DRAFT Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Headache
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From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Acute Headache.

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ABSTRACT

This clinical policy from the American College of Emergency Physicians addressed key issues in the evaluation and management of patients presenting to the emergency department with acute headache. A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical questions: 1) In the adult emergency department patient presenting with acute headache, are there risk stratification strategies that reliably identify the need for emergent neuroimaging? 2) In the adult emergency department patient treated for acute primary headache, are non-opioids preferred to opioid medications? 3) In the adult emergency department patient presenting with acute headache, does a normal noncontrast head computed tomography performed within 6 hours of headache onset preclude the need for further diagnostic workup for subarachnoid hemorrhage? 4) In the adult emergency department patient who is still considered to be at risk for subarachnoid hemorrhage after a negative noncontrast head computed tomography, is computed tomography angiography of the head as effective as lumbar puncture to safely rule out subarachnoid hemorrhage? Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

Headache is a common and often a potentially high-risk complaint seen by the emergency medicine physician. A query of the National Hospital Ambulatory Medical Care Survey for 2015 found that non-traumatic headache was identified as the fifth leading principle reason for emergency department (ED) visits, accounting for 3.8 million visits per year (2.8 % of all ED visits).[1] This prevalence impacts not only ED volumes but also resource utilization. Previous studies have shown that up to 14% of patients presenting with a headache complaint underwent imaging, with up to 5.5% of this group receiving a significant pathologic diagnosis.[2] Given the potentially complex and often undifferentiated clinical presentation of headache in the acute setting, emergency physicians must determine which patients need neuroimaging in the ED and which can be appropriately deferred and evaluated in the outpatient setting. Access to care can further complicate this decision process in clinical practice, but this variable is not accounted for in most studies. When evaluating the evidence, the outcome measures used in determining the need for neuroimaging in the ED must also be clinically relevant to practice. For example, diagnosing a brain tumor may not require immediate neurosurgery or even hospitalization, yet may clearly direct the disposition and follow-up timing of the patient. Further complicating the interpretation and creating variability across studies has been the rapid evolution of the imaging capabilities of the scanners. Where single-slice scanners began in the early 1970s, there are now multi-slice scanners with up to 320 detectors. This advancement has both drastically increased image resolution and reduced acquisition time.

According to the American College of Radiology Appropriateness Criteria for Headache, computed tomography (CT) scan or magnetic resonance imaging (MRI) of the head remain the best choice for headache

imaging when imaging is necessary.[3] The patient's presenting signs and symptoms should guide the provider to prioritize and select the modality best suited to evaluate the patient. Some patients need imaging of cerebrovasculature, which may include a CT angiography (CTA) or magnetic resonance angiography (MRA), or digital subtraction angiography (DSA). In contrast to MRI, CT scans expose the patient to radiation with a head CT delivering a dose of approximately 2 millisieverts (mSV) when compared to the exposure with one chest radiograph of 0.02 mSV.

The policy focuses on the ED evaluation of nontraumatic headaches following an acute onset of headache that is not consistent with an ongoing chronic disease process. While there are multiple potential pathologic causes of acute headache onset, a disproportionate amount of the literature is focused on rapid identification of subarachnoid hemorrhage (SAH). Although the policy recognizes the importance of diagnosing other catastrophic etiologies with similar presentations such as acute dural vein thrombosis, there is a paucity of studies to address critical questions specific to those etiologies. Therefore, these questions were derived recognizing that although data related to other high-risk diagnoses associated with headache would be considered, the literature, as a whole, is predominantly represented by studies focused on diagnosis of SAH.

This policy is an update of the 2008 American College of Emergency Physicians (ACEP) clinical policy on headache.[4]

METHODOLOGY

This clinical policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of MEDLINE, MEDLINE InProcess, SCOPUS, Embase, Web of Science, and the Cochrane Database of Systematic Reviews, were performed. All searches were limited to studies of adult humans published in English. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

This policy is a product of the ACEP clinical policy development process, including internal and external review, and is based on the existing literature; when literature was not available, consensus of Clinical Policies Committee members was used and noted as such in the recommendation (ie, Consensus recommendation). Internal

and external review comments were received from _____. Comments were received during a 60-day open-comment period, with notices of the comment period sent in an e-mail to ACEP members, published in *EM Today*, and posted on the ACEP Web site, and sent to other pertinent physician organizations. The responses were used to further refine and enhance this clinical policy; however, responses do not imply endorsement. Clinical policies are scheduled for review every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this clinical policy.

Assessment of Classes of Evidence

Two methodologists independently graded and assigned a preliminary Class of Evidence for all articles used in the formulation of this clinical policy. Class of Evidence is delineated whereby an article with design 1 represents the strongest study design and subsequent design classes (ie, design 2 and design 3) represent respectively weaker study designs for therapeutic, diagnostic, or prognostic studies, or meta-analyses (Appendix A). Articles are then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and conflicts of interest. Using a predetermined process combining the study's design, methodological quality, and applicability to the critical question, articles received a Class of Evidence grade. An adjudication process involving discussion with the original methodologist graders and at least one additional methodologist was then used to address any discordance in original grading, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or ultimately determined to not be applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the background and to inform expert consensus in the absence of robust evidence. Grading was done with respect to the specific critical questions; thus, the Class of Evidence for any one study may vary according to the question for which it is being considered. As such, it was possible for a single article to receive a different Class of Evidence rating when

addressing a different critical question. Question-specific Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence grading for each critical question (ie, Evidentiary Table), the subcommittee drafted the recommendations and the supporting text synthesizing the evidence using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of clinical certainty (eg, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate clinical certainty (eg, based on evidence from 1 or more Class of Evidence II studies or strong consensus of Class of Evidence III studies).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of adequate published literature, based on expert consensus. In instances in which consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

The recommendations and evidence synthesis were then reviewed and revised by the Clinical Policies Committee, which was informed by additional evidence or context gained from reviewers.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as consistency of results, uncertainty about effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient. This can assist the clinician in applying the recommendations to most patients but allows adjustment when applying to patients at the extremes of risk (Appendix C).

