 2 is a registered protocol with the Cochrane Collaboration and publication to the Cochrane Library as a full review is planned. A version of Chapter 3 has been published (Richer et al., 2007) with minor modifications made to the introduction and discussion. The contents of Chapter 4 will be submitted for publication.

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Chapter 1

1 Introduction

Migraine headaches are a common and disabling headache disorder with a prevalence of 3% to 10% in children and adolescents (Lipton, Scher et al. 2002). One-third of Canadian children aged 14 to 15 years report headache once a week (Dooley, Gordon et al. 2005). Children as young as 2 years of age may be affected and most adults with migraine have their first headache in early childhood or adolescence (Bille 1997). This disorder of recurring headache is often functionally disabling and may decrease a child's sense of well being (Powers, Patton et al. 2003; Kernick and Campbell 2009). Indeed, migraine headaches can be a tremendous source of anxiety for children and their parents, disrupting both school obligations and parental work responsibilities. Moreover these concerns may be amplified when there is uncertainty on the physician's part as to the best treatment.

While important advances in the treatment of headache have been made, the use of many of these treatments in children is limited. Outpatient therapy for migraine is often limited to simple analgesics such as acetaminophen and ibuprofen. Studies of specific anti-migraine drugs like the triptan class (selective serotonin (5-HT) 1B/1D receptor[1] agonists) in children have generally not

[1] Serotonin (5-HT) receptors are classified in seven families (5-HT_1 – 5-HT_7). The 5-HT_1 family includes subtypes 5-HT_{1A} – 5-HT_{1F}. Triptans are specific agonists of receptor subtypes 5-HT_{1B} and 5-HT_{1D} which are found in the central nervous system and blood vessels.

demonstrated significant improvement when compared with placebo (Major, Grubisa et al. 2003; Damen, Bruijn et al. 2005). As such the triptans are not approved for use in children in Canada or the United States. In the absence of effective outpatient therapy, the Emergency Department (ED) remains an important resource for children suffering from migraine (Bailey and McManus 2008).

The aim of my research was two-fold: (1) to systematically review existing evidence for the treatment of migraine in children; and (2) to study practice variation for migraine therapies used in the ED. The practice variation study was divided in two separate studies: (1) a regional study of EDs serving both children and adults; and (2) a national study of migraine treatment patterns among ten tertiary pediatric EDs in Canada. The data from these studies will help clinicians better understand the state of evidence for migraine therapy in children, establish local and national practice patterns in areas where evidence may be lacking, and finally serve to inform future research agendas and priorities.

1.1 Migraine – operational definition

In the absence of a reliable biomarker for migraine, the most current operational definition is specified in the second edition of the International Classification of Headache Disorders (ICHD-II, 2004). Migraine is a clinical disorder of pain characterized by moderate to severe unilateral, pulsatile headache over the anterior head regions that is associated with nausea, vomiting, photophobia (preference for dim light), and sonophobia (preference for quiet). Migraine is divided into two primary forms: (1) migraine with aura; and (2)

migraine without aura. Approximately 20% of children have migraine with an aura, which is a transient neurological symptom such as visual disturbance, sensory disturbance, or even sometime focal weakness that may precede the headache or occur during the attack.

The International Headache Society's (http://www.i-h-s.org/) original classification system was published in 1988. However, revisions were required to improve the sensitivity of the criteria for children (Winner, Martinez et al. 1995). For example migraine in children is frequently bilateral and located over both frontal headache regions, in contrast to the unilateral headache specified in the adult criteria. Generally, children also have a shorter duration of headache which may be as brief as one hour. Many of the proposed modifications have now been adopted in footnotes to the criteria for migraine in the second edition of the ICHD and their sensitivity for children improved (Hershey, Winner et al. 2005).

Young children may also manifest migraine in the form of migraine equivalents. Childhood periodic syndromes that are considered to be migraine equivalents include paroxysmal torticollis (a condition in which children usually less than 2 years of age periodically develop a sustained head tilt), benign paroxysmal vertigo (periodic attacks of vertigo usually in children 3 to 6 years of age), and cyclical vomiting (periodic attacks of sustained vomiting) (Lanzi, Zambrino et al. 1997; Winner 2005). While head pain is not a typical feature in any of these syndromes, children may often develop migraine with or without aura later in life.

1.2 Prevalence of headache and migraine in children

A number of studies have examined the prevalence of recurrent headache and migraine in children worldwide with similar observations. The prevalence of all headache types increases with age from 13% at 3 years to 37% of children by age 6 (Mortimer, Kay et al. 1992). A peak prevalence of 40-50% is reached by school age - 7 years and older (Bille 1962; Sillanpää and Anttila 1996). A Canadian study based on the National Longitudinal Survey of Children and Youth (NLSCY: 1996 to 1997) observed frequent headache one or more times per week in a quarter of children surveyed between 12 and 13 years of age (Gordon, Dooley et al. 2004).

Migraine is less common in the pre-school age group with prevalence estimates ranging between 1-5% (Pothmann, Frankenberg et al. 1994). The prevalence of recurrent headache in boys increases at the same rate in girls until 10 to 12 years of age (Bille 1962), but thereafter increases faster in girls (Abu-Arefeh and Russell 1994; Aromaa, Sillanpaa et al. 2000). The impact of puberty and sex hormones is significant and estrogen plays a pivotal role in migraine (Bousser 2004) as the prevalence continues to increase in females to almost twice the rate of boys by 18 years of age (Lipton, Stewart et al. 2001).

1.3 Quality of life and co-morbidities of children with migraine

The pain and suffering experienced by children with migraine is considerable and often best understood only by those with personal experience. The quality of life (QOL) in children with migraine is significantly impaired and children with frequent migraine estimate their QOL at the same level as children

with other chronic conditions like cancer and arthritis (Powers, Patton et al. 2003). In another study of 2815 Dutch school-children, QOL and quality of health measures were significant lower in children with migraine (Bandell-Hoekstra, Abu-Saad et al. 2002). A study using data from the Canadian Community Health Survey also found significant impairments in all domains of the SF-36 health-related QOL measure (Brna, Gordon et al. 2007; Brna, Gordon et al. 2008). The domains most affected included impairment of physical role, bodily pain, and general health.

A number of adult-based migraine disability scores have been developed including the migraine disability assessment - MIDAS (Stewart, Lipton et al. 2000), migraine severity assessment - MIGSEV (El Hasnaoui, Vray et al. 2004), and the short-form Headache Impact Test (HIT-6) (Kosinski, Bayliss et al. 2003). The Pediatric Migraine Disability Assessment Score (PedMIDAS) was developed based on the MIDAS to assess migraine-related disability in children (Hershey, Powers et al. 2001). It has proven to be a useful and reliable measure of disability for pediatric migraine sufferers (Hershey, Powers et al. 2004). QOL in children with headache may also be assessed using the PedsQL^{TM} 4.0 (Connelly and Rapoff 2006) on which children report lowered social functioning (Powers, Patton et al. 2004).

Increasing migraine disability is correlated with the frequency of migraine attacks and psychiatric co-morbidities (Hershey 2005). Children with frequent migraine often have associated anxiety or mood disorders (Seshia, Phillips et al. 2008). Moreover, children with frequent migraine also have increased suicidal

ideation independent of a mood disorder (Wang, Fuh et al. 2009). An important outcome of migraine therapy is to improve QOL (D'Amico, Solari et al. 2006) and a focus on the child's coping strategies or familial context may also be important (Frare, Axia et al. 2002). Treatment of associated co-morbidities may be required to significantly affect the child's outcome and may include multi-disciplinary approaches to treatment including pharmacological strategies, cognitive-behavioural therapy, coping strategies. The potential risks of failing to recognize the severity and impact of migraine in children by health-care providers and parents are significant.

1.4 Pathophysiology of migraine

The neurobiology of migraine is field of increasing interest with the development of an animal model that mimics many of the biological responses known to occur in migraine. In the model, an inflammation-inducing cocktail of histamine, bradykinin, prostaglandins, and substance P are applied to the meninges of the animal (most commonly a rat). This induces pain-signaling via the first division of the trigeminal nerve to the brainstem trigeminal nucleus caudalis. The pain signaling pathways can then be studied using electrophysiological methods to record neuronal activity.

The trigemino-vascular physiology of migraine is now the predominant neurobiological theory (Goadsby, Charbit et al. 2009). At the onset of a migraine attack, peripheral trigeminal afferents from the meningeal covering of the brain are activated and sensitized to fire at low thresholds (Strassman, Raymond et al. 1996). These 'pain signals' correspond to the pulsatile pain with every heartbeat

described by many migraineurs. The central trigeminal nucleus caudalis in the brainstem receives these signals and is in turn activated and sensitized to fire at much lower thresholds (Burstein and Jakubowski 2004). This 'central sensitization' may last several hours and is related to the clinical phenomenon of cutaneous allodynia whereby non-noxious stimuli to the skin of the forehead (e.g. brushing hair) are sensed as painful. A more generalized disturbance of sensory modulation explains the experience of associated migraine symptoms including nausea, vomiting, photophobia, and sonophobia.

Insight on the neurobiology of migraine has shed light on a number of clinical observations and opened new therapeutic avenues. For example, it has long been recognized among clinicians and patients with migraine that the earlier one treats the attack, the more likely it is to abort with effective treatment. The electrophysiological correlate of the clinical phenomenon is 'central sensitization' – meaning the success of treatment may depend on whether central pain pathways are sensitized or not. Serotonin 1b/1d receptor agonists are much less effective when given after the onset of central sensitization (Burstein, Collins et al. 2004) while non-specific cyclooxygenase (COX) inhibitors (ibuprofen, ketorolac, and naproxen) may still be effective (Jakubowski, Levy et al. 2005; Jakubowski, Levy et al. 2007). These observations may improve therapeutic strategies in the ED where patients are often treated late in the course of a migraine – long after the onset of central sensitization.

1.5 Overview of acute management of migraine in children

Migraine is associated both with pain and symptoms of nausea, photophobia, and sonophobia. As such the acute treatment of a migraine may help one aspect of the condition more than the others. Regardless, a reduction in head pain is the most commonly used primary outcome measure in medication trials. The primary classes of medication that may be used include the following: (1) acetaminophen; (2) non-steroidal anti-inflammatory drugs (NSAIDS or non-specific COX inhibitors); (3) serotonin receptor agonists; (4) opiates and opioids; (5) anti-nausea therapies or (6) dopamine antagonists. Less commonly used treatments may include valproate, diphenhydramine, magnesium, steroids, and intravenous fluid.

A qualitative review and practice parameter of migraine therapy in children has been published (Lewis, Ashwal et al. 2004). Sumatriptan nasal spray and ibuprofen were the only two medications with sufficient evidence to recommend their use. Recent quantitative reviews of acute migraine therapy (Major, Grubisa et al. 2003; Silver, Gano et al. 2008) do not include many publications of acute migraine therapies studied in children such as zolmitriptan nasal spray (Lewis, Winner et al. 2007) or do not included data released by the pharmaceutical companies through their clinical trial registries. These registries include GlaxoSmithKline (GSK Inc., North Carolina; http://www.gsk-clinicalstudyregister.com/) and AstraZeneca (AstraZeneca Canada Inc., Mississauga, Canada) (http://www.astrazenecaclinicaltrials.com/). A systematic review and meta-analysis of acute drug therapy for children with migraine is a

requisite first step in assessing the current state of evidence and identification of research priorities.

Chapter 2

2 Systematic review of acute pharmacological therapy[2]

2.1 Introduction

Treatment for migraine headaches includes both prophylactic and abortive strategies. Prophylactic agents are used to reduce the frequency and severity of migraine attacks are reviewed elsewhere (Damen, Bruijn et al. 2006). Abortive therapies are commonly employed to eliminate head pain and reduce the symptoms associated with migraine including nausea, sonophobia, and photophobia. Simple analgesics such as acetaminophen and ibuprofen (Hämäläinen, Hoppu et al. 1997) are the mainstay of acute migraine therapy in children. However, other agents such as ergot derivatives (e.g. dihydroergotamine) and the serotonin 1b/1d receptor agonists (triptans) may also be considered.

Evidence for the efficacy of acute migraine therapies in adults is considerable, but until recently randomized controlled trials (RCTs) in the pediatric population were less common. The American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child

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[2] This chapter is a registered protocol with the Cochrane Collaboration (http://www.cochrane.org/). Billingshurst, L., L. Richer, et al. (2006). "Drugs for treating acute migraine headaches in children and adolescents [Protocol]." The Cochrane Database of Systematic Reviews.

Neurology Society (Lewis, Ashwal et al. 2004) has published a practice parameter and qualitative review. This systematic review will serve to update the literature and provide a meta-analysis of the data.

2.2 Methods and Objectives

The objective of the study was to describe and assess the evidence from controlled clinical trials on the efficacy and tolerability of pharmacological interventions by any route of administration versus placebo or other drug treatments for acute migraine attacks in children less than 18 years of age. All prospective, controlled trials of pharmacological interventions for symptomatic (abortive) relief of acute migraine headaches in children were included if allocation to treatment groups was randomized or pseudo-randomized (based on some non-random process unrelated to the treatment selection or expected response). Studies were included regardless of design (i.e., parallel group or cross-over), publication status or language of publication. However, concurrent cohort comparisons and other non-experimental designs were excluded.

Studies involving pediatric patients (aged 3 to 17 years) with a diagnosis of migraine with or without aura were included (Appendix 1). Studies including both pediatric and adult patients were excluded unless results were reported separately for the pediatric patients. For the purposes of this review, a study was included if sufficient criteria were present to distinguish acute migraine from other primary headache disorders (e.g., episodic tension-type headache) and from secondary headache disorders (e.g., subarachnoid hemorrhage or raised intracranial

pressure). In all cases, at least minimum criteria were required for the diagnosis of probable migraine with or without aura as per the ICHD-II.

2.2.1 Types of interventions

Studies were included where patients were allocated to receive a pharmacological intervention, by any route of administration, for symptomatic treatment of an acute migraine attack. Acceptable comparator groups included placebo, or other active drug treatment. Standard care was not included as a comparator group. The use of prophylactic medication was identified, but discontinuation was not required for inclusion.

2.2.2 Types of outcome measures

Primary outcomes were selected based on the most commonly reported measures in the literature and suggested guidelines by the International Headache Society Clinical Trial Subcommittee (2000). Studies were required to report at least one of the primary outcome measures for inclusion. Primary outcome measures were assessed at 2 hours after intake of the treatment medication or comparator. The other outcomes were assessed when data were available.

The first primary outcome measure for efficacy was the absence of pain at 2 hours and before the use of rescue medication (pain-free). The second primary outcome measure was headache relief, defined as a decrease in headache intensity from severe or moderate to mild or none at 2 hours and before the use of rescue medication. When alternate definitions of pain intensity were used (e.g., numerical scale), the study was required to describe a level of relief that would be

meaningful to a patient and reflect a decrease in headache intensity similar to that assumed in the above definition.

Any adverse events were used as a primary outcome measure to assess harm. Adverse events were defined as any unwanted effect that occurred during treatment. Information regarding serious adverse events was documented when available. Withdrawal due to adverse events was recorded when available.

The following secondary outcome measures were included in the review:

(1) Use of rescue medication within 24 hours of taking the experimental drug or placebo

(2) Headache recurrence, defined as the initial relief of headache within 2 hours to mild or none with recurrence of headache to moderate or severe between 2 and 24 hours

(3) The presence of nausea at 2 hours

(4) The presence of vomiting at 2 hours

(5) The presence of sonophobia (preference for a quiet room) at 2 hours

(6) The presence of photophobia (preference for dim light) at 2 hours

2.2.3 Search methods for identification of studies

A search of electronic databases was conducted in collaboration with the research librarian using search strategies to identify the highest level of evidence for the topic. In addition, other sources listed below were searched manually. The following databases were systematically searched from inception to February 13, 2008: OvidSP MEDLINE™, Ovid MEDLINE™ In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials, Cochrane

Database of Systematic Reviews, Database of Reviews and Abstracts, EMBASE, International Pharmaceutical Abstracts, PsycINFO, and EBSCOhost CINAHL (Cumulative Index of Nursing and Allied Health).

The search strategies used a combination of keywords and subject headings, adapted for each database searched: migraine, headache, cephalgia, or cephalalgia, drug therapy, drug treatment, anti-migraine therapy, anti-migraine treatment, and treatment outcome, combined with drugs and treatment known to be used in the treatment of acute migraine in children and adolescents. These terms were combined with a pediatric filter designed by the Cochrane Child Health Field. There were no language or publication restrictions in this selection process. The complete search strategy is presented in Appendix 2.

2.2.4 Searching other resources

A grey literature search included reference lists of the included studies, meeting abstracts from the American Headache Society and International Headache Society Scientific meetings (2000 to 2008). The investigators contacted primary authors, experts in the area, and drug manufacturers (GlaxoSmithKline, AstraZeneca, Ortho-McNeil, Merck, and Pfizer) for information on recent, ongoing, or unpublished trials. GlaxoSmithKline (http://www.gsk-clinicalstudyregister.com) and AstraZeneca (http://www.astrazenecaclinicaltrials.com) have clinical trial registries and report on both published and unpublished studies. In addition, Current Controlled Trials (http://www.controlled-trials.com) was used using to search across multiple trial registries.

2.2.5 Trial Selection

Two independent reviewers examined the titles and abstracts from the original search to identify potentially relevant articles. Those studies with insufficient information in the title or abstract were also included as potentially relevant articles for further assessment. The full text of potentially relevant studies was then reviewed for inclusion and exclusion criteria by two independent reviewers. A third independent reviewer resolved disagreement between reviewers.

2.2.6 Data extraction and analysis

One reviewer (KR) extracted data using a standardized data abstraction form (Appendix 3). A second reviewed the data for accuracy and completeness (BV). Extracted data were recorded in Review Manager (Version 5; Cochrane Information Management System, http://ims.cochrane.org/). A third independent reviewer (LR) resolved discrepancies. Quality was assessed using the Jadad score (Jadad, Moore et al. 1996) and allocation concealment (adequate, unclear, or inadequate).

Review Manager was used for meta-analysis and testing of heterogeneity. Studies were pooled using a random effects model, where appropriate. Dichotomous outcomes were pooled and relative risks (RR) with 95% confidence intervals (CI) reported. For adverse events, data were combined using risk differences (RD) with 95% CIs. The overall weighted average placebo response rates for headache alleviation and pain-free proportions were calculated using the random effects model. Crossover trials were included in the analysis as carry-over

or period effects were not considered problems. Studies with missing data from either of the two primary outcomes were excluded from the analysis of efficacy; however, they were included in the analysis of adverse events. The I-squared (I^2) statistic was used to determine the presence of heterogeneity (Higgins and Thompson 2002). Thresholds for the interpretation of I^2 were as follows: (1) 0% to 40%: might not be important; (2) 30% to 60%: may represent moderate heterogeneity; (3) 50% to 90%: may represent substantial heterogeneity; (4) 75% to 100%: considerable heterogeneity (Higgins and Green 2008).

Reporting biases were assessed qualitatively by visually examining the symmetry of the funnel plot. Quantitative assessment of the publication (small study) bias was also performed using Stata (Version 10.1, College Station, Texas) by the rank correlation test (Begg and Mazumdar 1994) and Egger's test (Egger, Davey Smith et al. 1997).

2.2.7 Subgroup analysis and investigation of heterogeneity

The route of drug delivery was the only planned subgroup analysis for individual drugs. Additional sources of heterogeneity were examined by the following *a priori* analyses: (1) cross-over versus parallel study design; (2) methodological quality based on allocation concealment (i.e., adequate, unclear, or inadequate); (3) sources of funding (pharmaceutical, non-pharmaceutical, or unclear); and (4) the fixed effects model. All subgroup and sensitivity analyses were performed for the primary outcome measure pain-free using all triptan placebo-controlled studies.

2.3 Results

2.3.1 Description of studies

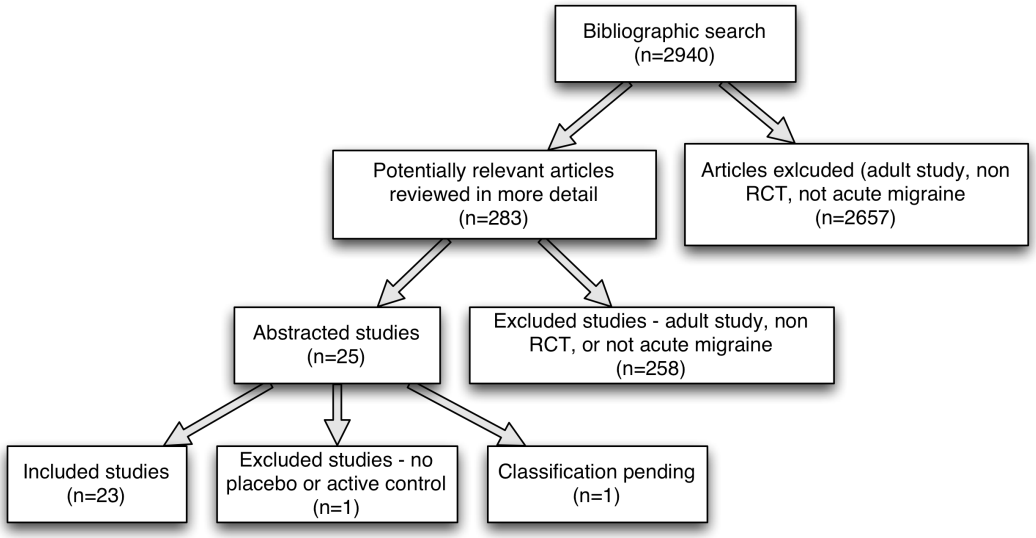
Figure 2.1 outlines progress through stages of the systematic review. A total of twenty-three randomized-controlled trials of migraine abortive medications in children were identified of which nineteen were of the triptan class of medications (serotonin 1b/1d receptor agonists) including almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Other medications studied included acetaminophen, ibuprofen, dihydroergotamine, prochlorperazine, and ketorolac. All but one of the studies was conducted in the outpatient setting with oral or intranasal preparations. The one study conducted in the Emergency Department compared intravenous prochlorperazine to ketorolac. All included studies reported on the primary outcome headache relief and data for the pain-free outcome was missing in only one study (Pitman 2000). One study of eletriptan (Pitman 2000) and one of ibuprofen (Lewis, Kellstein et al. 2002) did not report adverse events. One secondary study of rizatriptan vs. standard care (Visser, Winner et al. 2004) was excluded as the comparator was not randomized to placebo or an active treatment. Data for one study of nimesulide vs. acetaminophen (Soriani, Battistella et al. 2001) was requested, but not yet available and is pending classification.

2.3.2 Risk of bias for included studies

Publication bias was assessed using pain-free as the primary outcome for all placebo-controlled triptan studies. On visual inspection, the funnel plot (Figure

2.2) was reasonably symmetric suggesting minimal publication bias. The Harbord (p=0.126) and Egger (p=0.086) tests for funnel plot asymmetry were not significant.

Figure 2.1 Progress through stages of meta-analysis



Tables 2.1 and 2.2 outline the characteristics of the included studies. All studies were described as randomized and double blind, but the method of randomization was inadequately reported in 15 and described in general terms such 'randomized 1:1' or 'block randomization to two age groups'. Three studies clearly reported the method of blinding. A pharmaceutical company was the sponsor for seventeen studies, all of which were of the triptan class. All twenty-three studies adequately reported withdrawals and dropouts.

Table 2.1 Characteristics of included studies involving triptan migraine medications.

Medication (route)	**Design (centers)**	**Country (sponsor)**	**Age range (mean)**	**Proph.**	**Jadad**	**Alloc.**
Almotriptan vs. placebo (PO) (Linder, Mathew et al. 2008)	P (93) n=714	Americas (Ph)	12-17 (14.4)	NR	5	A
Eletriptan vs. placebo (PO) (Pitman 2000)	P n=277	US (Ph)	12-17 (14)	NR	5	A
Naratriptan vs. placebo (PO) (Rothner 1997)	P (44) n=300	US (Ph)	12-17 (14.3)	+	5	UNC
Rizatriptan vs. placebo (PO) (Ahonen, Hämäläinen et al. 2006)	C (2) n=96	Finland (UNC)	6.1-16.1 (12)	-	4	A
Rizatriptan vs. placebo (PO) (Visser, Winner et al. 2004)	P (44) n=291	US (Ph)	12-17 (14.2)	+	4	A
Rizatriptan vs. placebo (PO) (Winner, Lewis et al. 2002)	P (19) n=473	US (Ph)	12-17 (14)	+	3	UNC
Sumatriptan vs. placebo (PO) (Hämäläinen, Hoppu et al. 1997)	C (3) n=23	Finland (NPh)	8-18 (12.3)	-	4	UNC
Sumatriptan vs. placebo (PO) (GSKS2CT37)	P (14) n=92	Canada (Ph)	12-17 (13.6)	-	4	UNC
Sumatriptan vs. placebo (PO) (GSKS2CT40)	P (18) n=102	Europe (Ph)	12-17 (13.5)	-	4	UNC
Sumatriptan vs. placebo (PO) (GSKSUMB2003)	P (62) n=243	Int. (Ph)	12-17 (13.6)	-	4	UNC

Medication (route)	Design (centers)	Country (sponsor)	Age range (mean)	Proph.	Jadad	Alloc.
Sumatriptan vs. placebo (PO) (Winner, Prensky et al. 1997)	C (35) n=298	US (Ph)	12-17 (13.9)	+	4	UNC
Zolmitriptan vs. placebo (PO) (Rothner, Wasiewski et al. 2006)	P (40) n=645	Int. (Ph)	12-17 (14.2)	NR	5	A
Sumatriptan vs. placebo (IN) (Ahonen, Hämäläinen et al. 2004)	C n=83	Finland (Ph)	8-17 (12.4)	-	4	A
Sumatriptan vs. placebo (IN) (GSKSUM30009)	C n=59	Germany (Ph)	8-12 (9.7)	-	5	UNC
Sumatriptan vs. placebo (IN) (GSKSUM300042)	C (18) n=46	Nl (Ph)	12-17 (13.6)	-	4	UNC
Sumatriptan vs. placebo (IN) (Ueberall and Wenzel 1999)	C n=14	Germany (UNC)	6.6-9.8 (8.2)	-	4	UNC
Sumatriptan vs. placebo (IN) (Winner, Rothner et al. 2000)	P n=507	US (Ph)	12-17 (14.06)	+	5	UNC
Sumatriptan vs. placebo (IN) (Winner, Rothner et al. 2006)	P (65) n=478	US (Ph)	12-17 (14.3)	-	5	A
Zolmitriptan vs. placebo (IN) (Lewis, Winner et al. 2007)	C (17) n=275	US (Ph)	12-17 (14.2)	+	5	A

Route (PO = oral, IN = intranasal); Design (P = parallel, C = crossover);

Country (US = United States, Int. = International, Nl = Netherlands, UNC =

Unclear); Sponsor (Ph = Pharmaceutical, NPh = Non-pharmaceutical, UNC =

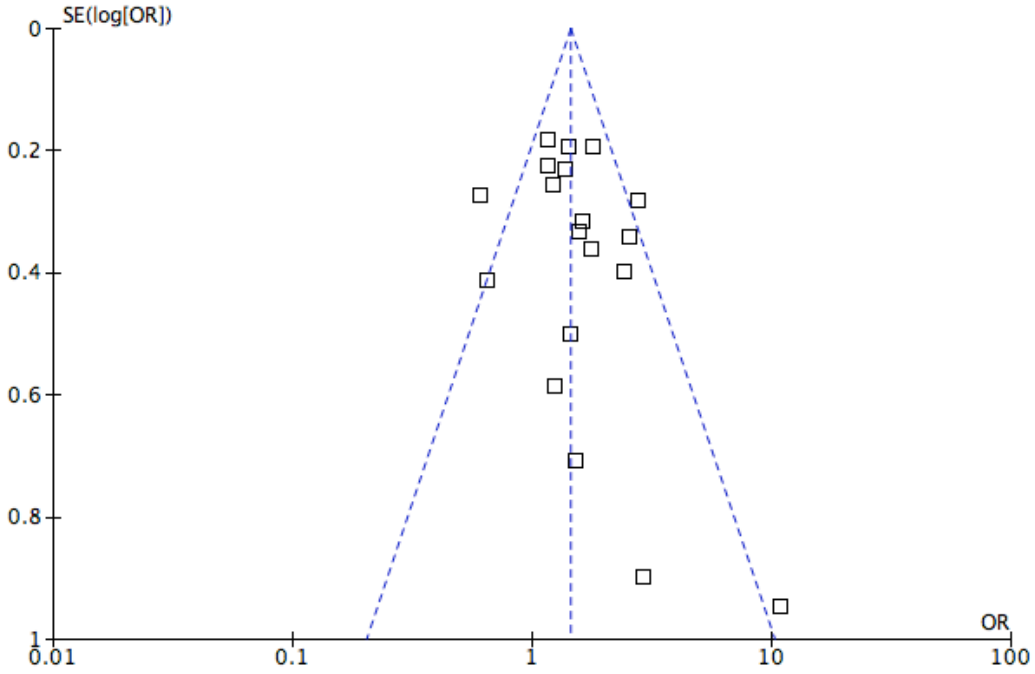
unclear); Proph. = Prophylaxis (+ = allowed, - = not permitted, NR = not reported); Alloc. = Allocation Concealment (A = adequate, UNC = unclear)

Table 2.2 Characteristics of included studies involving other migraine treatments.

Medication (route)	**Design (centers)**	**Country (sponsor)**	**Age range (mean)**	**Proph.**	**Jadad**	**Alloc.**
DHE vs. placebo (PO) (Hämäläinen, Hoppu et al. 1997)	C (3) n=12	Finland (NPh)	5-15 (10.3)	-	4	A
Ibuprofen vs. acetaminophen (PO) (Hämäläinen, Hoppu et al. 1997)	C (3) n=43	Finland (NPh)	4-15.8 (10.7)	NR	3	UNC
Ibuprofen vs. placebo (PO) (Lewis, Kellstein et al. 2002)	P n=84	US (NPh)	6-12 (9)	+	3	UNC
Prochlorperazine vs. ketorolac (IV) (Brousseau, Duffy et al. 2004)	P (2) n=62	US (NPh)	5-18 (13.7)	+	4	A

Route (PO = oral, IV = intravenous); Design (P = parallel, C = crossover); Country (US = United States); Sponsor (Ph = Pharmaceutical, NPh = Non-pharmaceutical, UNC = unclear); Proph. = Prophylaxis (+ = allowed, - = not permitted, NR = not reported); Alloc. = Allocation Concealment (A = adequate, UNC = unclear)

Figure 2.2 Funnel plot of all triptan studies versus placebo using; pain-free outcome.



2.3.3 Efficacy and safety of oral triptans (almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) vs. placebo

Twelve RCTs evaluated oral triptans versus placebo involving 3912 participants. The pooled result of all oral triptan medications showed no significant benefit for treatment over placebo (RR 1.16; 95% CI = 0.98 to 1.37); Figure 2.3) for the pain-free outcome or headache relief (RR 1.07; 95% CI = 0.95 to 1.21). As the results were not significant, the NNT was not calculated. Substantial heterogeneity was observed among the twelve studies (I^2 = 70%) for the headache relief outcome, but less among the twelve studies reporting pain-free (I^2=46%).

Compared with placebo, oral rizatriptan was the only individual triptan to show significance for the pain-free outcome (Figure 2.3), but was not significant for headache relief. Almotriptan was the only individual triptan to show significant headache relief (RR 1.27; 95% CI = 1.10 to 1.47), but no significant effect was observed for the pain-free outcome.

The use of rescue medications was significantly lower overall for triptans when compared with placebo (RR 0.76; 95% CI = 0.68 to 0.85), although sumatriptan (RR 0.70; 95% CI = 0.58 to 0.84)) was the only individual triptan to show a significant benefit. Heterogeneity among studies for the overall effect was low (I^2 = 1%). There was significant heterogeneity for the presence of nausea between studies (I^2 = 64%) with almotriptan (RR 1.69; 95% CI = 1.06 to 2.69) and sumatriptan (RR 1.71; 95% CI = 1.18 to 2.49) showing a modest increase in

nausea and rizatriptan (RR 0.52; 95% CI = 0.31 to 0.88) showing a decrease. Studies of eletriptan, naratriptan, rizatriptan, and sumatriptan reported the presence of vomiting, but no significant overall effect or individual effect was observed. The presence of sonophobia was similar for studies of eletriptan, naratriptan, rizatriptan, and sumatriptan and showed no overall effect, but almotriptan showed a small decrease at 2 hours (RR 0.77; 95% CI = 0.59 to 0.99). Studies of almotriptan, eletriptan, naratriptan, and sumatriptan reported on the presence of photophobia, but no significant overall effect was observed. Individually, almotriptan was the only triptan to show a decrease in photophobia (RR 0.76; 95% CI = 0.61 to 0.96).

Adverse events were more common overall for studies of oral triptans (Figure 2.3) with a risk difference of 0.13 (95% CI = 0.06 to 0.21); however heterogeneity was high (I^2=89%) for the overall estimate. No serious adverse events were reported. The most common adverse events included dizziness, somnolence, asthenia, dry mouth, and nausea/vomiting.

Figure 2.3 Forest plot of oral triptan versus placebo; pain-free outcome.

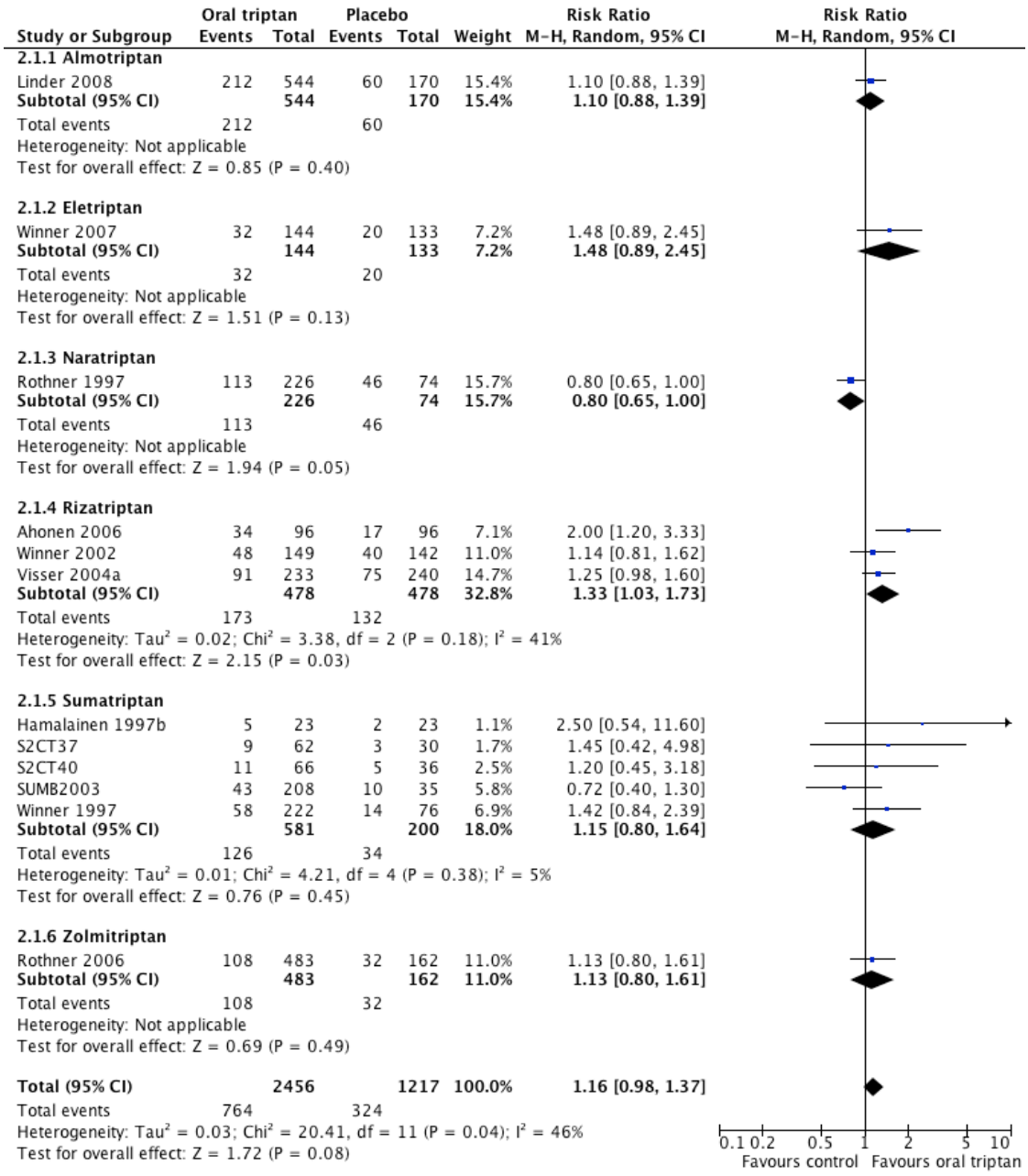
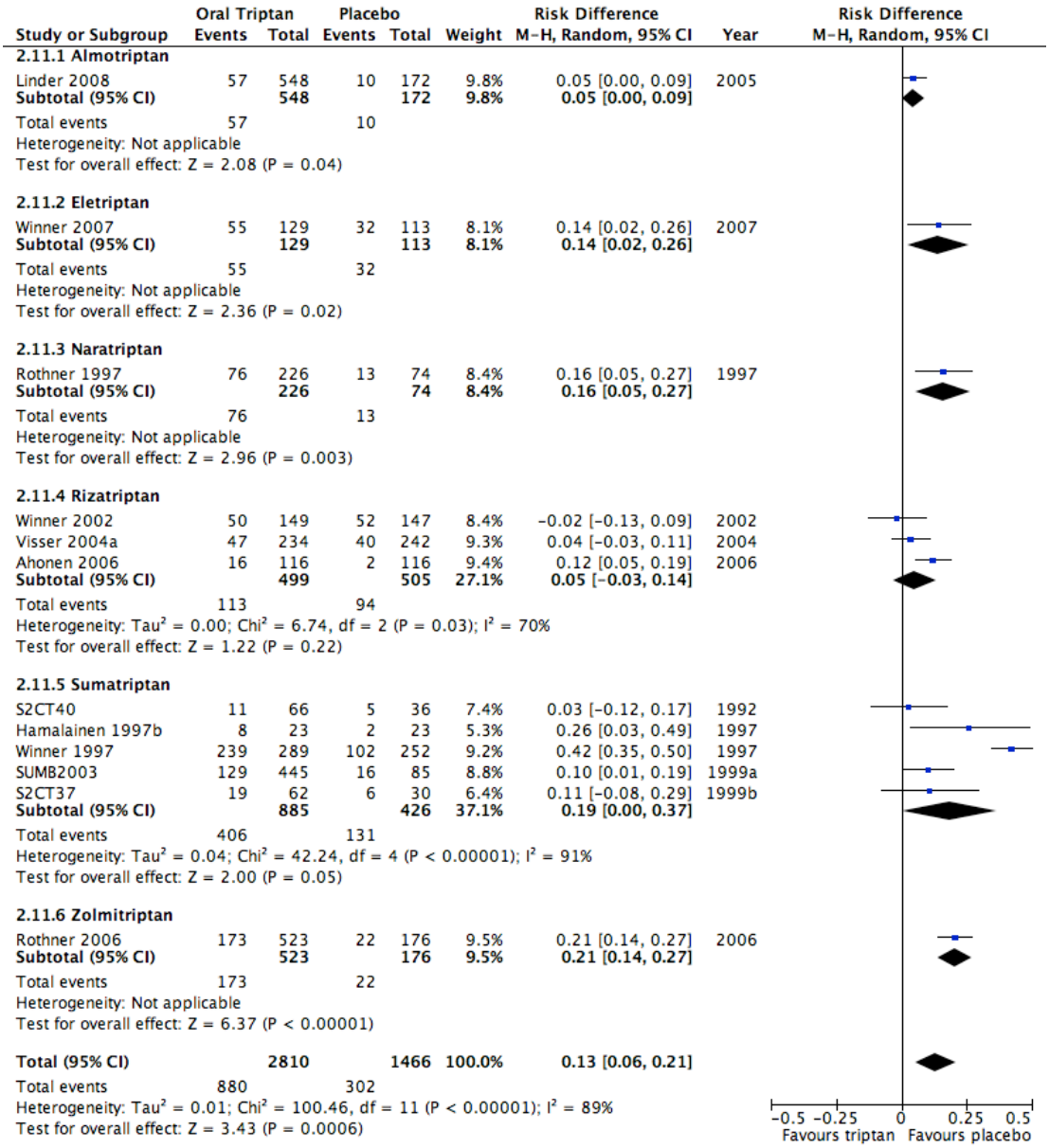


Figure 2.4 Forrest plot of all oral triptans versus placebo for adverse events



2.3.4 Efficacy and safety of intranasal triptans (sumatriptan and zolmitriptan) vs. placebo

Six studies of intranasal sumatriptan and one study of intranasal zolmitriptan were identified with a total of 1663 participants. For pain-free, both intranasal sumatriptan (RR 1.46; 95% CI = 1.23 to 1.73; Figure 2.4) and zolmitriptan (RR 2.07; 95% CI = 1.37 to 3.13; Figure 2.4) were superior to placebo. Heterogeneity was absent among the intranasal sumatriptan studies (I^2=0%). Headache relief was also significantly improved for sumatriptan (RR 1.32; 95% CI = 1.13 to 1.54) and the single zolmitriptan study (RR 1.24; 95% CI = 1.02 to 1.52) when compared with placebo.

Intranasal sumatriptan was numerically superior to oral sumatriptan for the pain-free outcome (Figure 2.5), but the ratio of relative risks (RRR) for comparison of two estimated RR (Altman and Bland 2003) was not statistically significant (RRR = 1.27; 95% CI = 0.85 to 1.89). Similarly, intranasal sumatriptan was numerically superior to oral sumatriptan for headache relief (RR 1.41; 95% CI = 1.11 to 1.78) vs. RR 1.03; 95% CI = 0.85 to 3.2), but the RRR was not statistically significant (RRR = 1.37; 95% CI = 0.68 to 2.77).

Intranasal zolmitriptan (RR 2.07; 95% CI = 1.37 to 3.13) was superior to oral zolmitriptan (RR 1.13; 95% CI = 0.80 to 1.61) for the pain-free outcome and the RRR was statistically significant (RRR = 2.19; 95% CI 1.07 to 3.15). There was also a significant difference between intranasal zolmitriptan (RR 1.24; 95% CI = 1.02 to 1.52) and oral zolmitriptan (RR 0.94; 95% CI = 0.80 to 1.10) for headache relief (RRR 1.32; 95% CI = 1.02 to 1.7).

Figure 2.5 Forest plot of intranasal triptans versus placebo; pain-free outcome

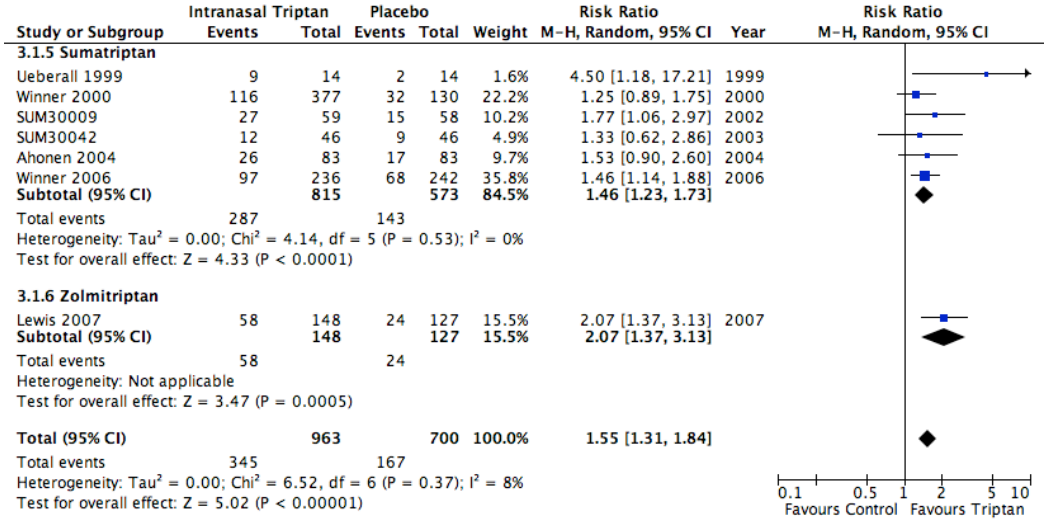
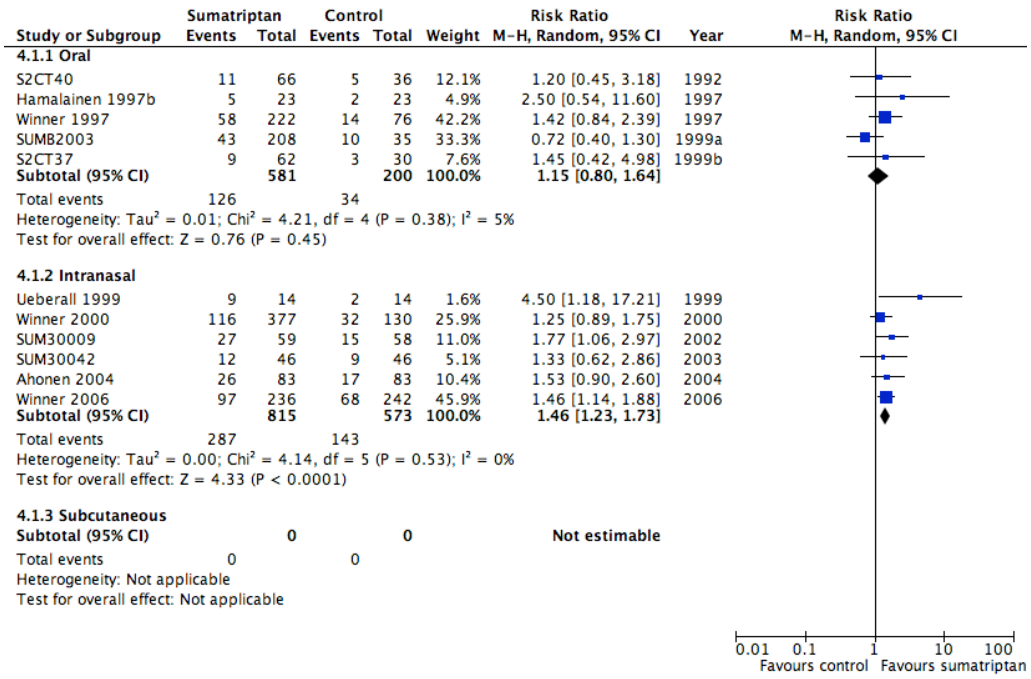


Figure 2.6 Forrest plot of oral sumatriptan versus intranasal sumatriptan



The use of rescue medications was less with the pooled analysis of intranasal sumatriptan (RR 0.74; 95% CI = 0.59 to 0.93) and the one study of zolmitriptan (RR 0.77; 95% CI = 0.59 to 0.99) when compared with placebo. A reduction in nausea was observed with sumatriptan (RR 0.70; 95% CI = 0.52 to 0.93), but not zolmitriptan. An effect on the presence of sonophobia and photophobia was similar to that observed with nausea. Sonophobia (RR 0.71; 95% CI = 0.61 to 0.82) and photophobia (RR 0.77; 95% CI = 0.64 to 0.92) were significantly reduced with intranasal sumatriptan, but not in the one study of zolmitriptan.

Adverse events were reported more commonly with intranasal sumatriptan and zolmitriptan with a risk difference of 0.13 (95% CI = 0.07 to 0.2). Taste disturbance, nasal symptoms and nausea were commonly reported. Heterogeneity was moderately high for the overall estimate at I^2=58%. No serious adverse events were reported.

2.3.5 Subgroup and sensitivity analysis

All sensitivity analyses comparing triptans to placebo for our primary outcome pain-free are summarized in Table 2.3. No significant reduction in the overall heterogeneity (I^2=53.8%; 19 studies) was observed with the sensitivity analysis of the statistical model (random vs. fixed effects). Heterogeneity was reduced when considering the route of delivery, allocation concealment, publication type, study design, and sponsorship. Studies of intranasal triptans, studies with adequate description of allocation concealment, studies published in

journals or in a clinical trial registry, crossover studies, and studies in which sponsorship was not stated were more homogeneous.

Table 2.3 Sensitivity analyses

	RR (95% CI)	**I^2**	***p***
Delivery route			
Oral (12 studies)	1.16 (0.98 to 1.36)	46.1%	0.040
Intranasal (7 studies)	1.56 (1.31 to 1.84)	7.9%	0.368
Allocation concealment			
Unclear (11 studies)	1.15 (1.00 to 1.33)	53.2%	0.019
Adequate (8 studies)	1.36 (1.21 to 1.52)	39.1%	0.118
Publication type			
Journal (13 studies)	1.36 (1.23 to 1.50)	30.8%	0.137
Abstract (3 studies)	0.91 (0.74 to 1.12)	56.3%	0.102
Not published (3 studies)	1.31 (0.77 to 2.26)	0.0%	0.971
Study design			
Crossover (8 studies)	1.80 (1.47 to 2.21)	0.0%	0.739
Parallel (11 studies)	1.16 (1.05 to 1.28)	44.6%	0.054
Sponsor			
Pharmaceutical (16 studies)	1.24 (1.13 to 1.36)	50.6%	0.011
Non-pharmaceutical (1 study)	2.50 (0.54 to 11.60)	NA	NA
Unclear (2 studies)	1.28 (1.17 to 1.40)	19.1%	0.266
Statistical model			
Random effects (19 studies)	1.30 (1.13 to 1.51)	53.8%	0.003
Fixed effects (19 studies)	1.28 (1.17 to 1.40)	53.8%	0.003

2.3.6 Placebo response rate for all triptans (oral and intranasal)

The placebo response rate overall for all nineteen triptan studies was 0.49 (95% CI = 0.44 to 0.54) for headache relief and 0.22 (95% CI = 0.18 to 0.25; Figure 2.6) for the nineteen studies reporting the pain-free outcome. The placebo response rate did not vary by route of drug delivery (i.e., oral versus intranasal).