This policy is not intended to be a complete manual on the evaluation and management of adult patients with acute headache but rather a focused examination of critical issues that have particular relevance to the current

practice of emergency medicine. Potential benefits and harms of implementing recommendations are briefly summarized within each critical question.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain adequate empirical data to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to answer the critical questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in EDs who are evaluating nontraumatic and/or nonpregnant patients with acute onset headache and nonfocal neurologic examination findings.

Inclusion Criteria. This guideline is intended for adult nontraumatic headaches.

Exclusion Criteria. This guideline is not intended for pediatric, pregnant, or trauma patients.

CRITICAL QUESTIONS

1. In the adult ED patient presenting with acute headache, are there risk stratification strategies that reliably identify the need for emergent neuroimaging?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Use the Ottawa SAH Rule (Age >40, complaint of neck pain or stiffness, witnessed loss of consciousness, onset with exertion, thunderclap headache, and limited neck flexion upon examination) as a highly sensitive decision rule to exclude patients presenting to the ED with a normal neurological examination and peak headache severity within 1 hour of onset of pain symptoms from further imaging.

While the presence of neck pain and neck stiffness on physical examination in ED patients with an acute headache are strongly associated with SAH, do not use a single physical sign and/or symptom to rule out SAH**.**

Level C recommendations. None specified.

Potential Benefit of Implementing the Recommendations:

- The use of decision rules may reduce incidence of missed SAH in the ED.
- The use of decision rules may expedite care and avoid unnecessary imaging and workup.

Potential Harm of Implementing the Recommendations:

- Due to its poor specificity, application of the decision rule to the incorrect headache patient population may increase unnecessary testing.
- Misapplication of the recommendation because of confusion with decision rule criteria for inclusion.
- Potential in rare cases for missed SAH resulting in neurologic morbidity or death.

Key words/phrases for literature searches: headache, primary headache, thunderclap headache, acute headache, acute onset headache, acute primary headache, sudden acute headache, sudden onset headache, non-traumatic headache, risk assessment, risk benefit, risk factor, risk stratification, sensitivity and specificity, decision support, decision support techniques, decision support system, clinical decision support system, emergent neuroimaging, emergency neuroimaging, emergency, emergency health service, hospital emergency service, emergency ward, emergency medicine, emergency care, emergency treatment, emergency department, emergency room, emergency service, and variations and combinations of the key words/phrases. Searches included January 1, 2007, to search dates of June 29, 2017, and July 3, 2017.

Study Selection: One hundred twenty-seven articles were identified in the searches. Thirty-six articles were selected from the search results for further review, with zero Class I, 2 Class II, and 2 Class III studies included for this critical question.

Although most patients with sudden-onset severe headache have benign causes, data suggest that between 10% and 15% have serious pathology, most commonly SAH.[5-7] Patients with sudden-onset (peaking within 1 hour) headaches have been demonstrated to have a 6% to 7% incidence of SAH.[8,9] Despite evidence of improving outcomes in this potentially treatable neurosurgical emergency, SAH remains a devastating condition with case fatality rates of up to 50%.[10,11] Early diagnosis can be critical as delayed diagnosis has been associated with rebleeding and worsening of outcomes.[12] As a result, a primary goal in ED patients presenting with a severe headache is to promptly and accurately identify or rule out SAH early in the presentation to further limit associated morbidity and mortality. To assist clinicians in risk stratifying which patients with headaches are at greatest risk for SAH and acute adverse events, decision tools have been proposed. Understanding the strengths and limitations of current decision tools, the imaging technology available, and possible biomarkers is essential to determine the need

for advanced brain imaging. If these tools or tests were able to rule out SAH, the advantages would not only improve overall diagnosis, but also improve patient safety with decreased radiation exposure. This policy question seeks to address whether there are risk stratification strategies that reliably rule out SAH and thereby eliminate the need for emergent neuroimaging.

Risk Stratification with Decision Tools

After a thorough literature search and methodological review, 2 Class II[9,13] and 2 Class III[14,15] studies were identified to address this clinical question. In a 2013 Class II study, Perry et al[9] reported on the ability of the Ottawa SAH Rule to exclude SAH based on clinical criteria without the need for head CT or lumbar puncture (LP). This prospective study enrolled ED patients whose chief complaint was a nontraumatic headache that reached maximal intensity within 1 hour. Of these 2,131 subjects, 132 (6.2%) were diagnosed with SAH. The study has evidence of selection bias as 605 potentially eligible patients were missed for inclusion, which equates to enrollment of 78% of study eligible patients. The authors collected multiple (n=19) historical and physical clinical variables that were identified in previous studies or felt to be clinically important in ED patients being considered for SAH. The Ottawa SAH Rule (figure 1) was derived from these variables. This rule identified all 132 of the SAH cases in their cohort. The sensitivity, specificity, (+) LR and (-) LR were 100.0% (95% confidence interval [CI] 97.2% to 100%), 15.3 (95% CI 13.8 to 16.9), 1.17 (95% CI 1.15 to 1.20), 0.024 (95% CI 0.001 to 0.39), respectively.[9] A validation of this study was later performed in 2017 by Perry et al.[14] This Class III study performed in a similar manner missed enrollment of a significant number of eligible patients, enrolling 1,153 of 1,743 (66.2%) patients meeting inclusion criteria. Of the 1,153 enrolled patients, 67 had SAH. All 67 of these cases were identified by the Ottawa SAH Rule. Although the CI should be noted as wider, the sensitivity was 100% (95% CI 94.6% to 100%) and specificity, 13.6% (95% CI 13.1% to 15.8%).[14]