2.3.7 Efficacy and safety of oral dihydroergotamine vs. placebo

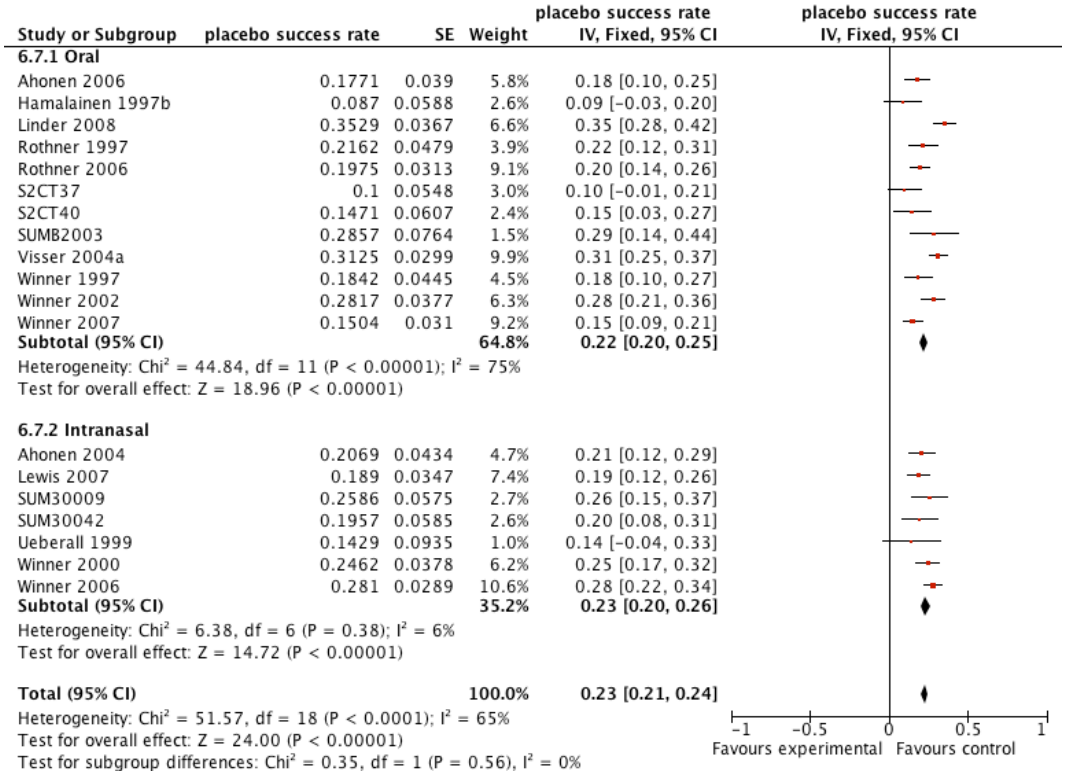
One crossover study compared dihydroergotamine (DHE) 20 µg/kg to placebo in 12 subjects. The estimated RR for the pain-free outcome was 11 in favor of DHE, but 95% CI was large (0.67 to 179.29) and not significant. The RR for headache relief was 3.50 (95% CI 0.91 to 13.53) and not significant. Two minor adverse events were reported in the DHE group. A higher dose of DHE (40 µg/kg) was also administered to the same subjects, but data was available for only nine and not analyzed further.

2.3.8 Efficacy and safety of ibuprofen and acetaminophen vs. placebo

In the pooled analysis, ibuprofen (RR 1.96; 95% CI = 1.30 to 2.95); I^2=0%) was superior to placebo in two studies of the pain-free outcome and headache relief (RR 1.54; 95% CI = 1.18 to 2.01; I^2=0%). In one study of acetaminophen however, the pain-free and headache relief outcomes were not significant ([RR 1.40; 95% CI = 0.76 to 2.58] and [RR 1.44; 95% CI = 0.89 to 2.33], respectively). Neither ibuprofen nor acetaminophen was statistically superior to placebo in the use of rescue medications. Headache recurrence was

significantly reduced with ibuprofen (RR 0.26; 95% CI = 0.11 to 0.60, I^2=0%) and acetaminophen (RR 0.25; 95% CI = 0.01 to 5.68) when compared with placebo. There was no difference in the rates of adverse events between ibuprofen and acetaminophen when compared with placebo.

Figure 2.7 Placebo response rate for all triptan medications comparing oral and intransal delivery for the pain-free outcome



2.3.9 Efficacy and safety of intravenous prochlorperazine vs. ketorolac

One study compared intravenous prochlorperazine 0.15 mg/kg to ketorolac 0.5 mg/kg after each child received a 10 mL/kg bolus of normal saline solution over 30 minutes. Prochlorperazine was superior to ketorolac for the pain-free outcome (RR 4.83; 95% CI = 1.17 to 20.03) and headache relief (RR 1.54; 95% CI = 1.07 to 2.20). The difference in the mean change in numerical pain scores (Nine Faces Pain Scale) favored prochlorperazine (mean difference 0.17; 95% CI = 0.03 to 0.31). There was no difference in adverse events.

2.4 Discussion

A total of twenty-three randomized-controlled trials of migraine abortive medications in children were identified which is very small in comparison to the over 1000 migraine-related RCTs listed in the Cochrane Central Register of Controlled Trials. Nineteen of the trials were of the triptan class of medications (serotonin 1b/1d receptor agonists) including almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Frequently used pain medications (acetaminophen and ibuprofen) have been evaluated in only two studies and only one study was conducted in the Emergency Department.

Unlike the adult studies of triptan medications, oral triptans were not superior to placebo in our pooled analysis for either the pain-free outcome or headache relief. Intranasal preparations of sumatriptan and zolmitriptan were, however, significantly better than placebo on both primary outcome measures.

The pharmacokinetics of the intranasal preparations may be one reason for their success in adolescents. Intranasal delivery allows for rapid absorption of un-metabolized drug to the central nervous system and earlier onset of action when compared with oral delivery (Rapoport and Winner 2006).

The high placebo response rates for children in studies of triptan medications are also often cited as the reason study outcomes have varied from the adult experience (Lewis, Winner et al. 2005). In our meta-analysis of pediatric triptan studies, the placebo responder rates were 23% for the pain-free outcome and 53% for headache relief; however, we did not observe a difference on the overall placebo response rates between oral and intranasal studies (Figure 2.6). If the response to placebo was the primary reason for the difference between adult and pediatric studies, one might have expected the intranasal studies to have a lower response than the oral studies. Notably, the single intranasal zolmitriptan trial employed a unique study design described as a 'double-diamond' with the hope of reducing the placebo response rate. In the study, each subject treated his or her migraine attack in a single-blind fashion with intranasal normal saline. If the subject responded within 15 minutes, they did not receive the randomized study drug or placebo. The placebo response rates were however similar to those observed in our meta-analysis – 54% and 19% respectively for headache relief and the pain-free outcome (Lewis, Winner et al. 2007).

Ibuprofen was the only simple analgesic medication with demonstrated efficacy in the treatment migraine in children. Acetaminophen, while often used by clinicians and parents alike, was not found to be significantly superior to

placebo in one study (Hämäläinen, Hoppu et al. 1997). Ibuprofen is an NSAID and non-specific inhibitor of COX isoforms - COX-1 and COX-2. Non-selective COX inhibition may be uniquely beneficial in migraine especially if treatment of the attack has been delayed (Jakubowski, Levy et al. 2007; Levy, Zhang et al. 2008). Studies of combined sumatriptan and naproxen are promising in adult studies (Lipton, Dodick et al. 2009), but have not been replicated in children.

Intravenous prochlorperazine and ketorolac were the only two medications studied in the ED setting. Prochlorperazine was found to be more effective and was generally well tolerated. Side-effects were reported in only two subjects both of whom received prochlorperazine and included agitation and mild muscle stiffness. No pediatric studies of other commonly used medications for migraine treatment in the ED (e.g. metoclopramide, other NSAIDs) were identified.

Compared with other qualitative and systematic reviews of acute migraine therapy in children, we identified the highest number of studies. Canadian guidelines based on adult studies were one of the first to be published (Pryse-Phillips, Dodick et al. 1997). A qualitative review of pediatric studies published on behalf of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society did not restrict study designs to RCTs and identified only five study agents (oral and intranasal sumatriptan, ibuprofen, acetaminophen, oral rizatriptan and oral zolmitriptan) (Lewis, Ashwal et al. 2004). The first systematic review of triptan medications for children identified only four RCTs (Major, Grubisa et al. 2003) and a similar study of all migraine drugs used in children identified only ten RCTs

(Damen, Bruijn et al. 2005). Finally, in the latest systematic review only eleven RCTs were identified (Silver, Gano et al. 2008). Our study is unique in that data from the GlaxoSmithKline (http://www.gsk-clinicalstudyregister.com) and Astrazeneca (http://www.astrazenecaclinicaltrials.com) clinical trial registries were included and an extensive search of the grey literature was conducted thereby increasing the study identification rate.

While the methods employed in our study were robust, they were time-consuming. The final search was dated to Feb 2008 so very recent studies may have been missed and this is a potential weakness of our work. The associated Cochrane Collaboration publication of this review will need to be updated frequently. We have also chosen to group all triptan medications together in the analysis of oral and intranasal preparations. Each triptan, while similar, has unique pharmacological and pharmacokinetic properties.

2.4.1 Implications for practice

Intranasal preparations of sumatriptan and zolmitriptan are superior to placebo in the treatment of acute migraine in children. These medications are safe with no increase in serious adverse events, while minor adverse events including nasal symptoms, taste disturbance, and nausea were increased. Ibuprofen is the only simple analgesic that is superior to placebo in aborting migraine headaches in children that has been studied to date. Finally, intravenous prochlorperazine is superior to ketorolac in the treatment of acute migraine in the ED and appears to be safe.

2.4.2 Implications for research

The response to placebo is a critical factor of particular relevance in studies of pain like migraine. Study design strategies to decrease the placebo responder rate will serve to better differentiate the active medication effect of relevance to children from the inherent neurobiology of central pain systems (i.e. the perception of pain is purely a construct of the central nervous system and thus very susceptible to suggestion/expectation). The physiology of the placebo response in migraine warrants evaluation as mental events induced by placebo may activate mechanisms similar to those activated by drugs (Colloca and Benedetti 2005). Future intervention studies of drugs or alternative therapies for migraine in children may need to be modified accordingly.

The rate of absorption and onset of action seem to be important factors in the success of migraine therapy as demonstrated in the intranasal studies of sumatriptan and zolmitriptan. The combination of medications like metoclopramide to increase the rate of absorption of oral analgesics like ibuprofen may serve to improve their efficacy (Azzopardi and Brooks 2008). Similarly, treating a migraine early in the attack may be more rewarding than if one delays treatment and warrants evaluation in children as it is being studied in adults (Goadsby, Zanchin et al. 2008; Goadsby 2008). Finally, more research on the safety and relative efficacy of migraine therapies employed on children in the ED is required.

Finally, pain freedom is the most clinically desirable outcome measure to patients. The International Headache Society Clinical Trials Subcommittee has

recognized this and recommends that pain-free be the primary outcome measure for migraine RCTs (Tfelt-Hansen, Block et al. 2000). In support of this recommendation, we observed that the overall effect sizes in our meta-analysis were often higher with pain-free as the outcome compared with headache relief. As such, pain free may not only be the preferred outcome measure on which to assess the efficacy of a migraine intervention, but may also provide better separation from placebo.

Chapter 3

3 Regional Practice Variation Study[3]

3.1 Introduction

Evidence on the acute management of a child with migraine in the Emergency Department (ED) is limited. In the only ED-based trial of interventions to treat acute migraine, intravenous prochlorperazine was found to be superior to ketorolac (Brousseau, Duffy et al. 2004). Among many options, effective agents identified in adult research include metoclopramide (Colman, Brown et al. 2004), valproate (Frazee and Foraker 2008), and dihydroergotamine (Swidan, Lake et al. 2005). How best to treat a child in the ED is debatable and highly influenced by adult studies.

In the absence of clinical evidence to support pediatric specific decision-making one might expect management choices to be based on the adult evidence. However, even in the adult EDs the evidence is often ignored. For example, while opioids are not considered effective first line agents and their use has been restricted to recalcitrant cases only (Ducharme 1999; Friedman, Kapoor et al. 2008; Friedman and Grosberg 2009), first line narcotic use has been reported as high as 50% (Colman, Rothney et al. 2004) in adult ED patients. Given the lack of

[3] A version of this chapter has been published. Richer, L., L. Graham, et al. (2007). "Emergency department management of acute migraine in children in Canada: a practice variation study." Headache **47**(5): 703-10.

data specific to the pediatric population, even greater variation of practice might be expected in the care of children with acute migraine presenting to the ED.

The objective of this study was to examine the management choices of emergency physicians treating children presenting with headache. The main question addressed was: How do emergency physicians currently manage pediatric migraine headaches? The research involved both a pediatric tertiary care ED as well as mixed pediatric and adult community EDs. Given the relative high use of opioids in the adult population, a secondary question addressed was: Does management differ between patients seen in the Pediatrics ED compared to the mixed adult and pediatric ED?

3.2 Methods

3.2.1 Study design

A retrospective chart review design was used to examine the treatment of acute migraine headache, with a particular focus on the analgesic agents employed. The audit followed the suggested guidelines for chart review in Emergency Medicine research (Gilbert, Lowenstein et al. 1996).

3.2.2 Case selection

Charts were identified from four regional hospital Emergency Departments (ED) in Edmonton, Alberta, Canada (Capital Health region) between July 2003 and June 2004, for patients aged 2 to 17 years with an International Classification of Diseases (ICD; 10^{th} revision) primary discharge diagnosis of migraine without aura (G430), migraine with aura (G431), other migraine (G438),

and migraine, unspecified (G439). In addition, the diagnosis of headache (R51) was also included in the review because many physicians assign the general diagnosis of headache when treating a migraine headache. At the time of the study, trained medical record nosologists coded each ED chart using ICD-10 criteria for up to 6 diagnoses. All four sites were urban teaching hospitals staffed by full-time emergency physicians whose responsibilities include medical student and resident instruction.

Each study subject was classified according to the most likely diagnosis: (1) *migraine* and (2) *other headache*. For the purpose of the study a clinical diagnosis of migraine by the treating physician was sufficient to classify the case as a migraine given that the physician was likely to make management choices based on their own clinical diagnosis. If there were sufficient data in the ED chart to support the diagnosis of migraine or probable migraine based on International Classification of Headache Disorders, 2nd edition (ICHD-II; Appendix 1) then the diagnostic coding was changed. *Other headache* was defined as insufficient data to support a diagnosis of migraine.

Secondary causes of headache were excluded including hydrocephalus, major or severe head trauma (i.e., intracranial hemorrhage, cerebral contusion, and skull fracture), central nervous system (CNS) infection and CNS neoplasm. Children reporting mild or moderate head trauma (i.e., no skull fracture or intracranial hemorrhage) within the preceding 4 weeks were included as were subjects reporting infectious symptoms (i.e., fever, cough, rhinorrhea, diarrhea) not referable to an intracranial infection (e.g., no meningismus, altered level of

consciousness, or neurological abnormalities). Infectious symptoms and minor head trauma were considered possible confounders in the analysis as previous studies have shown that head injury and upper respiratory tract infection are relatively common causes of headache in the pediatric population (Kan, Nagelberg et al. 2000; Lewis 2001).

The chart abstractor was trained, explicit definition and criteria for case selection and variables were provided, and standard abstraction forms were used. Items on the form included demographic factors, details about the initial presentation to the ED, symptoms prompting the visit, medication self-administered prior to ED presentation, examinations and investigations done, treatment provided in the ED, and outcomes of care. The chart abstractor was monitored with regard to performance comparing a randomized selection of charts between two abstractors, and blinding of the chart reviewer with regard to the etiologic relation between pediatric or adult emergency physicians and management choices.

3.2.3 Outcomes and explanatory variables

The primary outcome of interest was the first medication or management choice made by the treating emergency physician. In addition, two secondary outcomes measures were chosen as a measure of compliance with published treatment guidelines (Lewis, Ashwal et al. 2004) and the available evidence for acute migraine therapy in children (Chapter 2): (1) use of opioid medication; and (2) use of a parenteral dopamine antagonist (metoclopramide, prochlorperazine, chlorpromazine). Two primary explanatory variables were used: (1) mixed (the

three mixed adult and pediatric EDs) versus pediatric only EDs; and (2) headache type (migraine or other headache). Possible adverse events were recorded if documented in the ED record. Polypharmacy was defined as using two or more medications during the same ED admission. Additional explanatory variables included age, gender, use of pain medications prior to presentation to the emergency department, intravenous fluid therapy, and the need for a second attempt at treatment. A past history of headache in each study subject could not be readily determined by the available data in the charts and therefore this variable was not included. Blood work, lumbar puncture, and neuroimaging (computed tomography (CT) and magnetic resonance imaging (MRI)) ordered during the admission were also recorded. Outcome at discharge in terms of headache resolution or persistence of headache was identified as well as the disposition of the patient (hospital admission or discharge home). Repeat visits were identified, but if the return occurred within the same week, the child was assumed to be suffering from the same headache attack and this was only counted as one event.

3.2.4 Data Analysis

Data were analyzed using SPSS® (Chicago, Illinois). Proportions are presented with 95% confidence intervals (95% CIs) and calculated using $p \pm 1.96\sqrt{\frac{p(1-p)}{N}}$ where p is the estimated proportion and N is the sample size. Comparison of baseline characteristics between the mixed and pediatric-only ED cohorts was based on the calculated 95% CI. Comparisons for the primary outcome variables (dichotomous) are reported as Pearson chi-square (χ^2) tests.

Binary logistic regression was also performed on the primary outcome variables to control for possible confounding factors.

The Health Research Ethics Board of the University of Alberta approved the protocol for this study. The study was conceived and designed after the patient encounters had occurred; physicians were unaware that a study would be conducted at the time of the patient encounter.

3.3 Results

3.3.1 Sample population

In total, 382 children aged 2 to 17 years with migraine or other headache were identified presenting to four regional EDs (Edmonton, Alberta, Canada) during the study period. Table 3.1 summarizes the baseline characteristics of the cohort. Children presenting to the mixed ED were significantly older, more likely to have suffered a mild or moderate head injury within the preceding 4 weeks, and less likely to be diagnosed with migraine.

Table 3.1 Baseline characteristics of children with headache in both mixed adult/pediatric and pediatric-only Emergency Departments

	Total Cohort n=382	Mixed ED n=147	Pediatric ED n=235	
	Mean or % (95% CI)	Mean or % (95% CI)	Mean or % (95% CI)	
Demographic factors				
Mean Age	11.36 (11.01 - 11.71)	11.98 (11.63 - 12.33)	10.97 (10.62 - 11.32)	*
Female	47.6% (42.6% - 52.7%)	44.2% (39.2% - 49.2%)	49.8% (44.8% - 54.8%)	NS
Mild or Moderate Head Injury	12.6% (9.2% - 15.9%)	21.1% (17.0% - 25.2%)	7.2% (4.6% - 9.8%)	*
Took simple analgesic	24.9% (20.5% - 29.2%)	34.7% (29.9% - 39.5%)	18.7% (14.8% - 22.6%)	*
Infectious Symptoms	11.8% (8.5% - 15.0%)	13.6% (10.2% - 17.0%)	10.6% (7.5% - 13.7%)	NS
Intravenous started	11.5% (8.3% - 14.7%)	12.9% (9.6% - 16.3%)	10.6% (7.5% - 13.7%)	NS
Intravenous fluid bolus given	9.9% (6.9% - 12.9%)	9.5 % (6.6% - 12.5%)	10.2% (7.2% - 13.2%)	NS
Repeat ED visit	1.8% (0.5% - 3.2%)	1.4% (0.2% - 2.5%)	2.1% (0.7% - 3.6%)	NS
Type of headache				
Migraine	48.7% (43.7% - 53.7%)	42.2% (37.2% - 47.1%)	52.8% (47.8% - 57.8%)	*
Other headache	51.3% (46.3% - 56.3%)	57.8% (52.9% - 62.8%)	47.2% (42.2% - 52.2%)	

* $p < 0.05$

3.3.2 Investigations

Laboratory tests were ordered in 12% overall (95% CI = 8.8% to 15.3%), but more frequently in the mixed ED sites (17%; 95% CI = 13.2% to 20.8%) compared with the pediatric ED site (8.9%; 95% CI = 6.1% to 11.8%). A lumbar puncture was performed in nine patients (2.4%; 95% CI = 0.08% to 3.9%) with no difference between the mixed and pediatric ED cohorts. Neuroimaging with CT scan was performed in 109 subjects and 2 more had an MRI for a total of 111 scans (29.1%; 95% CI = 24.5% to 33.6%). Again there was no observed difference observed between mixed and pediatric ED cohorts. Pathological diagnoses based on neuroimaging included arachnoid cysts (n=2), optic glioma (n=1), sinus thrombosis (n=1) and sinusitis (n=1) for a total of 5 of 109 studies (4.6%; 95% CI = 0.7% to 8.5%).

3.3.3 ED Management

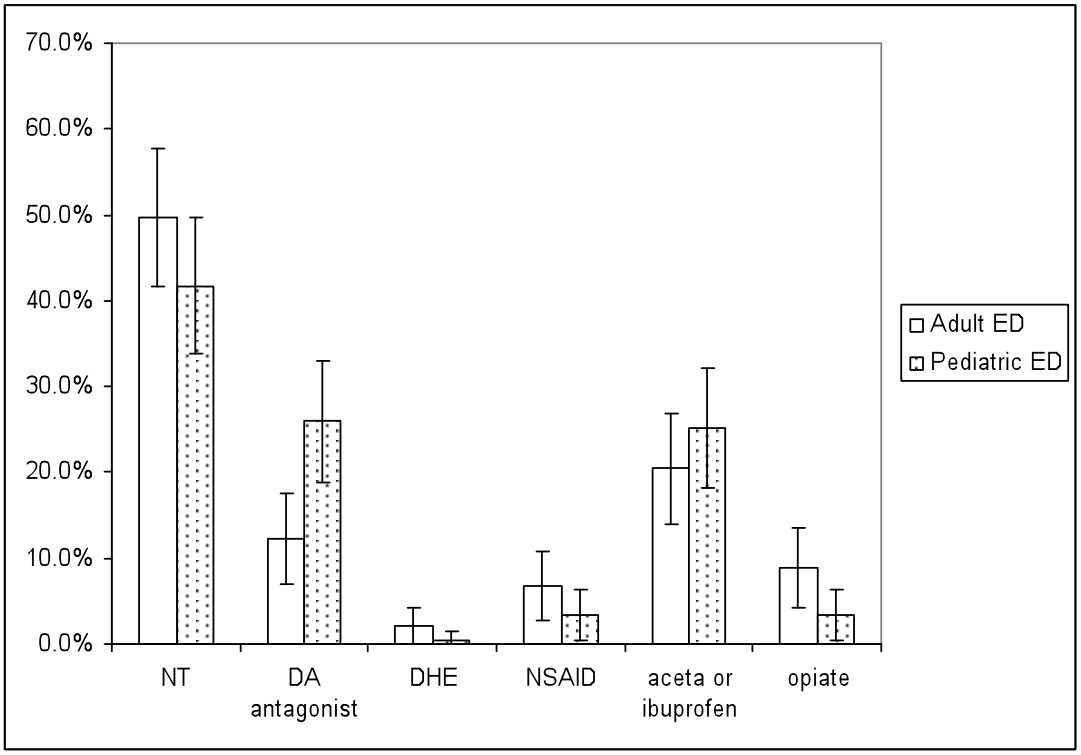
The most common management choice for all types of headache was no treatment in 169 subjects (44.2%; 95% CI = 39.3% to 49.2%). Simple oral analgesics were used first in 89 subjects (23.3%; 95% CI = 19.1% to 27.5%) of which ibuprofen was used in 47 and acetaminophen in 42. Dopamine antagonists were used first in 79 subjects (20.7%; 95% CI = 16.6% to 24.7%) of whom the majority (n=76) used metoclopramide. Prochlorperazine was used in only 3 subjects as a first-line treatment. Ketorolac was administered in 18 subjects (4.7%; 95% CI = 2.6% to 6.8%) and opioid medications (e.g., codeine, meperidine, morphine) were administered as first line agents in 21 subjects (5.5%; 95% CI = 3.2% to 7.8%). Dihydroergotamine (DHE) was used in 4 subjects (1%;

95% CI = 0% to 2.1%). Caffeine (n=2) or dimenhydrinate (n=2) was used infrequently. Polypharmacy (two or more medications) was used in 31.2% of the cohort (95% CI = 26.5% to 35.8%). No adverse events were documented.

3.3.4 Comparison between mixed and pediatric-only EDs

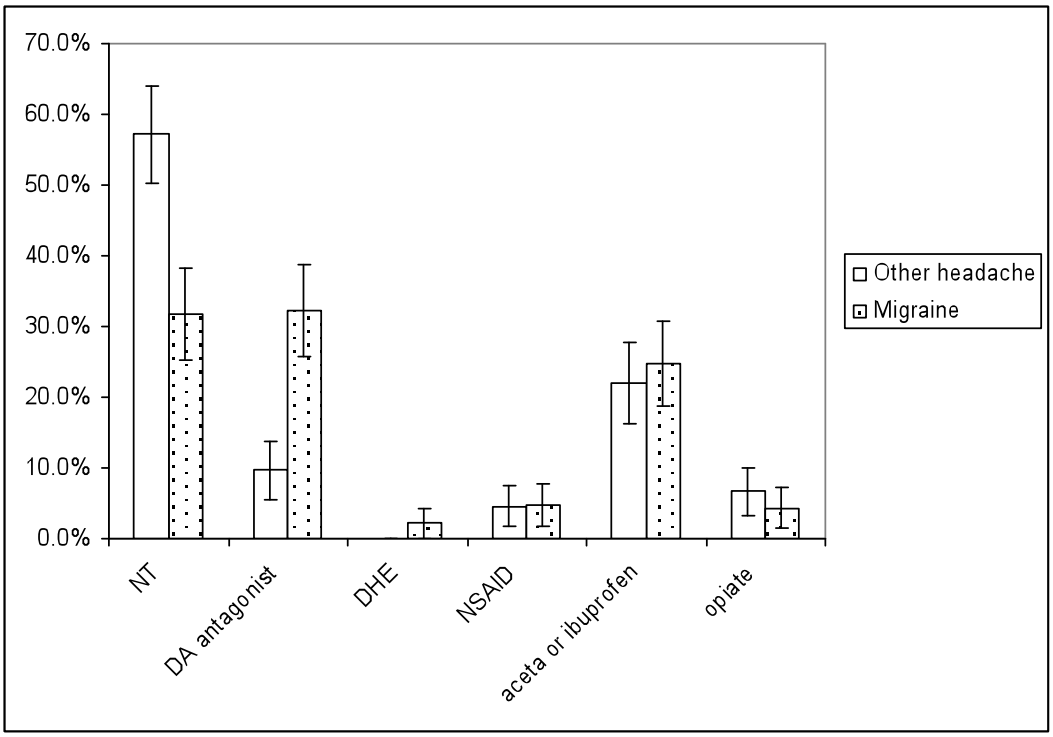
Figure 3.1 compares management or medication choices between the mixed vs pediatric EDs for children presenting with all headache types. There was a significant association between medication/management choices and whether the child was treated in a mixed vs pediatric ED (χ^2=19.695; df=5; p=0.001). Pediatric emergency physicians were significantly more likely to prescribe a dopamine antagonist (Figure 3.1; χ^2=10.366; df=1; p=0.001); however, no difference was observed among other medication/management choices (i.e., no treatment, simple analgesics, opioids, dihydroergotamine, NSAIDs). No significant differences were identified in the way children with post-traumatic headache or infectious symptoms were treated. When including all medications used for the duration of the ED visit, the physicians in mixed ED sites were also significantly more likely to use opioid medications when compared with pediatric emergency physicians (12.9 vs 6.8%; p=0.044), while pediatric emergency physicians were significantly more likely to use a dopamine antagonist (28.1% vs.18.4%; p = 0.031).

Figure 3.1 Comparison between mixed and pediatric EDs



Relative proportions of first management or medication choices comparing pediatric and adult emergency department cohorts. Error bars represent 95% confidence intervals. No treatment (NT); dopamine (DA) antagonist (metoclopramide, prochlorperazine); dihydroergotamine (DHE); non-steroidal anti-inflammatory (NSAID); acetaminophen (aceta); opioid (codeine, meperidine, morphine); emergency department (ED).

Figure 3.2 Comparison between children diagnosed with migraine vs. other headache



Relative proportions of first management or medication choices comparing subjects diagnosed with migraine and those with other headache types. Error bars represent 95% confidence intervals. No treatment (NT); dopamine (DA) antagonist (metoclopramide, prochlorperazine); dihydroergotamine (DHE); non-steroidal anti-inflammatory (NSAID); acetaminophen (aceta); opioid (codeine, meperidine, morphine); emergency department (ED).

3.3.5 Headache Types

Children diagnosed with migraine were treated differently than children diagnosed with other headache types as seen in Figure 3.2. Children with migraine were significantly more likely to receive drug therapy (68.3% vs. 42.9%; $p<0.001$) or a dopamine antagonist (32.3% vs. 9.7%; $p<0.001$). Overall, when considering all medications used for the duration of the ED visit, patients with a migraine diagnosis were significantly more likely to receive a dopamine antagonist (37.1% vs. 12.2%; $p<0.001$); however, they were just as likely to receive an opioid medication as *other headache* patients (9.1% vs. 9.2%; $p=0.988$).

3.3.6 Outcomes

Documentation of outcome at discharge was limited due to missing data and could not be assessed in the majority of the cohort (78.5%; 95% CI = 74.4% to 82.7%). Documentation of the headache outcome was better in the pediatric ED (22.1% vs 13.6%) compared with the adult EDs. Of those records in which the outcome could be assessed, complete headache resolution was observed in 13.9% (95% CI = 10.4% to 17.3%) and was significantly more common in the pediatric ED cohort (20%; 95% CI = 16% to 24%) compared with the adult ED cohort (4%; 95% CI = 2.1% to 6.1%). It is noteworthy that 10 of the 30 subjects with persistent headache had received an opioid medication. However in a *post-hoc* analysis on the headache outcome at discharge using binary logistic regression and controlling for age, head injury, and type of headache as well as opioid use,

treatment in a pediatric ED remained the only significant factor in predicting complete headache resolution (Wald statistic 4.777; df=1; p=0.03).

3.4 Discussion

Using four EDs across a linked Canadian health care region, this study examined the management of acute pediatric migraine headaches. The most common management choice by emergency physicians in this study was to deliver no specific drug therapy. This was followed by simple analgesics (e.g., ibuprofen, acetaminophen) prior to the delivery of more traditional migraine therapies (e.g., dopamine antagonists, ketorolac, opioids, and DHE). No patients received triptan medications.

Neuroimaging was performed in close to one third of children. Practice guidelines suggest that neuroimaging need not be performed in children on a routine basis unless there is an abnormality on the neurological examination, seizures, or a recent change in the headache pattern (Lewis, Ashwal et al. 2002). The proportion of neuroimaging studies seems high given these recommendations in a population of selected migraine subjects. Others have observed similar rates of CT scan use in a population of children presenting with all causes of headache (Lateef, Grewal et al. 2009). Interestingly, as few as 5% of the scans showed any abnormality and no more than half of these may have had any relationship to the headache. Reducing the use of neuroimaging, particularly CT scans, may have benefits to the patient through decreased radiation exposure, reduced the length of stay in EDs, and reduced overall costs. Confidence in the diagnosis of the cause

for headache in the absence of biological markers for primary headaches like migraine may be the main obstacle.

Children with infectious symptoms and a history of mild head trauma were treated similarly in our study. Overall, 12% of children had documented infectious symptoms, which is lower than might be expected based on previous reports. Kan (Kan, Nagelberg et al. 2000) found 28.5% of pediatric headaches presenting to an ED were associated with viral or respiratory illness. Our case definition required a discharge diagnosis of headache or migraine and thus children diagnosed with an infection may have been classified accordingly. A history of minor head trauma was reported in one of every eight children and did not appear to influence management choices. Reports of the efficacy of anti-migraine therapies in post-traumatic headache are noteworthy (Herd and Ludwig 1994). Whether children with a history of minor head trauma should be treated with migraine therapies may warrant further evaluation.

Children with the clinical diagnosis of migraine were more likely to be prescribed medication compared with those diagnosed with other headache types. One may speculate that the headache resolved in the untreated children, but the absence of reliable outcome data did not allow us to examine this. Another possible explanation is that the focus of the ED visit was diagnostic (i.e., what is causing the headache) for those without a diagnosis of migraine. There was no difference observed between mixed and pediatric EDs in the proportion of children receiving drug therapy. The development of improved diagnostic tools

for children with migraine may serve to reduce the use of ancillary test and increase the utilization of evidence-based treatment strategies.

Clinical practice guidelines for treating children with migraine in the ED are predominantly based on opinion and evidence derived from adult studies (Bailey and McManus 2008). While the efficacy of dopamine antagonists such as metoclopramide and prochlorperazine is well established in adult studies (Coppola, Yealy et al. 1995; Colman, Brown et al. 2004), there is only one randomized-controlled study in children comparing prochlorperazine to ketorolac (Brousseau, Duffy et al. 2004). Despite the available evidence for dopamine antagonists in adults, these agents were used more often in the pediatric-only ED (28% vs. 18%). The proportion prescribed a dopamine antagonist increased to 41% in those patients diagnosed with migraine. Interestingly the influence of adult teaching and evidence was prevalent as metoclopramide was still the most frequently prescribed dopamine antagonist. The practice appears to be safe as no serious adverse events were reported. Adult-based practice guidelines certainly do not recommend opioids as first-line treatment for migraine (Pryse-Phillips, Dodick et al. 1997). Nevertheless, almost 50% of adult patients received opioids as a first line treatment in a related study in the same health care region (Colman, Rothney et al. 2004). While opioids were used less frequently in children (approximately 12%), the mixed population EDs were still more likely to prescribe one.

Since ED pharmacological treatments were well documented we are confident in the validity of treatment variation; however, there are several

potential limitations. First, as in many retrospective studies, poor chart documentation was a problem particularly with headache outcome at discharge. Second, relapse data were not available, as patients were not contacted in follow-up. Finally, only one region's experience was examined, and this did not include rural hospitals, other provinces, or non-teaching hospitals. The bias associated with this may limit the generalizability of the results; however, it is likely to *underestimate* the practice variation that may exist outside of urban academic teaching hospitals

3.4.1 Implications for practice and research

In summary, significant variation in practice was observed between mixed population and pediatric-only EDs in the management of acute headaches in children. Limited evidence upon which to guide practice decisions is the most likely explanation for the practice variability. Neuroimaging studies were frequently ordered, but very infrequently contributed to the child's care. Most children presenting with headache to the ED did not receive any drug therapy, yet children with a physician diagnosis of migraine were more likely to be treated. The most commonly used medications were simple analgesics like acetaminophen and ibuprofen and dopamine antagonists like metoclopramide. A physician's diagnosis of migraine influenced their management decisions as dopamine antagonist were much more likely to be prescribed in patients with migraine as a diagnosis. Overall, children presenting to the pediatric-only ED were significantly more likely to receive a dopamine antagonist while opioids, not considered effective treatment for migraine, were prescribed more commonly in the mixed

EDs. Targeted educational and knowledge translation strategies may help to improve the care of children with migraine

The pediatric-only ED was more likely to prescribe evidence-based treatments like metoclopramide and simple analgesics while avoiding opioids. Clinical uncertainty exists in a number of areas including the use of oral analgesics vs. parenteral migraine therapies (e.g. dopamine antagonists) and the relative efficacy of metoclopramide versus other dopamine antagonist like prochlorperazine. An evaluation of practice variation among multiple tertiary pediatrics EDs will serve to more clearly establish national patterns and highlight critical research issues in the care of children with migraine.

Chapter 4

4 National Practice Variation Study

4.1 Introduction

Children with migraine headache often present to the Emergency Department (ED) when outpatient management has failed; however, only one trial has examined migraine abortive medications in children in this setting (Brousseau, Duffy et al. 2004). While there are published narrative reviews of the treatment of children with migraine in the ED (Kabbouche, Linder et al. 2005; Schobitz, Qureshi et al. 2006), definitive evidence-based guidelines have not been published. Not surprisingly, in a regional migraine headache study in Canada, significant variation between mixed population and pediatric-only EDs was observed (Richer, Graham et al. 2007). The pediatric EDs adhered more closely to treatment guidelines in the use of dopamine antagonists and less frequent use of opioids.

Pediatric emergency physicians would likely benefit from further research to help guide management decisions. The questions for clinicians in practice are numerous; however, an assessment of the *status quo* is a necessary first step in planning further research or a clinical trial. To our knowledge, there are no national practice variation studies examining the acute treatment of migraine in pediatric centers. Our objectives were to assess the following: (1) characteristics of the population of children being treated for migraine in Canadian pediatric

EDs; (2) treatment practices of pediatric emergency physicians; (3) current investigations being conducted; and (4) documented discharge management.

4.2 Methods

4.2.1 Pediatric Emergency Research Canada (PERC) Sites

The participating EDs were all academic pediatric-only emergency centers staffed generally by full-time certified emergency physicians who are part of Pediatric Emergency Research Canada (PERC; http://perc.srv.ualberta.ca), a nationally funded research network. Most sites function as regional referral sites for trauma, surgery, and complex congenital and acquired diseases in patients under the age of 17 (some variation in the upper age limit exists across the country). Ten tertiary pediatric ED, in six Canadian provinces provided data for this study.

4.2.2 Study design and case selection

A retrospective chart review of pediatric ED presentations for migraine or headache was conducted adhering to the suggested guidelines for chart reviews in emergency medicine research (Gilbert, Lowenstein et al. 1996). The charts of children 5 to 17 years of age seen in the ED between July 1, 2004 and June 30, 2005 with a discharge diagnosis of all "migraine" types or "headache" based on the International Classification of Disease (ICD) 9^{th} or 10^{th} revision were identified and screened for inclusion and exclusion criteria. Each ED presentation was screened if a subject had multiple visits as long as they occurred seven or more days apart.

Inclusion criteria included the following: (1) presence of headache at the time of physician assessment; (2) age 5 to 17 years; and (3) diagnosis of migraine by the emergency physician; or sufficient criteria for a diagnosis of migraine or probable migraine for those ED admissions coded only as headache. The following were required for a diagnosis of migraine or probable migraine when the ED admission was coded only as headache: (1) presence of headache, (2) two of nausea, emesis, photophobia, or sonophobia. Exclusion criteria included: (1) patients who left prior to being assessed by a physician; (2) patients in whom another disorder may explain the headache including intracranial shunt, intracranial mass, intracranial hemorrhage, and intracranial infection; (3) an ED visit within one week (7 days) of the initial presentation.

4.2.3 Data management

Standardized and validated electronic data extraction forms (Appendix 4) were implemented on a web-based clinical research data management system (OpenClinica®; Boston, Massachusetts, United States). The specific data items recorded included physician diagnosis (migraine or headache), patient demographics (age, sex), migraine characteristics and associated symptoms (unilateral, pulsatile, nausea, emesis, photophobia, sonophobia, aura, aura type, duration of current headache, frequency of headache, total number of headache attacks), medications used prior to the ED visit (migraine abortive medications, migraine prophylactic medications), season (Spring, Summer, Fall, Winter), investigations requested in the ED (imaging studies, lumbar puncture, consultation), use of an intravenous fluid bolus (defined as any volume of

intravenous fluid above that required for infusion of the parenteral medication), medications ordered and route administered, adverse events, admission to hospital, and discharge management (medication, consultation, investigations).

4.2.4 Data analysis

Data were analyzed with Stata® (College Station, Texas, United States). Categorical variables were described with proportions and 95% confidence intervals (CI), while continuous variables were described with means and 95% CIs. The primary unit of sampling was site so the data were analyzed as panel data clustered on site. Clustering was considered in the variance estimation using the survey methods in Stata® (Taylor series linearization) and population weight based on the average number of ED admissions per year.

The primary outcome variable was an aggregate marker of any 'evidence-based' treatment. Migraine abortive treatments with some evidence in children or use in the ED included the following: acetaminophen, ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDS), serotonin 1b/1d receptor agonists (triptans), dihydroergotamine, and dopamine antagonists (metoclopramide, prochlorperazine, chlorpromazine). The use of evidence-based treatment with no use of opioids was also examined and two secondary outcome variables: (1) no use of medication; (2) use of a dopamine antagonist (prochlorperazine, metoclopramide, chlorpromazine). Oxygen, diphenhydramine, dimenhydrinate, opioids (codeine, meperidine, morphine, and oxycodone), corticosteroids (prednisone, dexamethasone, methylprednisolone), benzodiazepines, muscle relaxants, and ondansetron were not included in the evidence-based group.

Practice variation was assessed using the chi-square test and displayed as a figure. Predictive factors for the use of evidence-based treatment (with or without opioids) and secondary outcome variables were assessed with logistic regression clustered on site with a conditional fixed-effects model. Predictive factors were included at a 5% level of significance and included age, sex, presence of aura and migraine associated symptoms (nausea, emesis, photophobia, sonophobia), duration of current headache, diagnosis of migraine, headache frequency, season, date of admission, and prior use of migraine abortive or prophylactic medications.

Ethics

The Health Research Ethics Board approved the protocol for this study at the University of Alberta and at every additional site. The study was conceived and designed after the patient encounters had occurred; physicians were unaware that a study would be conducted at the time of the patient encounter.

4.3 Results

4.3.1 Sample population

A total of 2515 hospital records were screened in 10 tertiary pediatric EDs in six Canadian provinces and 1694 (67.4%) met inclusion criteria. The most common reasons for exclusion were no headache at the time of assessment by a physician (n=509) and insufficient criteria for a diagnosis of migraine (n=213). Other reasons included intracranial hemorrhage (n=7), intracranial shunt (n=64), and an intracranial mass (n=28). The age (12.1 vs. 9.4 yrs) and sex (89.7 vs. 57.4% females) of the included and excluded groups were different.

4.3.2 Demographics and headache description

The mean age was 12.1 years (95% CI = 11.4 to 12.9) with a range of 5 to 17 years of which 57.4% (95% CI = 51.8 to 62.9) were females. The range of ages among the ten sites was 10.8 years (95% CI = 10.3 to 11.4) to 14 years (95% CI = 13.7 to 14.3). On average, children presented 2.19 days after the onset of the migraine attack (95% CI = 1.62 - 2.75). An aura was present in 27.2 % (95% CI = 19.9 to 35.9) of subjects overall and 14.5% (95% CI = 12.1 to 17.2) had migraine on more than 15 days per month. The time of year was equally distributed between seasons. The average length of stay in the ED was 4.4 hours (95% CI = 3.7 to 5.1) with a range of means between 2.9 hours (95% CI = 2.4 to 3.5) and 6 hours (95% CI = 5.4 to 6.6).

4.3.3 Medications used prior to the ED

Among all subjects presenting to the ED, 62.6% (95% CI = 55.7 to 68.9) had already used one or more abortive medications. The most common abortive medications used were oral analgesics (52.6%; 95% CI = 46.3 to 58.9) including acetaminophen and ibuprofen while only 2.2% (95% CI = 1.5 to 3.1) had used a triptan (serotonin 1b/1d agonist) medication. Overall, 4.7% (95% CI = 3.3 to 6.7) of subjects had used an opioid medication (e.g., codeine, meperidine, morphine, oxycodone).

Migraine prophylactic medications were recorded in only 6.1% (95% CI = 3.3 to 11.3). Among those subjects with migraine on more than 15 days per month, 82.1% (95% CI = 58.5 to 93.7) were not receiving prophylactic treatment. The most common prophylactic treatments were tricyclic antidepressants (e.g.,

nortriptyline and amitryptiline) in 38.9% (95% CI = 11.7 to 75.3). Alternative treatments (predominantly vitamin B2) were used in 24.4% (95% CI = 4.6 to 68.4) and topiramate was used in 8.9% (95% CI = 3.1 to 22.9). Cyproheptadine, pizotifen, propranolol, valproate, feverfew, and other medications each totaled 5% or less of those using a prophylactic medication.

4.3.4 Investigations

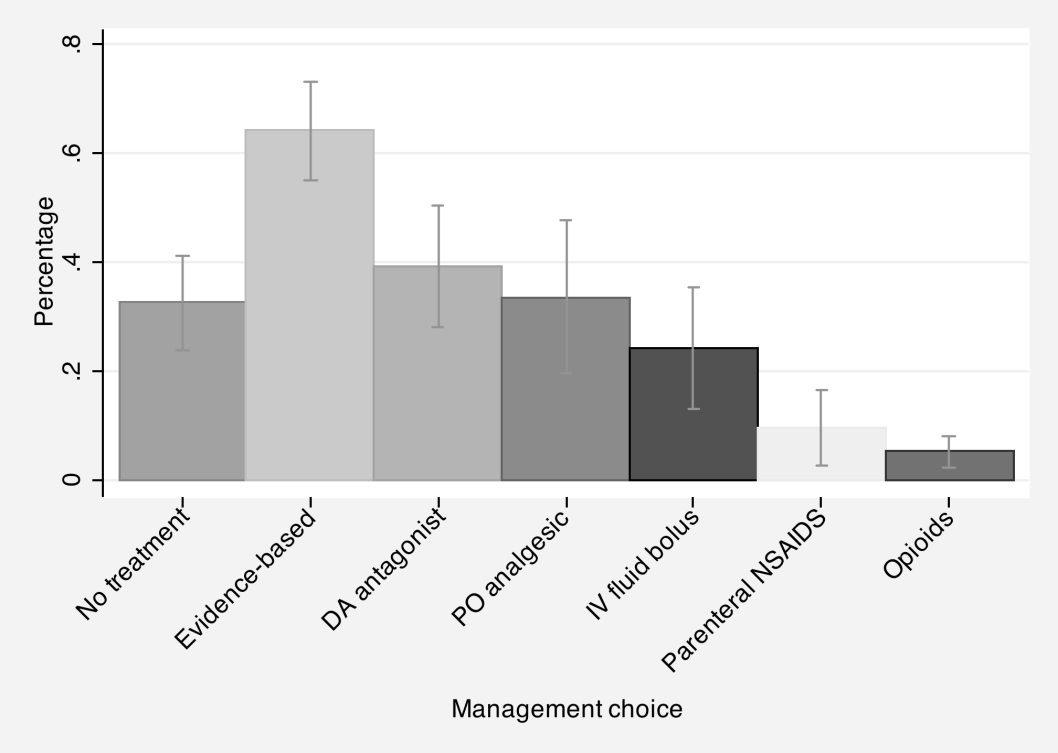
The most commonly ordered investigation was a computed tomography (CT) scan in 16.3 % (95% CI = 12.2 to 21.3) of which 8.2% (95% CI = 5.1 to 12.9) were abnormal. None of the abnormal scans altered management. Abnormalities included arachnoid cysts, previous infarction, and cerebral malformations. A lumbar puncture was performed in 2.1% overall (95% CI = 1 to 4.1) and none were abnormal. The ten EDs varied significantly in the use of CT ($p<0.001$) and lumbar puncture ($p=0.002$).

4.3.5 Evidence-based treatments

Figure 4.1 displays the most common management choices for the treatment of migraine in the ED. The diagnosis of migraine (OR 2.07; 95% CI = 1.23 to 3.48) by the treating physician and older age (OR 1.18; 95% CI = 1.09 to 1.27) were the strongest predictive factors for prescribing any medication. The presence of an aura decreased the likelihood of a medication being prescribed (OR 0.31; 95% CI = 0.14 to 0.70).

The use of ‘evidence-based’ treatment was observed in 64.2% overall (95% CI = 56.1 to 71.9) and Figure 4.2 displays the variation observed among the

Figure 4.1: Most common management choices for the treatment of migraine in the Pediatric Emergency Department.



Evidence-based (any one of a dopamine antagonist, oral analgesic, NSAID, triptan or dihydroergotamine (DHE)). DA antagonist (metoclopramide, prochlorperazine, chlorpromazine). PO analgesic (acetaminophen or ibuprofen). IV fluid bolus (intravenous fluid bolus). Parenteral NSAIDS (ketorolac, naproxen, diclofenac). Opioids (codeine, acetaminophen/codeine, meperidine, morphine, oxycodone). Proportions exceed 100% since multiple interventions were prescribed to some children.

ten sites. In the multi-variable adjusted analysis, older age (OR 1.15; 95% CI = 1.07 to 1.24) and the diagnosis of migraine (OR 1.84; 95% CI = 1.11 to 3.05) were associated with the use of evidence-base treatments. The same factors were observed when adjustment was made for the use of any opioids (i.e., not considered evidence-based) and with the use of a dopamine antagonist. Interestingly, children with an aura were less likely to be treated with a dopamine antagonist (OR 0.55; 95% CI = 0.32 to 0.92).

Overall, there was significant variability between sites (p=0.002 or less) for all medication classes except the use of antibiotics as displayed in Figure 4.2 and Table 4.1. The intravenous (IV) route was used in 48.4% of subjects overall (95% CI = 34.6 to 62.4) and a bolus of intravenous fluid was given to 24.3% (95% CI = 14.8 to 37.1). Dopamine antagonist medications were prescribed most frequently; 82.4% (95% CI = 60.4 to 93.5) received metoclopramide, 12.7 % (95% CI = 2.8 to 42.0) received prochlorperazine, and 4.9% (95% CI = 1.0 to 20.0) received chlorpromazine. Non-steroidal anti-inflammatory drugs (NSAIDS) were often prescribed in combination with a dopamine antagonist (36.5%; 95% CI = 21.3 to 55.1). Diphenhydramine was prescribed in 14% (95% CI = 3 to 46) of those who received a dopamine antagonist.