The 2016 extensive systematic review and meta-analysis of spontaneous SAH by Carpenter et al,[13] a Class II study, aimed to identify the diagnostic accuracy of clinical findings in patients with spontaneous SAH. Of 5,022 publications identified from existing search tools up to June 2015, 22 studies were included in this study but not all were directly related to this question. The authors looked at a number of clinical variables taken individually including altered mental status, arrival by ambulance, awoken from sleep by headache, blurred vision, bursting or

exploding at symptom onset, ED transfer, exertion at symptom onset, female gender, male gender, focal neurologic deficit, intercourse at symptom onset, loss of consciousness, nausea, neck stiffness, photophobia, vomiting, and worst headache of life. Of these 17 clinical variables, the pooled sensitivities ranged from 7% to 89% (average pooled sensitivity of 39%) and specificities ranged from 26% to 96% (average pooled specificity of 74%). Of note, even the characterization of the headache as "thunderclap," which is defined differently across multiple studies, was unreliable with a pooled sensitivity of 58% (95% CI 52% to 64%) and specificity of 50% (95% CI 48% to 52%). The results of the analysis demonstrated that none of the individual clinical variables, when used in isolation, had test characteristics that were good enough to reliably rule in or rule out a SAH diagnosis.[13]

Risk Stratification Based on Biomarkers

In addition to risk stratification with unique clinical variables, decision rules and time since headache onset, the use of biomarkers in the setting of headache have been investigated to rule out SAH. Few quality studies have been published to date. In a Class III study, Blum et al[15] evaluated 391 patients presenting to the ED with acute nontraumatic headache. Patients were prospectively enrolled into an observational cohort study with copeptin measured upon arrival. The primary endpoint was a serious secondary headache with a neurologic etiology requiring immediate intervention. Secondary endpoints were mortality and hospitalization at 3 months. Copeptin is a hypothalamic stress hormone that correlates with individual stress levels and may serve as a prognostic marker in various acute disease states. Therefore, the use of copeptin to discriminate benign versus serious headache might avoid additional testing, particularly CT imaging. Copeptin was associated with serious headache (defined as a headache that requires treatment of underlying disease or condition, that if left untreated, would risk permanent damage or death) with (odds ratio 2.03; 95% CI 1.52 to 2.70) with an area under the curve for primary endpoint of 0.70 (95% CI 0.63 to 0.76). Disease states identified included 8 patients (2%) with SAH, 7 (1.8%) with sinus vein thrombosis, 10 (2.6%) with intracranial hemorrhage, and 7 (1.8%) with viral meningitis. The study had several limitations including a sensitivity of only 91% for identification of serious secondary headache using the study's lowest laboratory cutoff. However, given the potential clinical impact, copeptin may be a promising biomarker to risk stratify nontraumatic headache patients as either benign or serious. Routine clinical use will require multicenter trial and validation.

Summary

Two Class II studies[9,13] and 2 Class III studies[14,15] were used to help identify risk stratification strategies to guide the use of neuroimaging in the evaluation of acute headache in the ED. The Ottawa SAH Rule has high sensitivity to rule out SAH. However, the rule lacks specificity with only 18% of patients who have a positive rule diagnosed with SAH. To date no studies have combined a risk stratification tool using both a decision rule and a biomarker such as copeptin. The early data is promising for the use of copeptin; however, the data is too limited at this time to include as part of a clinical recommendation. Additional protocols using biomarkers and validated decision rules should be investigated to provide clinicians with both the necessary sensitivity and specificity in this workup.

Future Research

Given the high potential for harm with missed serious pathology, risk stratification strategies must continue to focus on high sensitivity to ensure patient safety. However, this recognition must be balanced with the knowledge that further testing not only imparts exposure to radiation but is time consuming and adds cost to both the patient and the overall health care system. Therefore, additional specificity is needed to reduce unnecessary imaging as part of these workups. Future research should use existing validated risk stratification tools, like the Ottawa SAH Rule, combined with strategies that then reduce overall imaging while maintaining a high sensitivity. Continued work with biomarkers or panels of biomarkers that would accurately rule in or rule out significant pathology associated with acute severe headaches thereby avoiding acute ED brain imaging is warranted. The availability of reliable and immediately available laboratory testing would have dramatic impact on the evaluation of acute headache complaints in the ED.

2. In the adult ED patient treated for acute primary headache, are non-opioids preferred to opioid medications?

Patient Management Recommendations

Level A recommendations. Preferentially use non-opioid medications in the treatment of acute primary headaches in ED patients.

Level B recommendations. None specified.

Level C recommendations. None specified.

Potential Benefit of Implementing the Recommendations:

- Reduction of opioids for primary management of headaches in the ED.

Potential Harm of Implementing the Recommendations:

- None.

Key words/phrases for literature searches: headache, primary headache, thunderclap headache, acute headache, acute onset headache, acute primary headache, sudden acute headache, sudden onset headache, non-traumatic headache, migraine, opiate, opioids, analgesic, narcotic analgesic agent, drug therapy, emergency, emergency health service, hospital emergency service, emergency ward, emergency medicine, emergency care, emergency treatment, emergency department, emergency room, emergency service, and variations and combinations of the key words/phrases. Searches included January 1, 2007, to the search date of July 5, 2017.

Study Selection: Four hundred eighty-six articles were identified in the searches. Seventy-one articles were selected from the search results for further review, with zero Class I, 3 Class II, and 10 Class III studies included for this critical question.

Despite the recognition of a global opioid epidemic,[16] as well as multiple national guidelines that discourage use of opioids as first or second line treatment of headache in the acute setting, there remain practice patterns that use early implementation of this therapy. Failure to adopt these recommendations in clinical practice may be due to multiple variables, but evidence questioning the use of opioids as a first- or second- line treatment modality continues to mount along with societal scrutiny. In general, the likelihood of long-term opioid use increases with each additional day beyond a 3-day prescription as well as with greater prescribed cumulative dosing.[17-21] The American Academy of Neurology made reducing opioid usage in migraine care a primary goal in their Choosing Wisely campaign.[22]

In an effort to identify the prevalence of opioid medication use as abortive therapy in the ED treatment of migraines, Young et al[23] published a 2017 cross-sectional analysis of consecutive adult ED patients. This study using 3 different EDs with different patient populations to identify opioid treatment regimens for migraine headache. The results clearly demonstrated significant use of opioids in migraine management. Of the 1,222 visits

for migraine headaches, 35.8% had opioid medications ordered. Overall, opioid use was greatest in the community setting where it was ordered during 68.6% of visits. The urban emergency department used opioids in 40.9% of the migraine patients with 12.3% use in the academic medical center. Of note, opioids were used a greater percentage as a rescue agent (49.9% of visits) and were still used as a first-line agent in 29.5% of visits on average. The study demonstrated variability in practice with the community ED arm using opioids as a first-line agent 58.2% of the time compared to 35.3% in the urban ED and 6.9% in the academic medical center.[23] Unfortunately, in the ED, like most medical settings, the treatment of acute pain is based on limited evidence when considering direct comparisons of non-opioid versus opioids.[17,24,25] A comprehensive literature review of all non-opioids is beyond the scope of this paper.

The national opioid crisis related to use and abuse, has led to increased scrutiny centered on ED prescribing patterns with these medications. Headache management is an area that warrants clear guidelines related to clinical treatment alternatives to opioid administration. Although there are a significant number of studies that look at the acute management of headache, there is limited data that provides comparison data between opioid and non-opioid treatment. This systematic review identified a total three Class II[26-28,] and ten Class III[31-40] studies.

In a Class II study published by Friedman et al,[26] the authors compared outcomes among ED patients with migraine receiving IV hydromorphone versus those who received IV prochlorperazine and diphenhydramine. This was a double-blinded study that was halted by the data monitoring committee after enrollment of 127 patients due to clear benefit in the non-opioid arm of the study. The primary outcome included sustained headache relief for 48 hours after 1 dose of an investigational medication. This result was achieved in the prochlorperazine arm by 37 of 62 (60%) participants and in the hydromorphone arm by 20 of 64 (31%) participants (difference 28%, 95% CI 12 to 45, NNT 4, 95% CI 2 to 9). The secondary outcome was sustained headache relief after 1 or 2 doses of medication. Secondary outcomes were achieved in the prochlorperazine arm by 37 of 62 (60%) patients and in the hydromorphone arm by 26 of 64 (41%) patients (difference 19%, 95% CI 2 to 36, NNT 6, 95% CI 3 to 52). The authors concluded IV hydromorphone is substantially less effective than IV prochlorperazine for the treatment of acute migraine in the ED and should not be used as first-line therapy.

In a 2008 Class II systematic review, Friedman et al,[27] performed a metanalysis of randomized control trials comparing meperidine versus several other regimens (dihydroergotamine (DHE), ketorolac, or an antiemetic)

in the treatment of headache. In this study the authors looked at 899 citations and identified 19 trials for inclusion. Within the review's analysis, 11 studies were determined to have appropriate and available data. Four trials compared meperidine to DHE, 4 compared meperidine to an antiemetic, and 3 compared meperidine to ketorolac. The authors showed that meperidine was not superior in efficacy for pain control to the other regimens. However, meperidine was associated with more side effects than DHE. Meperidine was found to be less effective than DHE at providing headache relief (odds ratio 0.30; 95% CI 0.09 to 0.97). In regard to other adverse events, meperidine caused more dizziness (odds ratio 8.67; 95% CI 2.66 to 28.23) than the antiemetics. The authors also identified 2 studies that collected data on recurrence of symptoms after treatment. In one study they found patients treated with antiemetics had a lower rate of return to the hospital than those treated with meperidine (difference=20%; 95% CI 0% to 40%).[29] From the results of the other study looking at symptom recurrence, they suggest that the meperidine treated patients had a higher rate of recurrence in 24 hours than DHE (difference=7%; 95% CI -9% to 23%), but this conclusion should be tempered by the confidence intervals of this study crossing zero.[30]

Regarding Class III data that included direct comparison of non-opioids to opioids, a systematic review looking at the effectiveness of ketorolac in acute headache management by Taggart et al[31] identified 8 trials involving over 321 (141 ketorolac) patients. The authors found no difference in pain relief when studies compared ketorolac to meperidine but concluded that due to the addictive qualities related to the opioid that ketorolac should be the preferred agent.

In a 2011 Class III study by Taheraghdam et al[32] that also directly compared a non-opioid to an opioid agent, IV dexamethasone was studied versus IV morphine for acute migraine headache. Study participants were randomized to IV dexamethasone 8 mg or IV morphine 0.1 mg/kg. The results of the study demonstrated no significant clinical difference in Visual Analog Scale (VAS) at a baseline of 10 minutes, 1 hour, and 24 hours after drug administration compared to the morphine group.