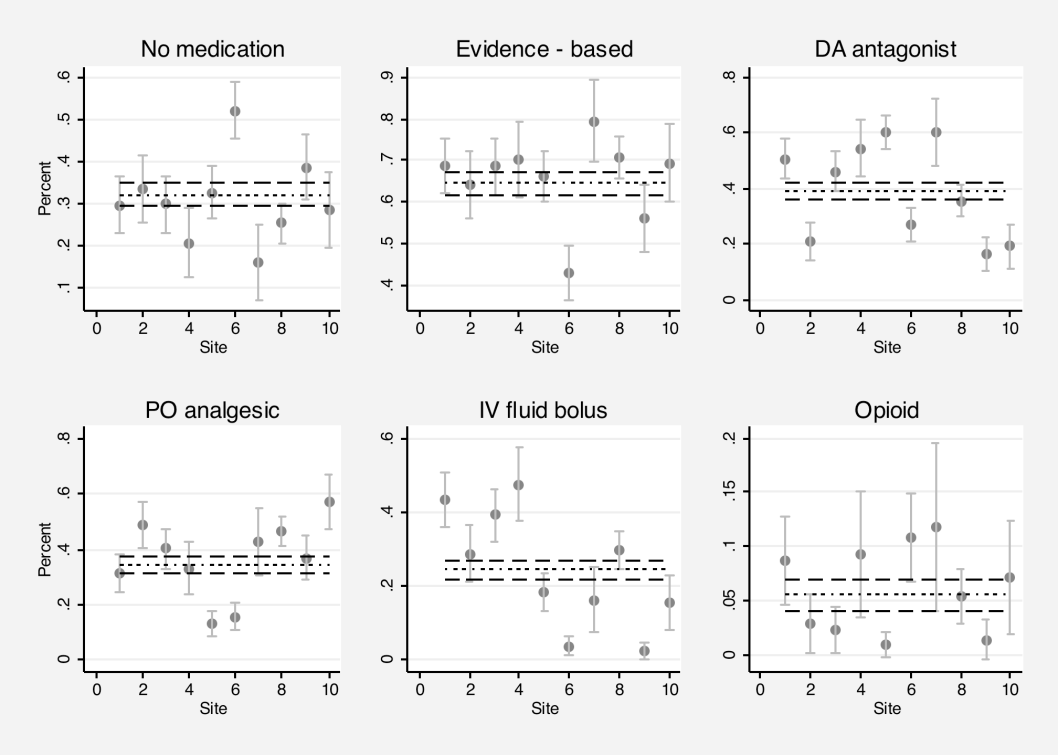
Oral analgesics included ibuprofen (66.3%; 95% CI = 59.8 to 72.3) and acetaminophen. Other parenteral NSAIDs (Figure 4.1) included predominantly ketorolac (70.9%; 95% CI = 21.8 to 95.5) and naproxen (20.9%; 95% CI = 2.3 to 74.5). Among all opioid medications administered (n=93; Figure 4.1), codeine was used in 39.1% (95% CI = 20.4 to 61.6), acetaminophen/codeine combined in

30.5% (95% CI = 15.5 to 51.2), and morphine in 27.6% (95% CI = 12.8 to 49.7) were the most frequently prescribed. Triptan medications were used infrequently and included eletriptan (n=1), sumatriptan (n=6) and zolmitriptan (n=1).

4.3.6 Adverse Effects

No serious adverse events were reported. Minor adverse events included vomiting (n=7), dizziness (n=3), nausea (n=2) and one each of dystonia, tachycardia, agitation, hypotension, and paresthesias. Dystonia, agitation, hypotension and paresthesias were observed in association with a dopamine antagonist.

Figure 4.2: Variation in practice for the most common management choices for pediatric migraine.



Sites are in no specific order and error bars are 95% confidence intervals. Evidence-based (any one of a dopamine antagonist, oral analgesic, NSAID, triptan or dihydroergotamine (DHE)). DA antagonist (metoclopramide, prochlorperazine, chlorpromazine). PO analgesic (acetaminophen or ibuprofen). IV fluid bolus (any volume of intravenous fluid above that required for infusion of the parenteral medication). Opioid (meperdine, codeine, acetaminophen/codeine, morphine, oxycodone).

Table 4.1: Medications prescribed for migraine in the Pediatric Emergency Department.

Medication	**%**	**95% CI**	**Range**	**Chi-square (p-value)**
Diphenhydramine	5.8	1.6 - 19	0 - 25	<0.001
Oxygen	3.6	0.6 - 19.5	0 - 31.3	<0.001
Dimenhydrinate	2.8	1.6 - 4.8	0.4 - 8.3	0.002
Corticosteroid[1]	2.5	1.3 - 4.8	0 - 6.2	<0.001
Benzodiazepine	1.4	0.5 - 3.9	0 - 10.3	<0.001
DHE	0.9	0.2 - 3.3	0 - 5.4	<0.001
Antibiotics (any)	0.8	0.5 - 1.4	0 - 1.6	0.694
Triptan[2]	0.5	0.1 - 2.6	0 - 4.3	<0.001

[1]Corticosteroid (dexamethasone, methylprednisolone, prednisone). [2]Triptan (eletriptan, sumatriptan, zolmitriptan).

4.3.7 Post-ED Care

The most frequently prescribed migraine abortive medications at discharge were ibuprofen (45.7%; 95% CI = 34.2 to 57.7), acetaminophen (17.2%; 95% CI = 12.1 to 23.8), and other NSAIDs (10.8%; 95% CI = 3.9 to 26.6). Triptans were prescribed in only 1% (95% CI = 0.5 to 2.2). Migraine prophylactic medications (e.g., amitryptiline, topiramate, propranolol, cyproheptadine, flunarizine, pizotofen, tegretol, gabapentin – in order of frequency) were prescribed in 10.2% overall (95% CI = 2.7 to 32). Of those with migraine on more than 15 days per month, only 30% (95% CI = 13.3 to 44.6) were prescribed prophylactic medication, but 47.7% (95% CI = 35.3 to 60.3) were referred to a neurologist or pediatrician. Opioid medications were prescribed in 5.4% (95% CI = 3.2 to 9.1), corticosteroids in 2.4% (95% CI = 0.5 to 11.6), and 2.2% of all subjects (95% CI = 1.3 to 3.6) were admitted to hospital.

4.4 Discussion

To our knowledge, this is the first national study of practice variation in the treatment of migraine headache in pediatric EDs. Pediatric EDs in Canada treat a similar population of children with migraine aged 10 and 14 years with small female predominance in all seasons. Of importance, children present to the ED an average of 2 or more days after the onset of the migraine and most of the children (60%) have already used an oral analgesic at home. As such, children presenting to the ED are relatively treatment resistant – a fact that should guide management approaches.

One third of patients who presented to the ED received no medication which is less than the 44% observed in the previously published regional practice variation study including 1 pediatric and 3 mixed adult-pediatric EDs (Richer, Graham et al. 2007). Nonetheless, 'evidence-based' treatment use was high, with approximately two-thirds of the sample receiving this level of care. Factors that predicted the use of 'evidence-based' treatment included older age and those in whom the physician made a diagnosis of migraine. As such, confidence in the diagnosis of migraine may help to improve management choices for children in the ED.

In the absence of more than one randomized-trial of migraine abortive treatment in the pediatric ED, it is not surprising then that there was significant practice variation among the ten pediatric EDs. Dopamine antagonists (predominantly metoclopramide) were the most frequently prescribed. While parenteral metoclopramide is an effective migraine abortive medication in adults (Colman, Brown et al. 2004), it has not been studied in children. The only randomized-controlled trial of intravenous prochlorperazine versus ketorolac, demonstrated prochlorperazine was more effective (Brousseau, Duffy et al. 2004). At least one adult study has found that prochlorperazine was superior to metoclopramide (Coppola, Yealy et al. 1995) and one other uncontrolled pediatric study of prochlorperazine indicates a very high response rate (Trottier, Bailey et al. 2009). In general, relatively few adverse events were observed, but most of those occurred with the use of dopamine antagonists. Whether prochlorperazine

and metoclopramide are comparable in safety and efficacy in children requires further evaluation.

Oral analgesics and NSAIDS are the second and third most commonly prescribed medication in the ED. Ibuprofen is superior to placebo, but not clearly superior to acetaminophen in the relief of headache associated with migraine (Hämäläinen, Hoppu et al. 1997; Lewis, Ashwal et al. 2002). Ibuprofen and other NSAIDS are non-specific COX1/COX2 inhibitors and these medications may also have unique properties of interest in the ED. Given that children presenting to the ED have had their headache for an average of 2 or more days – the use of a COX1/COX2 inhibitor alone or in combination with another agent may be uniquely effective under the assumption that central sensitization is established (Jakubowski, Levy et al. 2007). While the practice of combining medications (e.g., sumatriptan and naproxen) has been evaluated in some outpatient studies (Lipton, Dodick et al. 2009), there are no studies examining benefit in the ED. Nonetheless, the practice was relatively common in our study where an NSAID was prescribed in combination with a dopamine antagonist in over one-third of ED visits. Further examination of the efficacy of combined therapy in the ED appears warranted.

Migraine is a chronic disorder and children may not be getting effective outpatient care. Approximately 15% of children presenting to the ED reported headache on more than 15 days per month, but only 1 in 5 were being treated with prophylactic medications and in over 60%, an oral analgesic had already failed. Presentation to the ED reflects a failure of outpatient management and the

emergency physician has a unique opportunity to intervene not only for the current migraine attack, but on discharge as well. Specific migraine management strategies on discharge may reduce disability and improve outcomes, but these have not been studied. For example, the use of intranasal triptan medications may be appropriate for children in whom oral analgesics have failed (Damen, Bruijn et al. 2005). Similarly, children with frequently recurring migraine may benefit from prophylactic medication yet we observed that only 30% of children with headache on 15 or more days per month were prescribed such a medication at discharge. Prospective evaluation of evidence-based discharge plans in terms of reduced ED visits, improved quality of life, or reduced headache disability warrants further evaluation.

4.4.1 Implications for practice and research

Presentation to the ED with migraine represents failure of outpatient therapy and most children have already tried various oral analgesics. The emergency physician is uniquely positioned to intervene in this vulnerable population who generally present late in the course of a migraine attack. Confidence in the diagnosis of migraine by the treating physician was strongly associated with management choices and the use of evidence-based treatments. Improved migraine diagnostic tools for emergency physicians may secondarily improve the management of children with migraine and may be an appropriate target of future research.

Of the evidence-based medications, dopamine antagonists were the most common and included predominantly metoclopramide and prochlorperazine, but

these medications have not been compared in children. The dopamine antagonists were frequently prescribed in combination with a NSAID in over one-third of ED visits – a practice that may also benefit from further evaluation. Finally, emergency physicians have a unique opportunity to intervene in children whose outpatient therapy for migraine has failed and may benefit from modification of their outpatient migraine abortive and prophylactic plan. The safety and efficacy of implementing specific outpatient treatment protocols warrants prospective analysis.

Chapter 5

5 Summary and Conclusions

Migraine is a common disorder in children and may cause significant disability and impaired quality of life. More recent insights on the neurobiology of migraine have opened the door to the development of new acute migraine therapies like the triptan class of medications. While the number of therapeutic options has increased for the adult population, the same cannot be said for pediatrics. For example, the triptan class of medications is not even approved for use in children in North America even though nineteen of the twenty-three identified studies were of the triptan class. What is so different about the response of children to triptan medications that their efficacy in RCTs has not been convincing?

Two plausible explanations have been explored – the unique requirement of children for fast acting and rapidly absorbed medication and the high placebo response rate. The efficacy of intranasal preparations in adolescents lends support to the need for rapid onset of action. Yet many simply do not tolerate the spray or at least prefer an oral preparation (personal observation). Attempts to improve the absorption of oral triptans (e.g. combination with metoclopramide) may prove useful, as may an emphasis on early treatment.

5.1 Placebo response: Do clinical trials need to change?

Study designs to limit the placebo responder rate in pediatric trials of migraine therapy could benefit not only migraine studies, but also any study

where pain reduction is the primary outcome. The design employed in the intranasal zolmitriptan trial (Lewis, Winner et al. 2007) is noteworthy. In this unique study, each attack was treated initially with placebo normal saline within 30 minutes after the headache had reached moderate or severe intensity. If a headache response was achieved at 15 minutes the subject was excluded and not randomized to the study medication or another placebo treatment. Unfortunately, despite the effort to minimize the placebo effect, the placebo responder rate was 54% for headache relief and 19% for pain-free.

The expectation of treatment is central to the placebo response. One of the best illustrations of this concept is the trial of cholecystokinin (CCK) antagonist (proglumide) in post-operative pain. Using classical trial methodology and three arms – no treatment, placebo, and the CCK antagonist – pain reduction was best with the CCK antagonist followed by placebo, but absent with no treatment. However, when the CCK antagonist was administered covertly (without the patient aware of treatment), no pain reduction was observed (Benedetti, Amanzio et al. 1995). The CCK antagonist simply potentiated the placebo response through alternate 'expectation' pathways, but had no direct effect on pain pathways.

The core assumption with migraine drugs is that they act on the pain pathways involved with migraine, but in the presence of such a strong placebo response is this conclusion entirely correct? Migraine drugs may simply be potentiating the placebo response through alternate 'expectation' pathways. Covert administration of the drug however is the only way to tease this apart, so do we need to change clinical trials? The feasibility of hiding the administration

of drug delivered intranasally or orally as an outpatient is limited, but one could conceive an open-hidden paradigm in the ED setting and intravenous infusion. For example, an unknown temporal sequence of infusion might be used where the subject is aware of treatment, but does not know the sequence of drugs (Colloca and Benedetti 2005). If the migraine abortive therapy is acting through pain pathways, the reduction in headache should correlate with the timing of drug administration.

It is notable that 28 of 33 children in the intravenous prochlorperazine trial had significant pain reduction (i.e. 85% response). We observed that children generally present to the ED late in the course of an attack (i.e. two or more days after onset). Why is a dopamine antagonist, with no inherent pain reducing properties, so effective in children while other migraine-targeted medications like the triptans have not shown the same effectiveness? While dopamine receptors are present in neurons of the trigeminal nucleus (pain fibers of the face and meninges), dopamine is not clearly involved in the pathogenesis of migraine (Akerman and Goadsby 2007). The expectation of analgesia through the placebo response however may activate endogenous opioid systems equivalent to 8 mg of morphine (Levine and Gordon 1984). Moreover placebo mechanisms activate dopamine neurons in the nucleus accumbens – a key structure in the brain responsible for reward, motivation, and addiction (Zubieta and Stohler 2009). It seems plausible that dopamine antagonists may be acting by potentiating the response of placebo or 'expectation' systems. If the patient is aware of the treatment and expecting analgesia however, this distinction cannot be established.

The placebo response may be more than a nuisance in migraine trials and central to the effect of some migraine abortive therapies. The design and conduct of clinical trials with an open-hidden paradigm of drug administration may be at least begin to shed light on the effect of expectation in migraine therapy. The act of starting an IV may on its own initiate some pain reduction, as may the infusion of IV fluid. The treatment of children with migraine in the ED presents an opportunity to explore these questions and may inform not only migraine therapy, but also so many other conditions involving the treatment of pain.

5.2 Practice variation and the need for improved knowledge translation

With only one study of migraine therapy for children in the ED, it was not surprising that we observed significant practice variation between mixed population and pediatric-only EDs as well as tertiary pediatric EDs across Canada. Overall pediatric ED physicians were less likely to use opioids compared with their mixed adult-pediatric ED colleagues. This is a noteworthy especially given the evidence that opioids may serve to induce the progression and chronification of migraine over time (Bigal and Lipton 2008). Regardless, opioids were still used in 5% of children with headache in the ED. Targeted educational and knowledge translation strategies emphasizing the risks of using opioids and altering the progression of migraine over time seems especially relevant to children whom face several decades of migraine and possibly numerous ED visits.

While pediatric ED physicians were more likely to use evidence-based treatments, the practice was influenced strongly by the age of the child and the diagnosis of migraine. That is to say if the physician was confident that another

cause for headache was unlikely and the child was older, evidence-based treatment was more likely to be used. While intuitive, these observations may serve as a target for further research and intervention. Improved migraine diagnostic tools for emergency physicians, knowledge translation strategies and clinical practice guidelines may serve to improve the care of children.

5.3 Coordinated research systems and restricted resources

The need for the evaluation of commonly used medications in the ED with the rigor of an RCT has been stated more than once. Moreover, future studies may need to consider novel designs to differentiate an active medication effect on migraine pain from the potentiation of placebo/expectation systems. There are, however, a number of barriers that make the conduct of an RCT in the ED difficult. Physicians and nurses generally have limited time and space for research and enrolling a child into a study may prolong their ED visit while delaying the assessment of other children. Dedicated research personnel and space are necessary to minimize the impact on care delivery, but these resources are expensive to establish and maintain. Coordinated research networks like Pediatric Emergency Research Canada (PERC, http://www.perc.srv.ualberta.ca) offer a solution to some of these barriers. Our national practice variation study could not have succeeded without their support. Funding agencies need to empower these networks with money and access to resources.

Individual research teams and networks often have similar requirements for research personnel and infrastructure. For example, we used a web-based clinical data management system to collect data electronically from ten sites

across Canada. The web-based data collection forms enforced data validation at the time of entry and we were not required to handle or enter the data from thousands of paper forms. The cost of data management was thus limited to implementation of the clinical data management system. While we were fortunate to have access to the expertise required, not all research groups/networks are.

The potential benefits of leveraging experience and investments in technology like clinical research data management systems are attractive and have not gone unnoticed. Organizations like the Canadian Child & Youth Health Coalition (CCYHC, http://www.ccyhc.org/) have identified the need for a national clinical research strategy as a high priority. The development of such a strategy is critical with the ever-increasing demand for child health evidence and restricted research funds. Born from this concept, the Maternal, Infant, Child, and Youth Research Network (MICYRN, http://www.micyrn.ca) was established as a multi-disciplinary research initiative to support world-class clinical research nationwide. The MICYRN Steering Committee identified key initiatives like data management, research methodology, and knowledge translation – all of particular relevance to our research. The successful completion of a project like ours is a testimony to the benefits of collaboration. Addressing the questions derived from our work in future research studies will depend extensively on collaboration and further emphasizes the need for national coordination in an environment of restricted resources.

5.4 Summary of implications for research

The importance of headache as a child health problem is highlighted by its prevalence in children and adolescents. While not life threatening, migraine is a disorder that can significantly impair a child's sense of well-being. The study of migraine and therapeutic strategies to help children with this common and disabling disorder is a fertile area of research. Some areas with considerable clinical uncertainty and targets for future research include:

1. The evaluation of diagnostic strategies for children with migraine to improve diagnostic sensitivity.
2. The evaluation of study design issues in the development of RCTs for migraine in children.
3. The comparison of dopamine antagonists (i.e. metoclopramide and prochlorperazine) for efficacy and safety outcome measures.
4. The evaluation of combined or multi-mechanism therapeutic strategies.
5. The development and conduct of effective knowledge translation strategies.

While our studies may have raised more questions than answered, they do serve to highlight the need and may entice more researchers to devote their time to this topic. We also hope that our research may be used as a foundation to justify the need for RCTs to funding agencies.

Appendix 1 – Migraine diagnostic criteria

Migraine without aura

(A) At least 5 attacks of headache fulfilling B-D

(B) Headache attacks lasting 1 to 72 hours

(C) Headache has at least 2 of the following characteristics (unilateral or bilateral, pulsatile quality, moderate to severe intensity, or aggravation by routine activity)

(D) During the headache at least one of following (nausea and/or vomiting, photophobia)

(E) Not attributable to another disorder

Migraine with aura

(A)Criteria for migraine without aura are met and,

(B) At least 2 attacks of migraine include an aura

Probable migraine with or without aura

(A) At least 5 attacks of headache fulfilling B-D

(B) Headache attacks lasting 1 to 72 hours

(C) Headache has at least 2 of the following characteristics (unilateral or bilateral, pulsatile quality, moderate to severe intensity, or aggravation by routine activity)

(D) During the headache at least one of following (nausea and/or vomiting, photophobia)

(E) Not attributable to another disorder

Appendix 2 – Systematic review search strategy

Electronic Databases	Search Strategies
Ovid MEDLINE® Version: OvidSP_UI01.00.02 1950 to January Week 5 2008 Searched: 13.02.08 Results: 5010	1. exp Headache Disorders/ 2. vascular headaches/ 3. Headache/ 4. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).ti,ab. 5. or/1-4 6. exp Drug Therapy/ 7. (drug adj3 (therap$ or treatment?)).mp. 8. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp. 9. (ad or ae or dt or to).fs. 10. exp Treatment Outcome/ 11. exp Analgesics/ 12. "nonsteroidal anti-inflammatory agent?".mp. 13. "non-steroidal anti-inflammatory agent?".mp. 14. NSAID?.mp. 15. ibuprofen.mp. 16. (51146-57-7 or 15687-27-1).rn. 17. fenoprofen.mp. 18. 31879-05-7.rn. 19. flurbiprofen.mp. 20. 5104-49-4.rn. 21. ketoprofen.mp. 22. 22071-15-4.rn. 23. ketorolac.mp. 24. 74103-06-3.rn. 25. diclofenac.mp. 26. 15307-86-5.rn. 27. etodolac.mp. 28. 41340-25-4.rn. 29. sulindac.mp. 30. 38194-50-2.rn. 31. diflunisal.mp. 32. 22494-42-4.rn. 33. naproxen.mp. 34. 22204-53-1.rn. 35. oxaprozin.mp. 36. 21256-18-8.rn. 37. tiaprofenic acid.mp. 38. 33005-95-7.rn. 39. mefenamic acid.mp. 40. 61-68-7.rn. 41. indomethacin.mp. 42. 53-86-1.rn. 43. tolmetin.mp. 44. 26171-23-3.rn. 45. celecoxib.mp. 46. (169590-42-5 or 184007-95-2).rn. 47. meloxicam.mp. 48. 71125-38-7.rn.

49. piroxicam.mp.
50. 36322-90-4.rn.
51. tenoxicam.mp.
52. 59804-37-4.rn.
53. floctafenin$.mp.
54. 23779-99-9.rn.
55. nabumeton$.mp.
56. 42924-53-8.rn.
57. acetaminophen.mp.
58. 103-90-2.rn.
59. paracetamol.mp.
60. ergot$ alkaloid?.mp.
61. ergotamin$.mp.
62. 113-15-5.rn.
63. dihydroergotoxin$.mp.
64. 11032-41-0.rn.
65. dihydroergotamin$.mp.
66. 511-12-6.rn.
67. DHE.mp.
68. ergoloid mesylates.mp.
69. 8067-24-1.rn.
70. methysergide.mp.
71. 361-37-5.rn.
72. ziconotide.mp.
73. 107452-89-1.rn.
74. opioid$.mp.
75. opiate$.mp.
76. opium.mp.
77. 8008-60-4.rn.
78. meperidine.mp.
79. 57-42-1.rn.
80. alfentan#l.mp.
81. 71195-58-9.rn.
82. fentan#l.mp.
83. 437-38-7.rn.
84. rem#fentan#l.mp.
85. 132875-61-7.rn.
86. sufentan#l.mp.
87. 56030-54-7.rn.
88. levomethadyl.mp.
89. 43033-72-3.rn.
90. butorphanol.mp.
91. 42408-82-2.rn.
92. codein?.mp.
93. (6059-47-8 or 76-57-3).rn.
94. morphine.mp.
95. 57-27-2.rn.
96. pentazocin$.mp.
97. 359-83-1.rn.
98. (propoxyphen$ or dextro?propoxyphen$).mp.
99. 469-62-5.rn.
100. nalbuphin$.mp.
101. 20594-83-6.rn.
102. hydromorphon$.mp.
103. 466-99-9.rn.

104. oxycodon$.mp.
105. 76-42-6.rn.
106. oxymorphon$.mp.
107. 76-41-5.rn.
108. methadon$.mp.
109. 76-99-3.rn.
110. butalbital.mp.
111. 77-26-9.rn.
112. aspirin.mp.
113. acetylsalicylic acid.mp.
114. 50-78-2.rn.
115. caffeine.mp.
116. 58-08-2.rn.
117. "combination analgesic?".tw.
118. APAP.tw.
119. dichloralphenazone.mp.
120. isomethepten$.mp.
121. corticosteroid$.mp.
122. 8001-02-3.rn.
123. hydrocortisone.mp.
124. 50-23-7.rn.
125. prednisolone.mp.
126. 50-24-8.rn.
127. methylprednisolone.mp.
128. 83-43-2.rn.
129. dexamethasone.mp.
130. 50-02-2.rn.
131. tryptamin$.mp.
132. 61-54-1.rn.
133. triptan?.mp.
134. 464-06-2.rn.
135. sumatriptan.mp.
136. 103628-46-2.rn.
137. naratriptan.mp.
138. 121679-13-8.rn.
139. rizatriptan.mp.
140. 144034-80-0.rn.
141. zolmitriptan.mp.
142. 139264-17-8.rn.
143. almotriptan.mp.
144. 154323-57-6.rn.
145. eletriptan.mp.
146. 143322-58-1.rn.
147. frovatriptan.mp.
148. 158747-02-5.rn.
149. serotonin agonist?.mp.
150. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.
151. (antiemetic? or anti-emetic?).mp.
152. (antinauseant? or anti-nauseant?).mp.
153. chlorpromazine.mp.
154. 50-53-3.rn.
155. prochlorperazine.mp.
156. 58-38-8.rn.
157. perphenazine.mp.
158. 58-39-9.rn.