Other studies identified through the search were not designed to directly compare opioid versus non-opioid treatments; however, the studies clearly demonstrate the effectiveness of alternative non-opioid medications in the treatment of migraines and other primary headaches in the emergency department setting. These included 1 of the Class II studies[28] and 6 of the Class III studies.[35-40] Medications addressed in these studies establishing efficacy include valproate, ketorolac, prochlorperazine, metoclopramide, naproxen, sumatriptan, haloperidol, and

dexamethasone when it was used in conjunction with a standard therapy.

In the single Class II study by Freidman et al,[28] the efficacy of IV valproate versus IV metoclopramide and IV ketorolac was evaluated in an ED population presenting with acute migraine. This randomized double-blinded comparative efficacy trial investigated the difference between treatment groups on an 11-point verbal pain scale (0 to 10) at 1 hour. The study provides additional direct evidence as to the overall efficacy of these treatment modalities as alternative therapeutic options to opioids. The results of the primary endpoint showed that patients randomly allocated to valproate improved by 2.8 points (95% CI 2.3 to 3.3); those receiving metoclopramide improved by 4.7 points (95% CI 4.2 to 5.2); and those receiving IV ketorolac improved by 3.9 points (95% CI 3.3 to 4.5). Between-group assessment found that both metoclopramide and ketorolac outperformed valproate, with metoclopramide demonstrating the superior difference of the two as well as directly outperforming ketorolac. Ultimately, the findings were neither compelling nor consistent enough to make firm conclusions regarding either metoclopramide or ketorolac as a superior therapeutic agent.[28]

Two Class III specialty society systematic reviews[32,33] were identified. Both reviews were highly supportive of non-opioids for migraine treatment in the ED setting compared to opioids for first-line treatment of migraine pain in the ED. Specifically, in the American Headache Society Evidence Assessment of Parental Pharmacotherapies, Orr et al[33] placed opioids into the "May avoid-Level C" classification as a result of the lack of evidence demonstrating their efficacy and concern about sub-acute or long-term sequelae. In addition, recommendations included avoiding injectable morphine and hydromorphone as first-line therapy.

Of the Class III studies, a 2010 study by Friedman et al[35] attempted to address the issue of post-ED recurrent primary headache by investigating strategies comparing naproxen and sumatriptan. This problem of recurrent primary headache is poorly studied with limited data across all treatment modalities and likely contributes to a failure of ED therapy to sustain relief leading to patient dissatisfaction and repeat ED visits. Patients who had received parental treatment during that ED visit for primary headache were randomized at discharge to either naproxen 500 mg or sumatriptan 100 mg for headache recurrence after ED discharge. The authors chose a primary endpoint identified as a between-group difference in pain intensity change during the 2-hour period after taking either 500 mg naproxen or 100 mg sumatriptan. A validated 11-point (0 to 10) verbal numeric rating scale (NRS) was used to document the difference. Results showed that almost three quarters or 280

of 383 patients (73%; 95% CI 68% to 77%) reported a post-ED recurrent headache. Of these, 196 patients (51%; 95% CI 44% to 58%) took the investigational medication provided to them within 48 hours after discharge. The data analysis also revealed that naproxen 500 mg and sumatriptan 100 mg taken orally relieve post-ED recurrent primary headache and migraine in a similar manner. The sumatriptan group improved by 4.1 NRS points while the naproxen group improved by a mean of 4.3 NRS points (95% CI 0.7 to 1.1).

Summary

A thorough review of the literature for this question identified 3 class II[26-28] and 10 Class III[31-40] studies. One challenge for interpreting the acute primary headache literature related to opioid versus non-opioid management is the paucity of studies using direct comparison. However, in conjunction with the direct and indirect comparison studies, there is clear and overwhelming evidence to support the use of non-opioid management. Given the well-documented complications associated with opioid management, including its addictive properties with recurrent use for pain, non-opioids are strongly preferred in the management of acute primary headache, including migraines, in the ED. As a result, the use of opioids should be discouraged given the multiple other therapeutic options in this patient population.

In an effort to ensure sustained relief from post-ED headache recurrence, providers should consider discharge medication and education that helps reduce the need for a repeat ED visit. Based on the study by Friedman et al,[35] oral sumatriptan and naproxen are both proven medications that deliver relief in the event of pain recurrence in the first 48 hours post-ED discharge.

Future Research

Future research should involve alternative treatment modalities that provide equal and improved pain management compared to opioid medications. Research should focus in the area of developing ED strategies for acute headache management that both control the initial pain and also prevent or provide relief from post-ED recurrent primary headache. Given the high incidence of post-ED headache recurrence, patient care plans that begin in the ED must consider not only medication treatment, but also incorporate evidence-based protocols for

alternative pain management techniques including nerve blocks, acupuncture, distraction, relaxation, and other potentially non-traditional treatment strategies.

3. In the adult ED patient presenting with acute headache, does a normal noncontrast head CT performed within 6 hours of headache onset preclude the need for further diagnostic workup for subarachnoid hemorrhage?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Use a normal noncontrast head CT* result in which the CT was performed within 6 hours of symptom onset in an ED headache patient with a normal neurologic examination, to rule out nontraumatic SAH.

* Minimum third-generation scanner

Level C recommendations. None specified.

Potential Benefit of Implementing the Recommendations:

- Selected patients will no longer need to be subjected to LP or CTA as a part of ruling out a SAH.

Potential Harm of Implementing the Recommendations:

- In the evaluation of ED headache, LP after a normal head CT is a longstanding diagnostic regimen that will occasionally reveal alternative diagnoses. If the LP is no longer performed these diagnoses may be missed, particularly in patients for whom other diagnoses remain in the differential, eg, meningitis.
- The use of the recommendation could result in a rare missed SAH.