159. trifluoperazine.mp.
160. 117-89-5.rn.
161. (met#clopr#mide or metochlopramide).mp.
162. 364-62-5.rn.
163. scopolamin$.mp.
164. 51-34-3.rn.
165. dimenhydrinate.mp.
166. 523-87-5.rn.
167. dronabinol.mp.
168. 1972-08-3.rn.
169. nabilon$.mp.
170. 51022-71-0.rn.
171. thiethylperazine.mp.
172. 1420-55-9.rn.
173. trimethobenzamide.mp.
174. 138-56-7.rn.
175. ondansetron.mp.
176. 99614-02-5.rn.
177. granisetron.mp.
178. 109889-09-0.rn.
179. dolasetron.mp.
180. 115956-12-2.rn.
181. diphenhydramine.mp.
182. 58-73-1.rn.
183. hydroxyzine.mp.
184. 68-88-2.rn.
185. promethazine.mp.
186. 60-87-7.rn.
187. Valproic Acid.mp.
188. valproate.mp.
189. 99-66-1.rn.
190. divalproex sodium.mp.
191. 76584-70-8.rn.
192. Clonidine.mp.
193. 4205-90-7.rn.
194. fluid bolus.mp.
195. normal saline.mp.
196. magnesium.mp.
197. 7439-95-4.rn.
198. lidocaine.mp.
199. 137-58-6.rn.
200. Botulinum Toxin Type A/
201. botulinium toxin.mp.
202. botox.mp.
203. 93384-43-1.rn.
204. oxygen.mp.
205. 7782-44-7.rn.
206. placebo$.mp.
207. or/6-206
208. randomized controlled trial.pt.
209. clinical trial.pt.
210. randomi?ed.ti,ab.
211. placebo.ti,ab.
212. dt.fs.
213. randomly.ti,ab.

214. trial.ti,ab.
215. groups.ti,ab.
216. or/208-215
217. animals/
218. humans/
219. 217 not (217 and 218)
220. 216 not 219
221. exp Infant/
222. exp Child/
223. Adolescent/
224. Minors/
225. exp Puberty/
226. exp Pediatrics/
227. infant$.mp.
228. infancy.mp.
229. newborn$.mp.
230. baby.mp.
231. babies.mp.
232. neonat$.mp.
233. preterm$.mp.
234. prematur$.mp.
235. postmatur$.mp.
236. child$.mp.
237. kid.mp.
238. kids.mp.
239. toddler$.mp.
240. adolescen$.mp.
241. teen$.mp.
242. boy$.mp.
243. girl.mp.
244. girls.mp.
245. minor$.mp.
246. pubert$.mp.
247. pubescen$.mp.
248. pediatric$.mp.
249. paediatric$.mp.
250. peadiatric$.mp.
251. or/221-250
252. and/5,207,220,251

Ovid MEDLINE® In-Process & Other Non-Indexed Citations
OVID Version: OvidSP_UI01.00.02 February 12, 2008
Searched: 13.02.08
Results: 14

1. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).mp.
2. (drug adj3 (therap$ or treatment?)).mp.
3. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp.
4. (treatment adj5 outcome).mp.
5. analgesi$.mp.
6. "nonsteroidal anti-inflammatory agent?".mp.
7. "non-steroidal anti-inflammatory agent?".mp.
8. NSAID?.mp.
9. ibuprofen.mp.
10. fenoprofen.mp.
11. flurbiprofen.mp.
12. ketoprofen.mp.
13. ketorolac.mp.

14. diclofenac.mp.
15. etodolac.mp.
16. sulindac.mp.
17. diflunisal.mp.
18. naproxen.mp.
19. oxaprozin.mp.
20. tiaprofenic acid.mp.
21. mefenamic acid.mp.
22. indomethacin.mp.
23. tolmetin.mp.
24. celecoxib.mp.
25. meloxicam.mp.
26. piroxicam.mp.
27. tenoxicam.mp.
28. floctafenin$.mp.
29. nabumeton$.mp.
30. acetaminophen.mp.
31. paracetamol.mp.
32. ergot$ alkaloid?.mp.
33. ergotamin$.mp.
34. 113-15-5.rn.
35. dihydroergotoxin$.mp.
36. dihydroergotamin$.mp.
37. DHE.mp.
38. ergoloid mesylates.mp.
39. methysergide.mp.
40. ziconotide.mp.
41. opioid$.mp.
42. opiate$.mp.
43. opium.mp.
44. meperidine.mp.
45. alfentan#l.mp.
46. fentan#l.mp.
47. rem#fentan#l.mp.
48. sufentan#l.mp.
49. levomethadyl.mp.
50. butorphanol.mp.
51. codein?.mp.
52. morphine.mp.
53. pentazocin$.mp.
54. (propoxyphen$ or dextro?propoxyphen$).mp.
55. nalbuphin$.mp.
56. hydromorphon$.mp.
57. oxycodon$.mp.
58. oxymorphon$.mp.
59. methadon$.mp.
60. butalbital.mp.
61. aspirin.mp.
62. acetylsalicylic acid.mp.
63. caffeine.mp.
64. "combination analgesic?".tw.
65. APAP.tw.
66. dichloralphenazone.mp.
67. isomethepten$.mp.
68. corticosteroid$.mp.

69. hydrocortisone.mp.
70. prednisolone.mp.
71. methylprednisolone.mp.
72. dexamethasone.mp.
73. tryptamin$.mp.
74. triptan?.mp.
75. sumatriptan.mp.
76. naratriptan.mp.
77. rizatriptan.mp.
78. zolmitriptan.mp.
79. almotriptan.mp.
80. eletriptan.mp.
81. frovatriptan.mp.
82. serotonin agonist?.mp.
83. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.
84. (antiemetic? or anti-emetic?).mp.
85. (antinauseant? or anti-nauseant?).mp.
86. chlorpromazine.mp.
87. prochlorperazine.mp.
88. perphenazine.mp.
89. trifluoperazine.mp.
90. (met#clopr#mide or metochlopramide).mp.
91. scopolamin$.mp.
92. dimenhydrinate.mp.
93. dronabinol.mp.
94. nabilon$.mp.
95. thiethylperazine.mp.
96. trimethobenzamide.mp.
97. ondansetron.mp.
98. granisetron.mp.
99. dolasetron.mp.
100. diphenhydramine.mp.
101. hydroxyzine.mp.
102. promethazine.mp.
103. Valproic Acid.mp.
104. valproate.mp.
105. divalproex sodium.mp.
106. Clonidine.mp.
107. fluid bolus.mp.
108. normal saline.mp.
109. magnesium.mp.
110. lidocaine.mp.
111. botulinium toxin.mp.
112. botox.mp.
113. oxygen.mp.
114. placebo$.mp.
115. or/2-114
116. clinical study.sh.
117. randomi?ed.ti,ab.
118. placebo.ti,ab.
119. ae,dt,to.fs.
120. randomly.ti,ab.
121. trial.ti,ab.
122. groups.ti,ab.
123. or/116-122

124. animals/
125. humans/
126. 124 not (124 and 125)
127. 123 not 126
128. and/115,127
129. infant$.mp.
130. infancy.mp.
131. newborn$.mp.
132. baby.mp.
133. babies.mp.
134. neonat$.mp.
135. preterm$.mp.
136. prematur$.mp.
137. postmatur$.mp.
138. child$.mp.
139. kid.mp.
140. kids.mp.
141. toddler$.mp.
142. adolescen$.mp.
143. teen$.mp.
144. boy$.mp.
145. girl.mp.
146. girls.mp.
147. minor$.mp.
148. pubert$.mp.
149. pubescen$.mp.
150. pediatric$.mp.
151. paediatric$.mp.
152. peadiatric$.mp.
153. or/129-152
154. and/1,128,153

EMBASE
OVID Version:
OvidSP_UI01.00.02
1988 to 2008 Week 06
Searched: 13.02.08
Results: 13311

1. exp Headache Disorders/
2. vascular headaches/
3. Headache/
4. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).ti,ab.
5. or/1-4
6. exp Drug Therapy/
7. (drug adj3 (therap$ or treatment?)).mp.
8. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp.
9. (ad or ae or dt or to).fs.
10. exp Treatment Outcome/
11. exp Analgesics/
12. "nonsteroidal anti-inflammatory agent?".mp.
13. "non-steroidal anti-inflammatory agent?".mp.
14. NSAID?.mp.
15. ibuprofen.mp.
16. (51146-57-7 or 15687-27-1).rn.
17. fenoprofen.mp.
18. 31879-05-7.rn.
19. flurbiprofen.mp.
20. 5104-49-4.rn.
21. ketoprofen.mp.

22. 22071-15-4.rn.
23. ketorolac.mp.
24. 74103-06-3.rn.
25. diclofenac.mp.
26. 15307-86-5.rn.
27. etodolac.mp.
28. 41340-25-4.rn.
29. sulindac.mp.
30. 38194-50-2.rn.
31. diflunisal.mp.
32. 22494-42-4.rn.
33. naproxen.mp.
34. 22204-53-1.rn.
35. oxaprozin.mp.
36. 21256-18-8.rn.
37. tiaprofenic acid.mp.
38. 33005-95-7.rn.
39. mefenamic acid.mp.
40. 61-68-7.rn.
41. indomethacin.mp.
42. 53-86-1.rn.
43. tolmetin.mp.
44. 26171-23-3.rn.
45. celecoxib.mp.
46. (169590-42-5 or 184007-95-2).rn.
47. meloxicam.mp.
48. 71125-38-7.rn.
49. piroxicam.mp.
50. 36322-90-4.rn.
51. tenoxicam.mp.
52. 59804-37-4.rn.
53. floctafenin$.mp.
54. 23779-99-9.rn.
55. nabumeton$.mp.
56. 42924-53-8.rn.
57. acetaminophen.mp.
58. 103-90-2.rn.
59. paracetamol.mp.
60. ergot$ alkaloid?.mp.
61. ergotamin$.mp.
62. 113-15-5.rn.
63. dihydroergotoxin$.mp.
64. 11032-41-0.rn.
65. dihydroergotamin$.mp.
66. 511-12-6.rn.
67. DHE.mp.
68. ergoloid mesylates.mp.
69. 8067-24-1.rn.
70. methysergide.mp.
71. 361-37-5.rn.
72. ziconotide.mp.
73. 107452-89-1.rn.
74. opioid$.mp.
75. opiate$.mp.
76. opium.mp.

77. 8008-60-4.rn.
78. meperidine.mp.
79. 57-42-1.rn.
80. alfentan#l.mp.
81. 71195-58-9.rn.
82. fentan#l.mp.
83. 437-38-7.rn.
84. rem#fentan#l.mp.
85. 132875-61-7.rn.
86. sufentan#l.mp.
87. 56030-54-7.rn.
88. levomethadyl.mp.
89. 43033-72-3.rn.
90. butorphanol.mp.
91. 42408-82-2.rn.
92. codein?.mp.
93. (6059-47-8 or 76-57-3).rn.
94. morphine.mp.
95. 57-27-2.rn.
96. pentazocin$.mp.
97. 359-83-1.rn.
98. (propoxyphen$ or dextro?propoxyphen$).mp.
99. 469-62-5.rn.
100. nalbuphin$.mp.
101. 20594-83-6.rn.
102. hydromorphon$.mp.
103. 466-99-9.rn.
104. oxycodon$.mp.
105. 76-42-6.rn.
106. oxymorphon$.mp.
107. 76-41-5.rn.
108. methadon$.mp.
109. 76-99-3.rn.
110. butalbital.mp.
111. 77-26-9.rn.
112. aspirin.mp.
113. acetylsalicylic acid.mp.
114. 50-78-2.rn.
115. caffeine.mp.
116. 58-08-2.rn.
117. "combination analgesic?".tw.
118. APAP.tw.
119. dichloralphenazone.mp.
120. isomethepten$.mp.
121. corticosteroid$.mp.
122. 8001-02-3.rn.
123. hydrocortisone.mp.
124. 50-23-7.rn.
125. prednisolone.mp.
126. 50-24-8.rn.
127. methylprednisolone.mp.
128. 83-43-2.rn.
129. dexamethasone.mp.
130. 50-02-2.rn.
131. tryptamin$.mp.

132. 61-54-1.rn.
133. triptan?.mp.
134. 464-06-2.rn.
135. sumatriptan.mp.
136. 103628-46-2.rn.
137. naratriptan.mp.
138. 121679-13-8.rn.
139. rizatriptan.mp.
140. 144034-80-0.rn.
141. zolmitriptan.mp.
142. 139264-17-8.rn.
143. almotriptan.mp.
144. 154323-57-6.rn.
145. eletriptan.mp.
146. 143322-58-1.rn.
147. frovatriptan.mp.
148. 158747-02-5.rn.
149. serotonin agonist?.mp.
150. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.
151. (antiemetic? or anti-emetic?).mp.
152. (antinauseant? or anti-nauseant?).mp.
153. chlorpromazine.mp.
154. 50-53-3.rn.
155. prochlorperazine.mp.
156. 58-38-8.rn.
157. perphenazine.mp.
158. 58-39-9.rn.
159. trifluoperazine.mp.
160. 117-89-5.rn.
161. (met#clopr#mide or metochlopramide).mp.
162. 364-62-5.rn.
163. scopolamin$.mp.
164. 51-34-3.rn.
165. dimenhydrinate.mp.
166. 523-87-5.rn.
167. dronabinol.mp.
168. 1972-08-3.rn.
169. nabilon$.mp.
170. 51022-71-0.rn.
171. thiethylperazine.mp.
172. 1420-55-9.rn.
173. trimethobenzamide.mp.
174. 138-56-7.rn.
175. ondansetron.mp.
176. 99614-02-5.rn.
177. granisetron.mp.
178. 109889-09-0.rn.
179. dolasetron.mp.
180. 115956-12-2.rn.
181. diphenhydramine.mp.
182. 58-73-1.rn.
183. hydroxyzine.mp.
184. 68-88-2.rn.
185. promethazine.mp.
186. 60-87-7.rn.

187. Valproic Acid.mp.
188. valproate.mp.
189. 99-66-1.rn.
190. divalproex sodium.mp.
191. 76584-70-8.rn.
192. Clonidine.mp.
193. 4205-90-7.rn.
194. fluid bolus.mp.
195. normal saline.mp.
196. magnesium.mp.
197. 7439-95-4.rn.
198. lidocaine.mp.
199. 137-58-6.rn.
200. Botulinum Toxin Type A/
201. botulinium toxin.mp.
202. botox.mp.
203. 93384-43-1.rn.
204. oxygen.mp.
205. 7782-44-7.rn.
206. placebo$.mp.
207. or/6-206
208. exp clinical trial/
209. randomi?ed.ti,ab.
210. placebo.ti,ab.
211. (ae or dt or to).fs.
212. randomly.ti,ab.
213. trial.ti,ab.
214. groups.ti,ab.
215. or/208-214
216. animal/
217. human/
218. 216 not (216 and 217)
219. 215 not 218
220. exp adolescent/
221. exp child/
222. exp newborn/
223. exp Pediatrics/
224. infant$.mp.
225. infancy.mp.
226. newborn$.mp.
227. baby.mp.
228. babies.mp.
229. neonat$.mp.
230. preterm$.mp.
231. prematur$.mp.
232. postmatur$.mp.
233. child$.mp.
234. kid.mp.
235. kids.mp.
236. toddler$.mp.
237. adolescen$.mp.
238. teen$.mp.
239. juvenile$.mp.
240. boy$.mp.
241. girl.mp.

242. girls.mp.
243. minor$.mp.
244. pubert$.mp.
245. pubescen$.mp.
246. pediatric$.mp.
247. paediatric$.mp.
248. peadiatric$.mp.
249. or/220-248
250. and/5,207,219,249

PsycINFO 1985 to February Week 1 2008
Ovid
OVID Version: OvidSP_UI01.00.02
1985 to February Week 1 2008
Searched: 13.02.08
Results: 108

1. headache/
2. migraine headache/
3. muscle contraction headache/
4. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).ti,ab.
5. or/1-4
6. Drug Therapy/
7. exp drugs/
8. exp "side effects (drug)"/
9. (drug adj3 (therap$ or treatment?)).mp.
10. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp.
11. (ad or ae or dt or to).fs.
12. treatment outcomes/
13. (treatment adj5 outcome).mp.
14. analgesi$.mp.
15. "nonsteroidal anti-inflammatory agent?".mp.
16. "non-steroidal anti-inflammatory agent?".mp.
17. NSAID?.mp.
18. ibuprofen.mp.
19. fenoprofen.mp.
20. flurbiprofen.mp.
21. ketoprofen.mp.
22. ketorolac.mp.
23. diclofenac.mp.
24. etodolac.mp.
25. sulindac.mp.
26. diflunisal.mp.
27. naproxen.mp.
28. oxaprozin.mp.
29. tiaprofenic acid.mp.
30. mefenamic acid.mp.
31. indomethacin.mp.
32. tolmetin.mp.
33. celecoxib.mp.
34. meloxicam.mp.
35. piroxicam.mp.
36. tenoxicam.mp.
37. floctafenin$.mp.
38. nabumeton$.mp.
39. acetaminophen.mp.
40. paracetamol.mp.
41. ergot$ alkaloid?.mp.
42. ergotamin$.mp.
43. dihydroergotoxin$.mp.
44. dihydroergotamin$.mp.

45. DHE.mp.
46. ergoloid mesylates.mp.
47. methysergide.mp.
48. ziconotide.mp.
49. opioid$.mp.
50. opiate$.mp.
51. opium.mp.
52. meperidine.mp.
53. alfentan#l.mp.
54. fentan#l.mp.
55. rem#fentan#l.mp.
56. sufentan#l.mp.
57. levomethadyl.mp.
58. butorphanol.mp.
59. codein?.mp.
60. morphine.mp.
61. pentazocin$.mp.
62. (propoxyphen$ or dextro?propoxyphen$).mp.
63. nalbuphin$.mp.
64. hydromorphon$.mp.
65. oxycodon$.mp.
66. oxymorphon$.mp.
67. methadon$.mp.
68. butalbital.mp.
69. aspirin.mp.
70. acetylsalicylic acid.mp.
71. caffeine.mp.
72. "combination analgesic?".tw.
73. APAP.tw.
74. dichloralphenazone.mp.
75. isomethepten$.mp.
76. corticosteroid$.mp.
77. hydrocortisone.mp.
78. prednisolone.mp.
79. methylprednisolone.mp.
80. dexamethasone.mp.
81. tryptamin$.mp.
82. triptan?.mp.
83. sumatriptan.mp.
84. naratriptan.mp.
85. rizatriptan.mp.
86. zolmitriptan.mp.
87. almotriptan.mp.
88. eletriptan.mp.
89. frovatriptan.mp.
90. serotonin agonist?.mp.
91. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.
92. (antiemetic? or anti-emetic?).mp.
93. (antinauseant? or anti-nauseant?).mp.
94. chlorpromazine.mp.
95. prochlorperazine.mp.
96. perphenazine.mp.
97. trifluoperazine.mp.
98. (met#clopr#mide or metochlopramide).mp.
99. scopolamin$.mp.

100. dimenhydrinate.mp.
101. dronabinol.mp.
102. nabilon$.mp.
103. thiethylperazine.mp.
104. trimethobenzamide.mp.
105. ondansetron.mp.
106. granisetron.mp.
107. dolasetron.mp.
108. diphenhydramine.mp.
109. hydroxyzine.mp.
110. promethazine.mp.
111. Valproic Acid.mp.
112. valproate.mp.
113. divalproex sodium.mp.
114. Clonidine.mp.
115. fluid bolus.mp.
116. normal saline.mp.
117. magnesium.mp.
118. lidocaine.mp.
119. botulinium toxin.mp.
120. botox.mp.
121. oxygen.mp.
122. placebo$.mp.
123. or/6-122
124. clinical study.sh.
125. randomi?ed.ti,ab.
126. placebo.ti,ab.
127. ae,dt,to.fs.
128. randomly.ti,ab.
129. trial.ti,ab.
130. groups.ti,ab.
131. or/124-130
132. animals/
133. humans/
134. 132 not (132 and 133)
135. 131 not 134
136. and/123,135
137. infant$.mp.
138. infancy.mp.
139. newborn$.mp.
140. baby.mp.
141. babies.mp.
142. neonat$.mp.
143. preterm$.mp.
144. prematur$.mp.
145. postmatur$.mp.
146. child$.mp.
147. kid.mp.
148. kids.mp.
149. toddler$.mp.
150. adolescen$.mp.
151. teen$.mp.
152. boy$.mp.
153. girl.mp.
154. girls.mp.

155. minor$.mp.
156. pubert$.mp.
157. pubescen$.mp.
158. pediatric$.mp.
159. paediatric$.mp.
160. peadiatric$.mp.
161. or/137-160
162. and/5,136,161

International Pharmaceutical Abstracts
OVID Version: OvidSP_UI01.00.02
1970 to January 2008
Searched: 13.02.08
Results: 67

1. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).mp.
2. (drug adj3 (therap$ or treatment?)).mp.
3. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp.
4. (treatment adj5 outcome).mp.
5. analgesi$.mp.
6. "nonsteroidal anti-inflammatory agent?".mp.
7. "non-steroidal anti-inflammatory agent?".mp.
8. NSAID?.mp.
9. ibuprofen.mp.
10. (51146-57-7 or 15687-27-1).rn.
11. fenoprofen.mp.
12. 31879-05-7.rn.
13. flurbiprofen.mp.
14. 5104-49-4.rn.
15. ketoprofen.mp.
16. 22071-15-4.rn.
17. ketorolac.mp.
18. 74103-06-3.rn.
19. diclofenac.mp.
20. 15307-86-5.rn.
21. etodolac.mp.
22. 41340-25-4.rn.
23. sulindac.mp.
24. 38194-50-2.rn.
25. diflunisal.mp.
26. 22494-42-4.rn.
27. naproxen.mp.
28. 22204-53-1.rn.
29. oxaprozin.mp.
30. 21256-18-8.rn.
31. tiaprofenic acid.mp.
32. 33005-95-7.rn.
33. mefenamic acid.mp.
34. 61-68-7.rn.
35. indomethacin.mp.
36. 53-86-1.rn.
37. tolmetin.mp.
38. 26171-23-3.rn.
39. celecoxib.mp.
40. (169590-42-5 or 184007-95-2).rn.
41. meloxicam.mp.
42. 71125-38-7.rn.
43. piroxicam.mp.
44. 36322-90-4.rn.

45. tenoxicam.mp.
46. 59804-37-4.rn.
47. floctafenin$.mp.
48. 23779-99-9.rn.
49. nabumeton$.mp.
50. 42924-53-8.rn.
51. acetaminophen.mp.
52. 103-90-2.rn.
53. paracetamol.mp.
54. ergot$ alkaloid?.mp.
55. ergotamin$.mp.
56. 113-15-5.rn.
57. dihydroergotoxin$.mp.
58. 11032-41-0.rn.
59. dihydroergotamin$.mp.
60. 511-12-6.rn.
61. DHE.mp.
62. ergoloid mesylates.mp.
63. 8067-24-1.rn.
64. methysergide.mp.
65. 361-37-5.rn.
66. ziconotide.mp.
67. 107452-89-1.rn.
68. opioid$.mp.
69. opiate$.mp.
70. opium.mp.
71. 8008-60-4.rn.
72. meperidine.mp.
73. 57-42-1.rn.
74. alfentan#l.mp.
75. 71195-58-9.rn.
76. fentan#l.mp.
77. 437-38-7.rn.
78. rem#fentan#l.mp.
79. 132875-61-7.rn.
80. sufentan#l.mp.
81. 56030-54-7.rn.
82. levomethadyl.mp.
83. 43033-72-3.rn.
84. butorphanol.mp.
85. 42408-82-2.rn.
86. codein?.mp.
87. (6059-47-8 or 76-57-3).rn.
88. morphine.mp.
89. 57-27-2.rn.
90. pentazocin$.mp.
91. 359-83-1.rn.
92. (propoxyphen$ or dextro?propoxyphen$).mp.
93. 469-62-5.rn.
94. nalbuphin$.mp.
95. 20594-83-6.rn.
96. hydromorphon$.mp.
97. 466-99-9.rn.
98. oxycodon$.mp.
99. 76-42-6.rn.

100. oxymorphon$.mp.
101. 76-41-5.rn.
102. methadon$.mp.
103. 76-99-3.rn.
104. butalbital.mp.
105. 77-26-9.rn.
106. aspirin.mp.
107. acetylsalicylic acid.mp.
108. 50-78-2.rn.
109. caffeine.mp.
110. 58-08-2.rn.
111. "combination analgesic?".tw.
112. APAP.tw.
113. dichloralphenazone.mp.
114. isomethepten$.mp.
115. corticosteroid$.mp.
116. 8001-02-3.rn.
117. hydrocortisone.mp.
118. 50-23-7.rn.
119. prednisolone.mp.
120. 50-24-8.rn.
121. methylprednisolone.mp.
122. 83-43-2.rn.
123. dexamethasone.mp.
124. 50-02-2.rn.
125. tryptamin$.mp.
126. 61-54-1.rn.
127. triptan?.mp.
128. 464-06-2.rn.
129. sumatriptan.mp.
130. 103628-46-2.rn.
131. naratriptan.mp.
132. 121679-13-8.rn.
133. rizatriptan.mp.
134. 144034-80-0.rn.
135. zolmitriptan.mp.
136. 139264-17-8.rn.
137. almotriptan.mp.
138. 154323-57-6.rn.
139. eletriptan.mp.
140. 143322-58-1.rn.
141. frovatriptan.mp.
142. 158747-02-5.rn.
143. serotonin agonist?.mp.
144. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.
145. (antiemetic? or anti-emetic?).mp.
146. (antinauseant? or anti-nauseant?).mp.
147. chlorpromazine.mp.
148. 50-53-3.rn.
149. prochlorperazine.mp.
150. 58-38-8.rn.
151. perphenazine.mp.
152. 58-39-9.rn.
153. trifluoperazine.mp.
154. 117-89-5.rn.