Key words/phrases for literature searches: headache, migraine, subarachnoid hemorrhage, brain angiography, cerebral angiograph, computed tomography, computed tomographic angiography, neuroimaging, brain imaging, functional neuroimaging, neuroradiography, brain radiography, brain scan, diagnostic imaging, lumbar puncture, lumbar tap, spinal puncture, spinal tap, emergency, emergency health service, hospital emergency service, emergency ward, emergency medicine, emergency care, emergency treatment, emergency department, emergency room, emergency service, and variations and combinations of the key words/phrases. Searches included January 1, 2007, to the search date of July 3, 2017.

Study Selection: Five hundred ninety-four articles were identified in the searches. Fifteen articles were selected for further review, with zero Class I, 1 Class II, and 1 Class III studies included for this critical question.

Headache is a common presenting complaint in ED visits. For patients who have not had head trauma, the emergency physician is frequently trying to rule out the diagnosis of SAH. Patients whose history is suggestive of

SAH are often able to pinpoint a time of onset, and the gold standard of workup has historically been noncontrast head CT followed by LP.

Noncontrast head CT has long been known to be very sensitive at detecting SAH and has been the initial test of choice for many years.[13] Early-generation CT technology beginning with single-detector CTs showed a high sensitivity (sensitivity 93%)[41] for identifying small amounts of blood in the subarachnoid space but were inadequate to rule out SAH.

Data from earlier generation CT scanners had shown that this high sensitivity of CT wanes over the first hours after the onset of symptoms.[42] The high protein content of whole blood makes it denser than brain tissue and cerebrospinal fluid (CSF) and therefore acute blood appears hyperdense on CT images. In patients with SAH, blood proteins diffuse away or are absorbed or degraded over time, resulting in an increasingly isodense appearance on CT images which eventually disappears completely.[43] This process can take hours to several weeks depending on volume of blood and other factors.

Another issue that affects CT scan sensitivity for diagnosing acute non-traumatic SAH is the hemoglobin concentration. Patients who have low hemoglobin, particularly less than 10 mg/dL can have reduced contrast between blood and brain parenchyma, theoretically limiting the accuracy of CT interpretation for SAH. While recent radiology literature has focused on the ability to diagnose anemia on CT scans,[44] all of the recent studies included in this search regarding CT diagnosis of SAH have included patients regardless of hemoglobin level.

CT technology was pioneered in the 1970s and image quality, speed, and radiation dose have all improved significantly over time. Despite the continued improvement in image quality, the nomenclature regarding CT generations can be confusing, with no guarantee, for example, that a fifth-generation scanner would produce a better image than a third-generation scanner. Nevertheless, third-generation scanners were introduced in the early 1990s and scanners with multiple rows of detectors were introduced in late 1990s. The scanners used in the reviewed studies are generally described as being at least a third-generation scanner with multiple rows of detectors. The sheer number of available scanners and technologies does not readily allow for any type of direct comparison of machine quality.[45] For the purposes of answering this critical question, only studies using a third-generation or higher CT scanner with at least 4 rows of detectors were included.

Lumbar puncture is a time-consuming procedure, which prolongs ED length of stay and is associated with a high rate of inconclusive results, particularly in patients presenting early after the onset of symptoms.[46,47] LP is also uncomfortable for patients and can be associated with debilitating post-LP headache.[48]

Recent literature has focused on finding a subset of patients for whom a noncontrast head CT scan alone is sufficient to exclude the diagnosis of SAH. For this critical question, the specific subset of patients that present to the ED within 6 hours of symptom onset is the focus. After a thorough literature search and methodological grading, only 2 studies were identified (1 Class II[8] and 1 Class III[41]) to address this question.

A Class II study by Perry et al[8] looked prospectively at 3,132 patients across multiple centers in Canada. The study included patients over age 15 with acute (reaching maximum intensity within 1 hour of onset), nontraumatic headache with a Glasgow coma score (GCS) of 15 and excluded patients with focal neurologic deficits, history of SAH, papilledema, ventricular shunt, or brain neoplasm. CT scanners used at the different hospital sites were at least third-generation (4 to 320 slices per rotation), and results were interpreted by attending radiologists. Two hundred and forty patients were found to have SAH (7.7% incidence). Of the 953 patients who had a CT scan within 6 hours, 121 patients were identified to have SAH, with a sensitivity of 100% (95% CI 97% to 100%), a specificity of 100% (CI 99.5% to 100%), a negative predictive value of 100% (CI 99.5% to 100%), and a positive predictive value of 100% (CI 96.9% to 100%).

A 2016 Class III meta-analysis by Dubosh et al[41] pooled data on 8,907 patients from 5 studies who had noncontrast head CT within 6 hours of symptom onset. Of these 5 studies, one was the Class II Perry study discussed above. The other 4 studies were reviewed by our methodologists and received grades of X when reviewed individually and were not included as individual studies in the assessment of this critical question. Of the 8,907 pooled patients in this meta-analysis, 13 had SAH missed on the initial CT scan, 11 of which were from a single study. Overall incidence of missed SAH was 1.46 per 1000. Overall sensitivity on the CT was 98.7% (CI 97.1% to 99.4%) and specificity of 99.9% (CI 99.3% to 100%). The pooled likelihood ratio of a negative CT was 0.010 (CI 0.003 to 0.034).

Summary

With the addition of newer studies incorporating advanced CT scanning capabilities, the clinical strategy for evaluating SAH has evolved to provide clinicians an alternative to the previously suggested protocol of a head CT followed by a LP. Through a careful history and physical, clinicians can use the high sensitivity of noncontrast head CTs within the first 6 hours of onset of pain and symptoms to reliably rule out SAH without a performance of a LP. As a result, a normal noncontrast head CT performed within 6 hours of symptom onset in neurologically intact patients is sufficient to preclude further diagnostic workup for SAH.