155. (met#clopr#mide or metochlopramide).mp.
156. 364-62-5.rn.
157. scopolamin$.mp.
158. 51-34-3.rn.
159. dimenhydrinate.mp.
160. 523-87-5.rn.
161. dronabinol.mp.
162. 1972-08-3.rn.
163. nabilon$.mp.
164. 51022-71-0.rn.
165. thiethylperazine.mp.
166. 1420-55-9.rn.
167. trimethobenzamide.mp.
168. 138-56-7.rn.
169. ondansetron.mp.
170. 99614-02-5.rn.
171. granisetron.mp.
172. 109889-09-0.rn.
173. dolasetron.mp.
174. 115956-12-2.rn.
175. diphenhydramine.mp.
176. 58-73-1.rn.
177. hydroxyzine.mp.
178. 68-88-2.rn.
179. promethazine.mp.
180. 60-87-7.rn.
181. Valproic Acid.mp.
182. valproate.mp.
183. 99-66-1.rn.
184. divalproex sodium.mp.
185. 76584-70-8.rn.
186. Clonidine.mp.
187. 4205-90-7.rn.
188. fluid bolus.mp.
189. normal saline.mp.
190. magnesium.mp.
191. 7439-95-4.rn.
192. lidocaine.mp.
193. 137-58-6.rn.
194. botulinium toxin.mp.
195. botox.mp.
196. 93384-43-1.rn.
197. oxygen.mp.
198. 7782-44-7.rn.
199. placebo$.mp.
200. or/2-199
201. clinical study.sh.
202. randomi?ed.ti,ab.
203. placebo.ti,ab.
204. ae,dt,to.fs.
205. randomly.ti,ab.
206. trial.ti,ab.
207. groups.ti,ab.
208. or/201-207
209. animals/

	210. humans/ 211. 209 not (209 and 210) 212. 208 not 211 213. and/200,212 214. infant$.mp. 215. infancy.mp. 216. newborn$.mp. 217. baby.mp. 218. babies.mp. 219. neonat$.mp. 220. preterm$.mp. 221. prematur$.mp. 222. postmatur$.mp. 223. child$.mp. 224. kid.mp. 225. kids.mp. 226. toddler$.mp. 227. adolescen$.mp. 228. teen$.mp. 229. boy$.mp. 230. girl.mp. 231. girls.mp. 232. minor$.mp. 233. pubert$.mp. 234. pubescen$.mp. 235. pediatric$.mp. 236. paediatric$.mp. 237. peadiatric$.mp. 238. or/214-237 239. and/1,213,238
EBM Reviews Ð Cochrane Central Register of Controlled Trials 1st Quarter 2008 OVID Version: OvidSP_UI01.00.02 Searched: 13.02.08 Results: 1725	1. exp Headache Disorders/ 2. (headache adj3 disorder?).mp. 3. vascular headaches/ 4. Headache/ 5. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).ti,ab. 6. or/1-5 7. exp Drug Therapy/ 8. (drug adj3 (therap$ or treatment?)).mp. 9. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp. 10. (ad or ae or dt or to).fs. 11. exp Treatment Outcome/ 12. exp Analgesics/ 13. "nonsteroidal anti-inflammatory agent?".mp. 14. "non-steroidal anti-inflammatory agent?".mp. 15. NSAID?.mp. 16. ibuprofen.mp. 17. fenoprofen.mp. 18. flurbiprofen.mp. 19. ketoprofen.mp. 20. ketorolac.mp. 21. diclofenac.mp. 22. etodolac.mp. 23. sulindac.mp.

24. diflunisal.mp.
25. naproxen.mp.
26. oxaprozin.mp.
27. tiaprofenic acid.mp.
28. mefenamic acid.mp.
29. indomethacin.mp.
30. tolmetin.mp.
31. celecoxib.mp.
32. meloxicam.mp.
33. piroxicam.mp.
34. tenoxicam.mp.
35. floctafenin$.mp.
36. nabumeton$.mp.
37. acetaminophen.mp.
38. paracetamol.mp.
39. ergot$ alkaloid?.mp.
40. ergotamin$.mp.
41. dihydroergotoxin$.mp.
42. dihydroergotamin$.mp.
43. DHE.mp.
44. ergoloid mesylates.mp.
45. methysergide.mp.
46. ziconotide.mp.
47. opioid$.mp.
48. opiate$.mp.
49. opium.mp.
50. meperidine.mp.
51. alfentan#l.mp.
52. fentan#l.mp.
53. rem#fentan#l.mp.
54. sufentan#l.mp.
55. levomethadyl.mp.
56. butorphanol.mp.
57. codein?.mp.
58. morphine.mp.
59. pentazocin$.mp.
60. (propoxyphen$ or dextro?propoxyphen$).mp.
61. nalbuphin$.mp.
62. hydromorphon$.mp.
63. oxycodon$.mp.
64. oxymorphon$.mp.
65. methadon$.mp.
66. butalbital.mp.
67. aspirin.mp.
68. acetylsalicylic acid.mp.
69. caffeine.mp.
70. "combination analgesic?".tw.
71. APAP.tw.
72. dichloralphenazone.mp.
73. isomethepten$.mp.
74. corticosteroid$.mp.
75. hydrocortisone.mp.
76. prednisolone.mp.
77. methylprednisolone.mp.
78. dexamethasone.mp.

79. tryptamin$.mp.
80. triptan?.mp.
81. sumatriptan.mp.
82. naratriptan.mp.
83. rizatriptan.mp.
84. zolmitriptan.mp.
85. almotriptan.mp.
86. eletriptan.mp.
87. frovatriptan.mp.
88. serotonin agonist?.mp.
89. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.
90. (antiemetic? or anti-emetic?).mp.
91. (antinauseant? or anti-nauseant?).mp.
92. chlorpromazine.mp.
93. prochlorperazine.mp.
94. perphenazine.mp.
95. trifluoperazine.mp.
96. (met#clopr#mide or metochlopramide).mp.
97. scopolamin$.mp.
98. dimenhydrinate.mp.
99. dronabinol.mp.
100. nabilon$.mp.
101. thiethylperazine.mp.
102. trimethobenzamide.mp.
103. ondansetron.mp.
104. granisetron.mp.
105. dolasetron.mp.
106. diphenhydramine.mp.
107. hydroxyzine.mp.
108. promethazine.mp.
109. Valproic Acid.mp.
110. valproate.mp.
111. divalproex sodium.mp.
112. Clonidine.mp.
113. fluid bolus.mp.
114. normal saline.mp.
115. magnesium.mp.
116. lidocaine.mp.
117. Botulinum Toxin Type A/
118. botulinium toxin.mp.
119. botox.mp.
120. oxygen.mp.
121. placebo$.mp.
122. or/7-121
123. exp Infant/
124. exp Child/
125. Adolescent/
126. Minors/
127. exp Puberty/
128. exp Pediatrics/
129. infant$.mp.
130. infancy.mp.
131. newborn$.mp.
132. baby.mp.
133. babies.mp.

134. neonat$.mp.
135. preterm$.mp.
136. prematur$.mp.
137. postmatur$.mp.
138. child$.mp.
139. kid.mp.
140. kids.mp.
141. toddler$.mp.
142. adolescen$.mp.
143. teen$.mp.
144. boy$.mp.
145. girl.mp.
146. girls.mp.
147. minor$.mp.
148. pubert$.mp.
149. pubescen$.mp.
150. pediatric$.mp.
151. paediatric$.mp.
152. peadiatric$.mp.
153. or/123-152
154. and/6,122,153

EBM Đ Cochrane Database of Systematic Reviews
EBM Đ Database of Reviews and Abstracts (DARE)
OvidSP_UI01.00.02
1st Quarter 2008

Searched: 13.02.08
Results: DARE 7
CDSR 70

1. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).ti,ab.
2. (drug adj3 (therap$ or treatment?)).mp.
3. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp.
4. (ad or ae or dt or to).fs.
5. (treatment adj5 outcome).mp.
6. analgesi$.mp.
7. "nonsteroidal anti-inflammatory agent?".mp.
8. "non-steroidal anti-inflammatory agent?".mp.
9. NSAID?.mp.
10. ibuprofen.mp.
11. fenoprofen.mp.
12. flurbiprofen.mp.
13. ketoprofen.mp.
14. ketorolac.mp.
15. diclofenac.mp.
16. etodolac.mp.
17. sulindac.mp.
18. diflunisal.mp.
19. naproxen.mp.
20. oxaprozin.mp.
21. tiaprofenic acid.mp.
22. mefenamic acid.mp.
23. indomethacin.mp.
24. tolmetin.mp.
25. celecoxib.mp.
26. meloxicam.mp.
27. piroxicam.mp.
28. tenoxicam.mp.
29. floctafenin$.mp.
30. nabumeton$.mp.
31. acetaminophen.mp.
32. paracetamol.mp.

33. ergot$ alkaloid?.mp.
34. ergotamin$.mp.
35. dihydroergotoxin$.mp.
36. dihydroergotamin$.mp.
37. DHE.mp.
38. ergoloid mesylates.mp.
39. methysergide.mp.
40. ziconotide.mp.
41. opioid$.mp.
42. opiate$.mp.
43. opium.mp.
44. meperidine.mp.
45. alfentan#l.mp.
46. fentan#l.mp.
47. rem#fentan#l.mp.
48. sufentan#l.mp.
49. levomethadyl.mp.
50. butorphanol.mp.
51. codein?.mp.
52. morphine.mp.
53. pentazocin$.mp.
54. (propoxyphen$ or dextro?propoxyphen$).mp.
55. nalbuphin$.mp.
56. hydromorphon$.mp.
57. oxycodon$.mp.
58. oxymorphon$.mp.
59. methadon$.mp.
60. butalbital.mp.
61. aspirin.mp.
62. acetylsalicylic acid.mp.
63. caffeine.mp.
64. "combination analgesic?".tw.
65. APAP.tw.
66. dichloralphenazone.mp.
67. isomethepten$.mp.
68. corticosteroid$.mp.
69. hydrocortisone.mp.
70. prednisolone.mp.
71. methylprednisolone.mp.
72. dexamethasone.mp.
73. tryptamin$.mp.
74. triptan?.mp.
75. sumatriptan.mp.
76. naratriptan.mp.
77. rizatriptan.mp.
78. zolmitriptan.mp.
79. almotriptan.mp.
80. eletriptan.mp.
81. frovatriptan.mp.
82. serotonin agonist?.mp.
83. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.
84. (antiemetic? or anti-emetic?).mp.
85. (antinauseant? or anti-nauseant?).mp.
86. chlorpromazine.mp.
87. prochlorperazine.mp.

88. perphenazine.mp.
89. trifluoperazine.mp.
90. (met#clopr#mide or metochlopramide).mp.
91. scopolamin$.mp.
92. dimenhydrinate.mp.
93. dronabinol.mp.
94. nabilon$.mp.
95. thiethylperazine.mp.
96. trimethobenzamide.mp.
97. ondansetron.mp.
98. granisetron.mp.
99. dolasetron.mp.
100. diphenhydramine.mp.
101. hydroxyzine.mp.
102. promethazine.mp.
103. Valproic Acid.mp.
104. valproate.mp.
105. divalproex sodium.mp.
106. Clonidine.mp.
107. fluid bolus.mp.
108. normal saline.mp.
109. magnesium.mp.
110. lidocaine.mp.
111. botulinium toxin.mp.
112. botox.mp.
113. oxygen.mp.
114. placebo$.mp.
115. or/2-114
116. infant$.mp.
117. infancy.mp.
118. newborn$.mp.
119. baby.mp.
120. babies.mp.
121. neonat$.mp.
122. preterm$.mp.
123. prematur$.mp.
124. postmatur$.mp.
125. child$.mp.
126. kid.mp.
127. kids.mp.
128. toddler$.mp.
129. adolescen$.mp.
130. teen$.mp.
131. boy$.mp.
132. girl.mp.
133. girls.mp.
134. minor$.mp.
135. pubert$.mp.
136. pubescen$.mp.
137. pediatric$.mp.
138. paediatric$.mp.
139. peadiatric$.mp.
140. or/116-139
141. and/1,115,140

CINAHL® (Cumulative Index to Nursing & Allied Health Literature)	**#** **Query**
EBSCO	S7
1937-present	S6 and S4
Searched: 18.02.08	S6
Results: 344	S5 and S3
	S5
	S2 and S1
	S4
	(MH "Infant+") or (MH "Child+") or (MH "Adolescence") or (MH "Puberty+") or (MH "Pediatrics+") or infant* or infanc* or newborn* or baby or neonat* or preterm* or prematur* or postmatur* or child* or kid or kids or toddler* or adolescen* or teen* or boy* or girl or girls* or minor* or pubert* or pubescen* or pediatric* or paediatric* or peadiatric*
	S3
	((MH "Random Assignment") or (MH "Random Sample+") or (MH "Crossover Design") or (MH "Clinical Trials+") or (MH "Comparative Studies") or (MH "Control (Research)+") or (MH "Control Group") or (MH "Factorial Design") or (MH "Quasi-Experimental Studies+") or (MH "Placebos") or (MH "Meta Analysis") or (MH "Sample Size") or (MH "Research, Nursing") or (MH "Research Question") or (MH "Research Methodology+") or (MH "Evaluation Research+") or (MH "Concurrent Prospective Studies") or (MH "Prospective Studies") or (MH "Nursing Practice, Research-Based") or (MH "Solomon Four-Group Design") or (MH "One-Shot Case Study") or (MH "Pretest-Posttest Design+") or (MH "Static Group Comparison") or (MH "Study Design") or (MH "Clinical Research+")) or (clinical nursing research or random* or cross?over or placebo* or control* or factorial or sham* or meta?analy* or systematic review* or blind* or mask* or trial*)
	S2
	((MH "Drug Therapy+") or (MH "Drug Therapy, Combination+") or (MH "Drug Combinations+") or (MH "Drug Therapy+") or MH "Drug Therapy, Combination+" or MH "Drug Combinations+" or drug w3 therap* or drug w3 treatment* or anti-migrain* w3 therap* or antimigrain* w3 treatment* or (MH "Treatment Outcomes+") or (MH "Analgesics+") or "nonsteroidal anti-inflammatory agent?" or "non-steroidal anti-inflammatory agent?" or ibuprofen or fenoprofen or flurbiprofen or Ketorolac or Diclofenac or Etodolac or Sulindac or Diflunisal or Naproxen or Oxaprozin or "tiaprofenic acid" or "mefenamic acid" or Indomethacin or Tolmetin or Celecoxib) or (Meloxicam or Piroxicam or Tenoxicam or Floctafenin* or nabumeton* or acetaminophen or ergot* w1 alkaloid* or ergotamin* or dihydroergotoxin* or dihydroergotamin* or DHE or ergoloid w1 mesylates or methysergide or ziconotide or opioid* or opiate*) or (opium or alfentan?l or fentan?l or rem?fentan?l or sufentan?l or levomethadyl or butorphanol or codein* or morphine or pentazocin* or propoxyphen* or dextro-propoxyphen* or dextropropoxyphen* or nalbuphin* or hydromorphon* or oxycodon*)
	S1
	(MH "Headache+" or MH "Vascular Headache+") or TI (migraine* or headache* or head-ache* or cephalgia or cephalalgia) or AB (migraine* or headache* or head-ache* or cephalgia or cephalalgia)

RCT filter used in Ovid searches adapted from:
Cochrane Highly Sensitive Search Strategy (2005) Revision from
Glanville JM, Lefebvre C, Miles JNV, Camosso-Stefinovic J. How to identify randomized controlled trials in Medline: ten years on. J Med Libr Assoc 2006; 94(2):130-6

Appendix 3 – Data extraction form for Systematic Review

RevMan ID:		Reviewer ID:
Authors:		
Title:		
Journal citation:		
Year of publication:	Language:	Country of Origin:
Study Design: Randomized/blinded _____ Cross-over _____ Randomized / not blinded _____		
Study Period:		
Treatment (brief):		
Randomization method:		
Sponsorship: Pharmaceutical company _____ Other _____ Not mentioned _____ Specify:		
Comments on study: e.g. design, methods, method of randomization, definitions used, inclusion/exclusion criteria used Contact with authors? Outcome?		

QUALITY:		
		Check one
A	Allocation was not concealed (e.g. quasi-randomisation)	
	Allocation concealment was not stated or was unclear	
	Disclosure of allocation was a possibility	
	Allocation was concealed (e.g. numbered, sealed opaque envelopes drawn NON consecutively)	
B	Inclusion and exclusion criteria were not clearly defined in the text	
	Inclusion and exclusion criteria were clearly defined in the text	
C	Outcomes of patients who withdrew or were excluded after allocation were NEITHER detailed separately NOR included in an intention to treat	
	Outcomes of patients who withdrew or were excluded after allocation were EITHER detailed separately OR included in an intention to treat analysis OR the text stated there were no withdrawals (circle one)	
	Unclear	
D	Treatment and control groups were NOT adequately described at entry	
	Treatment and control groups were adequately described at entry. A minimum of 4 admission/presentation details were described (e.g. age, sex, type of intervention, severity of illness)	
E	The text stated that care programs other than trial options were NOT identical	
	The text stated that care programs other than trial options were identical	
	No comment on the care programs other than trial options	
F	Outcome measures were NOT clearly defined in the text	
	Outcome measures were clearly defined in the text	
G	Outcome assessors were NOT blind to the allocation of patients	
	Outcome assessors were blind to the allocation of patients	
H	The timing of the measurement of the outcomes was NOT appropriate	
	The timing of the measurement of the outcomes was appropriate	
Jadad Score: /5 Comments on quality:		

METHODS:

Subject-blinded: yes _____ no _____ unclear _____

Physician-blinded: yes _____ no _____ unclear _____

Outcome assessor-blinded: yes _____ no _____ unclear _____

PARTICIPANTS:

Number of eligible participants:	Number enrolled in study:
Exclusions:	
Number of males:	Number of females:

Ages of participants (age range and mean age):

INTERVENTION:

Treatment Group	Pharmacologic or Non-pharmacologic Intervention (Specify)	Dose	Timing	Route of Delivery	No. per group
1					
2					
3					
4					

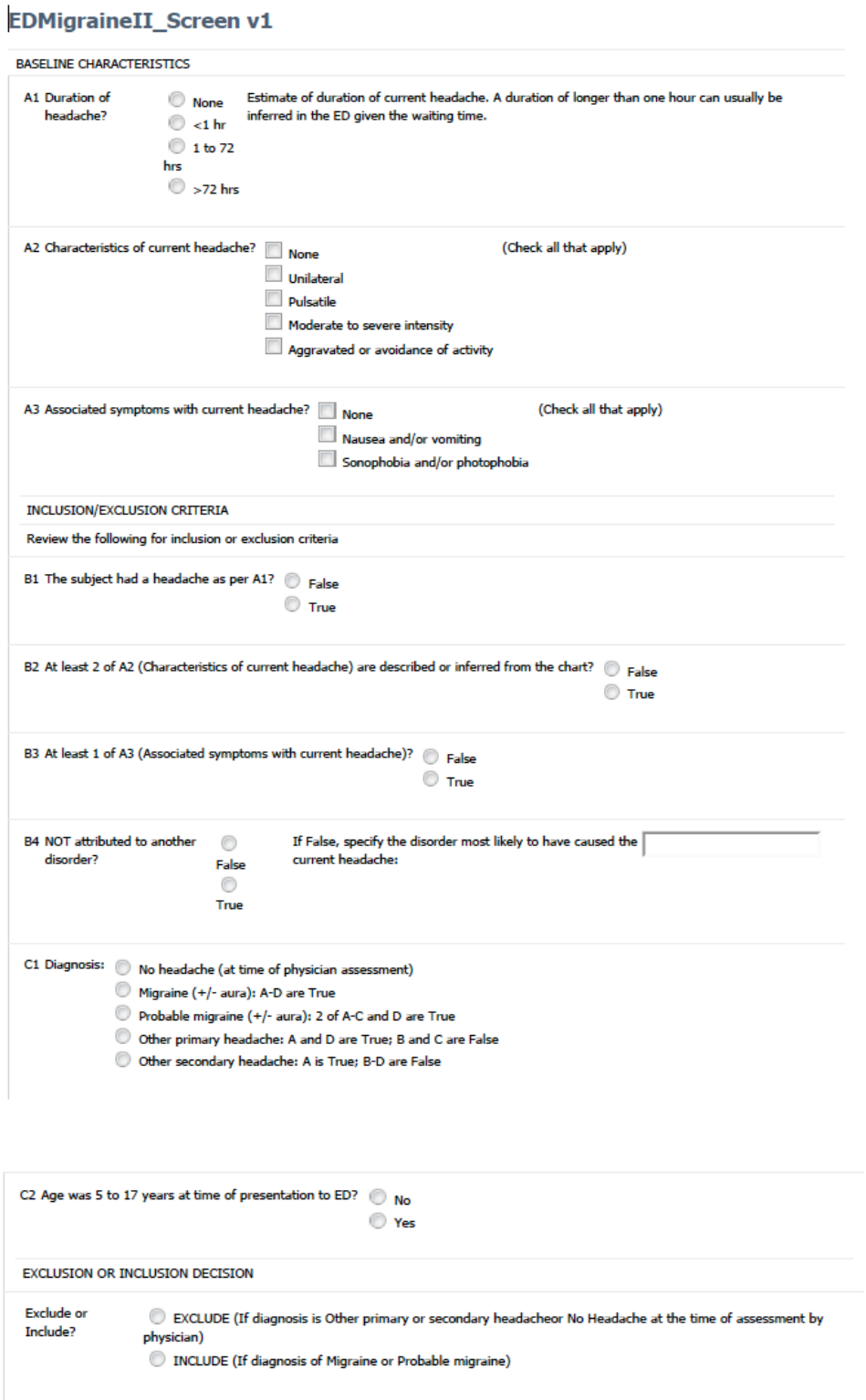
COMMENT ON TREATMENT:

Withdrawals: Yes _____ No _____ Unclear _____

Comment on withdrawals/dropouts:

OUTCOMES (List all reported)				
Indicate primary (1º) and secondary (2º) outcomes	Group 1	Group 2	Group 3	Group 4
Pain-free Scale: Defn: Time:				
Headache relief Scale: Defn: Time:				
Use of rescue medications Defn: Time:				
Headache recurrence Defn: Time:				
Presence of nausea Defn: Time:				
Presence of vomiting Defn: Time:				
Presence of photophobia Defn: Time:				
Presence of sonophobia (phonophobia) Defn: Time:				
Adverse events (any)				
Comments on Treatment:				

Appendix 4 – Practice variation study screening and abstraction forms



EDMigraineII_Screen v1

BASELINE CHARACTERISTICS

A1 Duration of headache? ○ None ○ <1 hr ○ 1 to 72 hrs ○ >72 hrs — Estimate of duration of current headache. A duration of longer than one hour can usually be inferred in the ED given the waiting time.

A2 Characteristics of current headache? (Check all that apply)
☐ None
☐ Unilateral
☐ Pulsatile
☐ Moderate to severe intensity
☐ Aggravated or avoidance of activity

A3 Associated symptoms with current headache? (Check all that apply)
☐ None
☐ Nausea and/or vomiting
☐ Sonophobia and/or photophobia

INCLUSION/EXCLUSION CRITERIA

Review the following for inclusion or exclusion criteria

B1 The subject had a headache as per A1? ○ False ○ True

B2 At least 2 of A2 (Characteristics of current headache) are described or inferred from the chart? ○ False ○ True

B3 At least 1 of A3 (Associated symptoms with current headache)? ○ False ○ True

B4 NOT attributed to another disorder? ○ False ○ True — If False, specify the disorder most likely to have caused the current headache: _____

C1 Diagnosis:
○ No headache (at time of physician assessment)
○ Migraine (+/- aura): A-D are True
○ Probable migraine (+/- aura): 2 of A-C and D are True
○ Other primary headache: A and D are True; B and C are False
○ Other secondary headache: A is True; B-D are False

C2 Age was 5 to 17 years at time of presentation to ED? ○ No ○ Yes

EXCLUSION OR INCLUSION DECISION

Exclude or Include?
○ EXCLUDE (If diagnosis is Other primary or secondary headacheor No Headache at the time of assessment by physician)
○ INCLUDE (If diagnosis of Migraine or Probable migraine)

EDMigraineII_ChartReview_r1 v2

DEMOGRAPHICS

A1 Date of ED visit? _____ mm/dd/yyyy Date of birth? _____ mm/dd/yyyy

A2 Gender?
- ○ Female
- ○ Male

A3 Migraine aura is described?
- ○ No
- ○ Unsure
- ○ Yes

If Yes, type:
- ○ None
- ○ Visual
- ○ Sensory
- ○ Weakness
- ○ Speech
- ○ Vertigo
- ○ Ataxia
- ○ Other

If Other, describe: _____

A4 Past history of headache?
- ○ Unsure
- ○ New onset (1 to 4 attacks)
- ○ Recurrent (5 or more attacks)

A5 Estimate number of years with headache:
- ○ Unsure
- ○ Acute (< 1 mo)
- ○ Subacute (1 mo to 1 year)
- ○ Chronic (> 1 year)

A6 Frequency of headache?
- ○ Unsure
- ○ Infrequent (0-4/mo)
- ○ Frequent (5-15/mo)
- ○ Chronic daily pattern (>15/mo)

A7 Pattern of headache over time?
- ○ Unsure
- ○ Stable(no change in pattern)
- ○ Improving (less frequent or less severe)
- ○ Worsening (worsening frequency or severity)

MEDICATIONS USED FOR HEADACHE PRIOR TO ED VISIT

Migraine medication that the patient was already taking or had taken at the time of ED presentation.