Future Research

A significant portion of the available literature used CT scanners more than a decade old including third-generation machines with as few as 4 rows of detectors. It is unknown whether a more sensitive scanner could reliably exclude SAH later in the course of a patient's presentation. Further prospective data sets could potentially increase the 6-hour window and decrease the workup for additional patients. Another area that needs clarity is what is the best strategy in patients who are considered at highest risk for the presence of a ruptured aneurysm. Although this subset of patients is included in current larger data sets, it is unknown if this population of patients have any higher risk for missed SAH.

4. In the adult ED patient who is still considered to be at risk for SAH after a negative noncontrast head CT, is CTA of the head as effective as LP to safely rule out SAH?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Perform CTA of the head or a LP to safely rule out SAH in the adult ED patient who is still considered to be at risk for SAH after a negative noncontrast head CT.

Use shared decision making to select the best modality for each individual patient after weighing the potential for false positive imaging and the pros and cons associated with LP.

Potential Benefit of Implementing the Recommendations:

- This has the benefit of avoiding the performance of a LP, a procedure that is time consuming, has a low diagnostic yield, has a high rate of traumatic taps, has a high rate of uninterpretable test results, and is associated with a relatively high rate of post-LP headaches.

Potential Harm of Implementing the Recommendations:

- The use of CT angiography may identify incidental cerebral aneurysms that lead to an unnecessary invasive procedure. In addition, there is increased radiation exposure and the potential to miss alternative medical diagnoses that would have been made by LP.
- The ease of ordering CT angiography may increase the rate of testing.

Key words/phrases for literature searches: headache, migraine, headache disorders, subarachnoid hemorrhage, brain angiography, cerebral angiography, computed tomography, neuroradiography, computed tomographic angiography, functional neuroimaging, lumbar puncture, lumbar tap, spinal puncture, spinal tap, emergency, emergency health service, hospital emergency service, emergency ward, emergency medicine, emergency care, emergency treatment, emergency department, emergency room, emergency service, and variations and combinations of the key words/phrases. Searches included January 1, 2007, to search dates of June 30, 2017, and July 3, 2017.

Study Selection: Four hundred sixty-three articles were identified in the searches. Thirty-eight articles were selected for the search results for further review, with zero Class I, zero Class II, and 6 Class III studies included for this critical question.

ED headache patients considered at risk for SAH may be ruled out by the use of a clinical decision rule (ie the Ottawa SAH Rule) or by a negative head CT performed within 6 hours of symptom onset. In those patients not ruled out by these means and where additional evaluation is pursued, a negative head CT followed by a negative LP is traditionally considered a complete negative workup. Despite this, many patients often do not have a LP performed in this situation, only 39% in one study.[9,49,50] With the increased availability of a CTA in the ED, some have proposed replacing the LP with a CTA in this diagnostic workup. The 2014 American College of Radiology Appropriateness Criteria Headache does not address the use of CT/LP versus CT/CTA for the diagnosis of SAH.

This critical question addresses whether a CTA is as effective as LP to safely rule out SAH in ED nontraumatic headache patients whom have had an initial negative noncontrast head CT. After a thorough literature search and methodological review, 6 Class III[13,48,51-54] studies were identified to address this clinical question. However, only 1 of these studies, Carstairs et al,[51] a Class III study published in 2006, directly compared ED headache patients that had CT/LP versus CT/CTA. This Class III prospective study enrolled consecutive ED patients at a tertiary care military medical center presenting with a headache concerning for SAH. All patients had noncontrast head CT and CTA performed. If the noncontrast CT did not reveal a diagnosis of SAH, the patient underwent LP. Of 131 patients meeting enrollment criteria, 15 did not consent to participate and 10 did not

complete the study, leaving 106 study subjects. A confirmed aneurysm or SAH was identified in five (4.3%) patients. Of these five, CTA was positive in all the cases. For LP, 2 cases were positive, 2 were negative, and in 1 case the patient refused the LP. Of the 100 cases without aneurysm or SAH, in 1 patient, the CTA was found to be a false positive after DSA was performed. The sensitivity of CT/LP versus CT/CTA in this study was 40.0% (95% CI 14.7% to 94.7%) versus 100% (95% CI 47.8% to 100.0%), respectively. Having only 5 cases of SAH in this study led to very wide CIs.

CT Angiography for the Diagnosis of Cerebral Aneurysm

Although not directly comparing CT/LP versus CT/CTA ED patients, 2 Class III studies[52,53] report on the excellent ability of head CTA to diagnose cerebral aneurysms compared to the gold standard radiologic test, DSA. The first of these Class III studies reported in 2007 by El Khadi et al[52] was a prospective radiological study enrolling consecutive patients that had a CT diagnosis of nontraumatic acute SAH. All subjects then underwent CTA (16-row detector). If the CTA was negative, a DSA was performed. Using DSA as the gold standard for identification of aneurysm at the time of surgery in cases where DSA was not performed, 134 aneurysms were identified. CTA identified 133 of these with a sensitivity of 99.3% (95% CI 95.9% to 99.9%). Further, the authors reported no complications such as acute renal failure, allergic reactions, or dye extravasation at injection site.

The second Class III publication was reported by Menke et al[53] in 2011. This meta-analysis included studies where the study topic was the primary diagnosis of cerebral aneurysm. They identified patients clinically suspected of having a cerebral aneurysm who had a CTA performed as the index diagnostic test. The reference standard for the study was a DSA or its combination with neurosurgical findings. Forty-five studies were identified for analysis. Of the 3,643 pooled patients, 86% had nontraumatic SAH and 77% had cerebral aneurysms. Overall, CTA had a pooled sensitivity of 97.2% (95% CI 95.8% to 98.2%). Unfortunately, the authors did not report on complications associated with the performance of CTA and DSA.