B1 Acute migraine therapy prior to the ED visit?
- ☐ None
- ☐ Acetaminophen
- ☐ Ibuprofen
- ☐ Triptan

Other: _____

- [ ] Opioid
- [ ] Other (provide name)

B2 Migraine prophylactic (preventative) medication prior to the ED visit?

- [ ] None
- [ ] Cyproheptadine
- [ ] Pizotifen
- [ ] Vitamin B2
- [ ] Feverfew
- [ ] Propranolol
- [ ] Topiramate
- [ ] Valproate
- [ ] Ami/Nortriptyline
- [ ] Other (provide name)

Other:

INVESTIGATION(S)

C1 Lumbar puncture?

- ( ) No
- ( ) Unsure
- ( ) Yes

Result:

- ( ) None
- ( ) Normal
- ( ) Abnormal (specify)

Describe:

C2 Neuroimaging?

- [ ] None
- [ ] MRI
- [ ] CT head
- [ ] Skull xray
- [ ] Sinus films
- [ ] Other (specify)

If Other, specify:

C3 Neuroimaging result?

- ( ) None
- ( ) Normal
- ( ) Abnormal (specify)

If Abnormal, desribe:

C4 Consultation in ED?

- [ ] None
- [ ] Neurology
- [ ] Neurosurgery
- [ ] Pediatrics
- [ ] Rheumatology
- [ ] Psychiatry
- [ ] Psychology
- [ ] Infectious disease
- [ ] Nephrology
- [ ] Gastroenterology
- [ ] Cardiology
- [ ] General surgery

Other:

MANAGEMENT

D1 Intravenous started?
- No
- Unsure
- Yes

Fluid blus given?
- No
- Unsure
- Yes

MEDICATION(S)

List all medications in the order in which they were given.

C1 Medication:
- None
- Acetaminophen (Tylenol)
- Acetaminophen/Codeine (Tylenol 3)
- Almotriptan (Axert)
- Chlorpromazine (Largactil)
- Codeine
- Demerol
- Dihydroergotamine (DHE)
- Eletriptan (Relpax)
- Ibuprofen (Advil/Motrin)
- Ketorolac (Toradol)
- Metoclopramide (Maxeran)
- Morphine
- Naproxen (Naprosyn)
- Naratriptan (Amerge)
- Prochlorperazine (Stemetil)
- Rizatriptan (Maxalt)
- Sumatriptan (Imitrex)
- Zolmitriptan (Zomig)
- Other (Specify)

Other: _____

Route:
- Unsure
- PO
- IV
- SC
- IN
- IM
- PR

C2 Medication:
- None
- Acetaminophen (Tylenol)
- Acetaminophen/Codeine (Tylenol 3)
- Almotriptan (Axert)
- Chlorpromazine (Largactil)
- Codeine
- Demerol
- Dihydroergotamine (DHE)
- Eletriptan (Relpax)
- Ibuprofen (Advil/Motrin)
- Ketorolac (Toradol)
- Metoclopramide (Maxeran)
- Morphine
- Naproxen (Naprosyn)
- Naratriptan (Amerge)
- Prochlorperazine (Stemetil)

Other: _____

Route:
- Unsure
- PO
- IV
- SC
- IN
- IM
- PR

- Rizatriptan (Maxalt)
- Sumatriptan (Imitrex)
- Zolmitriptan (Zomig)
- Other (Specify)

C3 Medication:

- None
- Acetaminophen (Tylenol)
- Acetaminophen/Codeine (Tylenol 3)
- Almotriptan (Axert)
- Chlorpromazine (Largactil)
- Codeine
- Demerol
- Dihydroergotamine (DHE)
- Eletriptan (Relpax)
- Ibuprofen (Advil/Motrin)
- Ketorolac (Toradol)
- Metoclopramide (Maxeran)
- Morphine
- Naproxen (Naprosyn)
- Naratriptan (Amerge)
- Prochlorperazine (Stemetil)
- Rizatriptan (Maxalt)
- Sumatriptan (Imitrex)
- Zolmitriptan (Zomig)
- Other (Specify)

Other: _____

Route:

- Unsure
- PO
- IV
- SC
- IN
- IM
- PR

C4 Medication:

- None
- Acetaminophen (Tylenol)
- Acetaminophen/Codeine (Tylenol 3)
- Almotriptan (Axert)
- Chlorpromazine (Largactil)
- Codeine
- Demerol
- Dihydroergotamine (DHE)
- Eletriptan (Relpax)
- Ibuprofen (Advil/Motrin)
- Ketorolac (Toradol)
- Metoclopramide (Maxeran)
- Morphine
- Naproxen (Naprosyn)
- Naratriptan (Amerge)
- Prochlorperazine (Stemetil)
- Rizatriptan (Maxalt)
- Sumatriptan (Imitrex)
- Zolmitriptan (Zomig)
- Other (Specify)

Other: _____

Route:

- Unsure
- PO
- IV
- SC
- IN
- IM
- PR

C5 Medication:

- None
- Acetaminophen (Tylenol)
- Acetaminophen/Codeine (Tylenol 3)
- Almotriptan (Axert)
- Chlorpromazine (Largactil)
- Codeine
- Demerol
- Dihydroergotamine (DHE)
- Eletriptan (Relpax)
- Ibuprofen (Advil/Motrin)
- Ketorolac (Toradol)
- Metoclopramide (Maxeran)
- Morphine
- Naproxen (Naprosyn)
- Naratriptan (Amerge)
- Prochlorperazine (Stemetil)
- Rizatriptan (Maxalt)
- Sumatriptan (Imitrex)
- Zolmitriptan (Zomig)
- Other (Specify)

Other:

Route:

- Unsure
- PO
- IV
- SC
- IN
- IM
- PR

OTHER COMMENTS/EXPLANATION

Provide any additional comments that may clarify the treatments ordered in the ED.

C9 Comments?

HEADACHE OUTCOME

D1 Headache outcome at discharge?

- Unsure
- Resolved headache
- Improved headache
- Persistent headache

DISCHARGE PLAN

Advice documented by the physician for the patient to pursue as an outpatient. May include medication, additional consultation, or other investigations.

D2 Discharge medication prescibed?
- ( ) No
- ( ) Unsure
- ( ) Yes

If yes, what medication(s)? _____

D3 Request for outpatient consultation after discharge?
- [ ] None
- [ ] Neurology
- [ ] Neurosurgery
- [ ] Pediatrics
- [ ] Rheumatology
- [ ] Psychiatry
- [ ] Psychology
- [ ] Infectious disease
- [ ] Nephrology
- [ ] Gastroenterology
- [ ] Cardiology
- [ ] General surgery

Other: _____

D4 Request for outpatient investigation(s)?
- [ ] None
- [ ] CT
- [ ] MRI
- [ ] EEG
- [ ] Xray
- [ ] Other (specify)

Other: _____

References

Ahonen, K., M. L. Hämäläinen, et al. (2006). "A randomized trial of rizatriptan in migraine attacks in children." Neurology **67**(7): 1135-1140.

Ahonen, K., M. L. Hämäläinen, et al. (2004). "Nasal sumatriptan is effective in treatment of migraine attacks in children: A randomized trial." Neurology **62**(6): 883-887.

Akerman, S. and P. J. Goadsby (2007). "Dopamine and migraine: biology and clinical implications." Cephalalgia **27**(11): 1308-1314.

Altman, D. G. and J. M. Bland (2003). "Interaction revisited: the difference between two estimates." BMJ **326**(7382): 219.

Aromaa, M., M. Sillanpaa, et al. (2000). "A population-based follow-up study of headache from age 7 to 22 years." J Headache Pain **1**: 11-15.

Azzopardi, T. D. and N. A. Brooks (2008). "Oral metoclopramide as an adjunct to analgesics for the outpatient treatment of acute migraine." Annals of Pharmacotherapy **42**(3): 397-402.

Bailey, B. and B. C. McManus (2008). "Treatment of children with migraine in the emergency department: a qualitative systematic review." Pediatric emergency care **24**(5): 321-330.

Bandell-Hoekstra, I. E., H. H. Abu-Saad, et al. (2002). "Coping and Quality of Life in relation to headache in Dutch schoolchildren." Eur J Pain **6**(4): 315-321.

Begg, C. B. and M. Mazumdar (1994). "Operating characteristics of a rank correlation test for publication bias." Biometrics **50**(4): 1088-1101.

Benedetti, F., M. Amanzio, et al. (1995). "Potentiation of placebo analgesia by proglumide." Lancet **346**(8984): 1231.

Bigal, M. E. and R. B. Lipton (2008). "Concepts and mechanisms of migraine chronification." Headache **48**(1): 7-15.

Bille, B. (1997). "A 40-year follow-up of school children with migraine." Cephalalgia **17**(4): 488-491; discussion 487.

Bille, B. S. (1962). "Migraine in school children. A study of the incidence and short-term prognosis, and a clinical, psychological and electroencephalographic comparison between children with migraine and matched controls." Acta Paediatrica Supplement **136**: 1-151.

Bousser, M. (2004). "Estrogens, Migraine, and Stroke." Stroke **35**(11_suppl_1): 2652-2656.

Brna, P., K. Gordon, et al. (2007). "Health-related quality of life among Canadians with migraine." J Headache Pain **8**(1): 43-48.

Brna, P., K. Gordon, et al. (2008). "Canadian adolescents with migraine: impaired health-related quality of life." Journal of Child Neurology **23**(1): 39-43.

Brousseau, D. C., S. J. Duffy, et al. (2004). "Treatment of pediatric migraine headaches: a randomized, double-blind trial of prochlorperazine versus ketorolac." Annals of Emergency Medicine **43**(2): 256-262.

Burstein, R., B. Collins, et al. (2004). "Defeating migraine pain with triptans: A race against the development of cutaneous allodynia." Ann Neurol **55**(1): 19-26.

Colloca, L. and F. Benedetti (2005). "Placebos and painkillers: is mind as real as matter?" Nat Rev Neurosci **6**(7): 545-552.

Colman, I., M. D. Brown, et al. (2004). "Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials." BMJ **329**(7479): 1369-1373.

Colman, I., A. Rothney, et al. (2004). "Use of narcotic analgesics in the emergency department treatment of migraine headache." Neurology **62**(10): 1695-1700.

Connelly, M. and M. A. Rapoff (2006). "Assessing health-related quality of life in children with recurrent headache: reliability and validity of the PedsQLTM 4.0 in a pediatric headache sample." Journal of pediatric psychology **31**(7): 698-702.

Coppola, M., D. M. Yealy, et al. (1995). "Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache." Ann Emerg Med **26**(5): 541-546.

D'Amico, D., A. Solari, et al. (2006). "Improvement in quality of life and activity limitations in migraine patients after prophylaxis. A prospective longitudinal multicentre study." Cephalalgia **26**(6): 691-696.

Damen, L., J. Bruijn, et al. (2006). "Prophylactic treatment of migraine in children. Part 2. A systematic review of pharmacological trials*." Cephalalgia **26**(5): 497-505.

Damen, L., J. K. Bruijn, et al. (2005). "Symptomatic treatment of migraine in children: a systematic review of medication trials." Pediatrics **116**(2): e295-302.

Dooley, J. M., K. E. Gordon, et al. (2005). "Self-reported headache frequency in canadian adolescents: validation and follow-up." Headache **45**(2): 127-131.

Ducharme, J. (1999). "Canadian Association of Emergency Physicians Guidelines for the acute management of migraine headache." J Emerg Med **17**(1): 137-144.

Egger, M., G. Davey Smith, et al. (1997). "Bias in meta-analysis detected by a simple, graphical test." BMJ **315**(7109): 629-634.

El Hasnaoui, A., M. Vray, et al. (2004). "Assessment of migraine severity using the MIGSEV scale: relationship to migraine features and quality of life." Cephalalgia **24**(4): 262-270.

Frare, M., G. Axia, et al. (2002). "Quality of life, coping strategies, and family routines in children with headache." Headache **42**(10): 953-962.

Frazee, L. A. and K. C. Foraker (2008). "Use of intravenous valproic acid for acute migraine." Ann Pharmacother **42**(3): 403-407.

Friedman, B. W. and B. M. Grosberg (2009). "Diagnosis and management of the primary headache disorders in the emergency department setting." Emerg Med Clin North Am **27**(1): 71-87, viii.

Friedman, B. W., A. Kapoor, et al. (2008). "The relative efficacy of meperidine for the treatment of acute migraine: a meta-analysis of randomized controlled trials." Annals of Emergency Medicine **52**(6): 705-713.

Gilbert, E. H., S. R. Lowenstein, et al. (1996). "Chart reviews in emergency medicine research: Where are the methods?" Annals of Emergency Medicine **27**(3): 305-308.

Goadsby, P., G. Zanchin, et al. (2008). "Early vs. non-early intervention in acute migraine— 'Act when Mild (AwM)'. A double-blind, placebo-controlled trial of almotriptan." Cephalalgia **28**(4): 383-391.

Goadsby, P. J. (2008). "The 'Act when Mild' (AwM) study: a step forward in our understanding of early treatment in acute migraine." Cephalalgia **28 Suppl 2**: 36-41.

Goadsby, P. J., A. Charbit, et al. (2009). "Neurobiology of migraine." Neuroscience: 1-15.

Gordon, K. E., J. M. Dooley, et al. (2004). "Self-reported headache frequency and features associated with frequent headaches in Canadian young adolescents." Headache **44**(6): 555-561.

Hämäläinen, M. L., K. Hoppu, et al. (1997). "Oral dihydroergotamine for therapy-resistant migraine attacks in children." Pediatr Neurol **16**(2): 114-117.

Hämäläinen, M. L., K. Hoppu, et al. (1997). "Sumatriptan for migraine attacks in children: a randomized placebo-controlled study. Do children with migraine respond to oral sumatriptan differently from adults?" Neurology **48**(4): 1100-1103.

Hämäläinen, M. L., K. Hoppu, et al. (1997). "Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study." Neurology **48**(1): 103-107.

Herd, A. and L. Ludwig (1994). "Relief of posttraumatic headache by intravenous chlorpromazine." J Emerg Med **12**(6): 849-851.

Hershey, A. D. (2005). "What is the impact, prevalence, disability, and quality of life of pediatric headache?" Current Pain & Headache Reports **9**(5): 341-344.

Hershey, A. D., S. W. Powers, et al. (2001). "PedMIDAS: development of a questionnaire to assess disability of migraines in children." Neurology **57**(11): 2034-2039.

Hershey, A. D., S. W. Powers, et al. (2004). "Development of a patient-based grading scale for PedMIDAS." Cephalalgia **24**(10): 844-849.

Hershey, A. D., P. Winner, et al. (2005). "Use of the ICHD-II criteria in the diagnosis of pediatric migraine." Headache **45**(10): 1288-1297.

Higgins, J. and S. Green, Eds. (2008). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008], The Cochrane Collaboration. Available from www.cochrane-handbook.org.

Higgins, J. P. and S. G. Thompson (2002). "Quantifying heterogeneity in a meta-analysis." Stat Med **21**(11): 1539-1558.

IHS, H. C. S. o. t. (2004). "The International Classification of Headache Disorders, 2nd edition." Cephalalgia **24**(Supplement 1): 1-150.

Jadad, A. R., R. A. Moore, et al. (1996). "Assessing the quality of reports of randomized clinical trials: is blinding necessary?" Control Clin Trials **17**(1): 1-12.

Jakubowski, M., D. Levy, et al. (2005). "Terminating migraine with allodynia and ongoing central sensitization using parenteral administration of COX1/COX2 inhibitors." Headache **45**(7): 850-861.

Jakubowski, M., D. Levy, et al. (2007). "Sensitization of central trigeminovascular neurons: blockade by intravenous naproxen infusion." Neuroscience **148**(2): 573-583.

Kabbouche, M. A., S. L. Linder, et al. (2005). "Acute treatment of pediatric headache in the emergency department and inpatient settings." Pediatric Annals **34**(6): 466-471.

Kan, L., J. Nagelberg, et al. (2000). "Headaches in a pediatric emergency department: etiology, imaging, and treatment." Headache **40**(1): 25-29.

Kernick, D. and J. Campbell (2009). "Measuring the impact of headache in children: a critical review of the literature." Cephalalgia **29**(1): 3-16.

Kosinski, M., M. S. Bayliss, et al. (2003). "A six-item short-form survey for measuring headache impact: the HIT-6." Quality of life research : an

international journal of quality of life aspects of treatment, care and rehabilitation **12**(8): 963-974.

Lanzi, G., C. A. Zambrino, et al. (1997). "Periodic syndrome and migraine in children and adolescents." Italian Journal of Neurological Sciences **18**(5): 283-288.

Lateef, T., M. Grewal, et al. (2009). "Headache in Young Children in the Emergency Department: Use of Computed Tomography." Pediatrics **124**(1): e12-e17.

Levine, J. D. and N. C. Gordon (1984). "Influence of the method of drug administration on analgesic response." Nature **312**(5996): 755-756.

Levy, D., X. C. Zhang, et al. (2008). "Sensitization of meningeal nociceptors: inhibition by naproxen." Eur J Neurosci **27**(4): 917-922.

Lewis, D., S. Ashwal, et al. (2004). "Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society." Neurology **63**(12): 2215-2224.

Lewis, D. W. (2001). "Headache in the pediatric emergency department." Semin Pediatr Neurol **8**(1): 46-51.

Lewis, D. W., S. Ashwal, et al. (2002). "Practice parameter: evaluation of children and adolescents with recurrent headaches: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society." Neurology **59**(4): 490-498.

Lewis, D. W., D. Kellstein, et al. (2002). "Children's ibuprofen suspension for the acute treatment of pediatric migraine." Headache **42**(8): 780-786.

Lewis, D. W., P. Winner, et al. (2007). "Efficacy of zolmitriptan nasal spray in adolescent migraine." Pediatrics **120**(2): 390-396.

Lewis, D. W., P. Winner, et al. (2005). "The placebo responder rate in children and adolescents." Headache **45**(3): 232-239.

Linder, S. L., N. T. Mathew, et al. (2008). "Efficacy and Tolerability of Almotriptan in Adolescents: A Randomized, Double-Blind, Placebo-Controlled Trial." Headache **48**(9): 1326-1336.

Lipton, R., D. Dodick, et al. (2009). "Consistency of response to sumatriptan/naproxen sodium in a placebo-controlled, crossover study." Cephalalgia: 1-11.

Lipton, R. B., A. I. Scher, et al. (2002). "Migraine in the United States: epidemiology and patterns of health care use." Neurology **58**(6): 885-894.

Lipton, R. B., W. F. Stewart, et al. (2001). "Epidemiology and economic impact of migraine." Curr Med Res Opin **17 Suppl 1**: s4-12.

Major, P. W., H. S. Grubisa, et al. (2003). "Triptans for treatment of acute pediatric migraine: a systematic literature review." Pediatr Neurol **29**(5): 425-429.

Mortimer, M. J., J. Kay, et al. (1992). "Childhood migraine in general practice: clinical features and characteristics." Cephalalgia **12**(4): 238-243; discussion 186.

Pitman, V. (2000). "Efficacy, safety and tolerability of oral eletriptan (40 mg) for the treatment of acute migraine in adolescents (12-17 years)."**????**: 424.

Pothmann, R., S. V. Frankenberg, et al. (1994). "Epidemiology of headache in children and adolescents: evidence of high prevalence of migraine." Int J Behav Med **1**(1): 76-89.

Powers, S. W., S. R. Patton, et al. (2003). "Quality of life in childhood migraines: clinical impact and comparison to other chronic illnesses." Pediatrics **112**(1 Pt 1): e1-5.

Powers, S. W., S. R. Patton, et al. (2004). "Quality of life in paediatric migraine: characterization of age-related effects using PedsQL 4.0." Cephalalgia **24**(2): 120-127.

Pryse-Phillips, W. E., D. W. Dodick, et al. (1997). "Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society." CMAJ **156**(9): 1273-1287.

Rapoport, A. and P. Winner (2006). "Nasal delivery of antimigraine drugs: clinical rationale and evidence base." Headache **46 Suppl 4**: S192-201.

Richer, L. P., L. Graham, et al. (2007). "Emergency Department Management of Acute Migraine in Children in Canada: A Practice Variation Study." Headache **47**(5): 703-710.

Rothner, A. (1997). "Efficacy and safety of naratriptan tablets in adolescent migraine." J Neurol Sci **150**: S106.

Rothner, A., W. Wasiewski, et al. (2006). "Zolmitriptan Oral Tablet in Migraine Treatment: High Placebo Responses in Adolescents." Headache **46**(1): 101-109.

Schobitz, E., F. Qureshi, et al. (2006). "Pediatric Headaches inthe Emergency Department." Curr Pain Headache Rep **10**(5): 391-396.

Seshia, S., D. Phillips, et al. (2008). "Childhood chronic daily headache: a biopsychosocial perspective." Developmental medicine and child neurology **50**(7): 541-545.

Sillanpää, M. and P. Anttila (1996). "Increasing prevalence of headache in 7-year-old schoolchildren." Headache **36**(8): 466-470.

Silver, S., D. Gano, et al. (2008). "Acute treatment of paediatric migraine: a meta-analysis of efficacy." J Paediatr Child Health **44**(1-2): 3-9.

Soriani, S., P. Battistella, et al. (2001). "Nimesulide and acetaminophen for the treatment of juvenile migraine: a study for comparison of efficacy, safety, and tolerability." Headache **12**: 233-236.

Stewart, W. F., R. B. Lipton, et al. (2000). "Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers." Pain **88**(1): 41-52.

Strassman, A. M., S. A. Raymond, et al. (1996). "Sensitization of meningeal sensory neurons and the origin of headaches." Nature **384**(6609): 560-564.

Swidan, S. Z., A. E. Lake, et al. (2005). "Efficacy of intravenous diphenhydramine versus intravenous DHE-45 in the treatment of severe migraine headache." Current pain and headache reports **9**(1): 65-70.

Tfelt-Hansen, P., G. Block, et al. (2000). "Guidelines for controlled trials of drugs in migraine: second edition." Cephalalgia **20**(9): 765-786.

Trottier, E., B. Bailey, et al. (2009). "Clinical Outcomes of Children Treated with Intravenous Prochlorperazine for Migraine in a Pediatric Emergency Department." Journal of Emergency Medicine: 8.

Ueberall, M. A. and D. Wenzel (1999). "Intranasal sumatriptan for the acute treatment of migraine in children." Neurology **52**(7): 1507-1510.

Visser, W. H., P. Winner, et al. (2004). "Rizatriptan 5 mg for the acute treatment of migraine in adolescents: results from a double-blind, single-attack study and two open-label, multiple-attack studies." Headache **44**(9): 891-899.

Wang, S. J., J. L. Fuh, et al. (2009). "Migraine and suicidal ideation in adolescents aged 13 to 15 years." Neurology **72**(13): 1146-1152.

Winner, P. (2005). "Childhood periodic syndromes and migraine." Current pain and headache reports **9**(3): 197-201.

Winner, P., D. Lewis, et al. (2002). "Rizatriptan 5 mg for the acute treatment of migraine in adolescents: a randomized, double-blind, placebo-controlled study." Headache **42**(1): 49-55.

Winner, P., W. Martinez, et al. (1995). "Classification of pediatric migraine: proposed revisions to the IHS criteria." Headache **35**(7): 407-410.

Winner, P., A. Prensky, et al. (1997). "Adolescent migraine: Efficacy and safety of sumatriptan tablets." J Neurol Sci **150**(Supp 1): S172.

Winner, P., A. Rothner, et al. (2006). "Sumatriptan Nasal Spray in Adolescent Migraineurs: A Randomized, Double-Blind, Placebo-Controlled, Acute Study." Headache **46**(2): 212-222.

Winner, P., A. D. Rothner, et al. (2000). "A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatment of acute migraine in adolescents." Pediatrics **106**(5): 989-997.

Zubieta, J.-K. and C. S. Stohler (2009). "Neurobiological mechanisms of placebo responses." Annals of the New York Academy of Sciences **1156**: 198-210.