Ability of CT/LP to Rule Out SAH in ED Headache Patients

Another Class III study, Perry et al[54] reported on the excellent sensitivity of CT/LP for ruling out SAH in ED headache patients. Although this study did not directly compare CT/LP versus CT/CTA, it enrolled consecutive

ED nontraumatic acute headache patients older than 15 years old. If the noncontrast head CT was negative, the patients underwent LP. If the LP results were negative, after ED discharge, they were followed for 6 to 36 months using a structured follow-up process. Of the 592 patients enrolled, 61 had a SAH (10.3%). All cases of SAH were identified on initial CT or LP, sensitivity of 100% (95% CI 94% to 100%).

Low Diagnostic Yield of LP and CTA

Another Class III study Perry et al[48] reported on the low diagnostic yield associated with LP. The cohort of patients used in this study was derived from a prospective study that enrolled consecutive nontraumatic acute ED headache patients older than 15 years with normal neurologic examinations. Those that underwent LP for SAH assessment were included in this substudy. The decision to perform a LP was at the discretion of the ED physician. Of the 4,141 patients enrolled, 1,739 underwent LP and enrolled in this substudy. Of the 1,739 cases undergoing LP only 15 (0.9%) cases of SAH were diagnosed, a number needed to diagnose of 116. Only six of these 15 underwent neurosurgical intervention increasing the number needed to diagnose to 290. If CTA replaces LP in this diagnostic work-up, CTA will also likely yield a large number needed to test to diagnose one SAH. However, whether LP or CTA is used, the significance of a missed or delayed diagnosis of a sentinel bleed SAH can be catastrophic[55] and likely justifies the low diagnostic yields of these tests.

Lumbar Puncture CSF RBC Diagnosis of SAH

The 2015 Class III study of Perry et al[48] discussed above reported on the diagnosis of SAH using the final tube CSF RBC count. Unfortunately, a large proportion of the LPs were traumatic taps. In 641 of the 1,739 LP cases (36.9%) there was at least 1 x 10^6/L RBCs in the final CSF tube. Of the 1,739 LP cases, 15 (0.9%) were diagnosed with SAH. Additionally, they found that a RBC count less than 2000 x 10^6/L and a negative xanthochromia excluded SAH. Despite a sensitivity of 100% (95% CI 74% to 100%), the limited number of SAH cases had a corresponding wide CI potentially limiting its usefulness.

In a Class III systematic review published in 2016 by Carpenter et al,[13] the authors looked at RBC count greater than 1000 x 10^6/L for diagnosing SAH. The authors performed an extensive literature review to identify studies of ED acute headache patients concerning for SAH. They found 5,022 publications. After critical review of

these publications, they included 22 studies in their analysis. From the 22 included studies they pooled data from 2 studies and found that a RBC count greater than 1000 x 10^6/L was not a good indicator to rule out SAH with a pooled sensitivity of 76% (95% CI 60% to 88%).

Traumatic LPs occur commonly and make test interpretation difficult and decrease the specificity and diagnostic yield of the test.[48,56-60] Some authors arbitrarily define a traumatic tap as one in which there is greater than 400 x 10^6/L RBCs in the CSF.[61,62] Using this definition, the traumatic tap rate has been reported to be 15% to 20%.[61,62] There have been a number of reported methods to differentiate traumatic from non-traumatic taps that use an absolute number of RBCs in the final CSF tube, a percentage reduction of RBCs from the first CSF tube to the last, presence of xanthochromia, white blood cell count proportional to peripheral blood, absence of crenated RBCs, CSF opening pressure, clot formation, ferritin essay, D-dimer assay, or absence of erythrophages. Unfortunately, none of these methods by themselves or in combination are agreed to be reliable.[48,56-60,63-65] In addition, a falling RBC count in sequential CSF tube samples is not felt to be a reliable rule-out strategy unless the final count is zero or near zero as a traumatic tap can occur in the presence of a true SAH.[64]

When left with a potential traumatic tap or uninterpretable LP, patients typically undergo further diagnostic testing. These tests may include a repeat LP from a different site, CTA, DSA, or MRA.

Additional Concerns with LP Testing

Approximately 15% of positive LP patients with SAH are due to perimesencephalic bleeding. This entity has normal cerebral angiography testing (CTA, DSA, or MRA) with no established vascular cause for the bleeding.[66,67] The cause for perimesencephalic SAH is not entirely understood and may represent many different etiologies such as venous bleeding, vasospasm, capillary telangiectasia, or perforating artery bleeding.[67,68] The prognosis for perimesencephalic SAH is felt to be benign in almost all cases and no neurosurgical interventions are indicated.[69]

The strategy of CT/LP requires further angiography (CTA, DSA, or MRA) in this small group of patients to delineate the cause. CT/CTA would eliminate the need for LP in these patients.

Another issue with LP is the relatively common complication of a post-LP headache, which is reported in 4% to 30% of cases depending on the type (traumatic versus nontraumatic) and the gauge of needle used.[70,71] The

698 headache is due to a persistent CSF leak from a dural tear caused by the LP needle during the process of obtaining
699 CSF fluid samples. The headaches can be severe, prolonged, and may require treatment such as prolonged rest in a
700 recumbent position, analgesics, epidural blood patching, and hospitalization.

701 Another downside of ED performance of the LP is the physician time needed to complete this procedure.
702 This invasive procedure can be technically difficult especially in obese patients. Although this is a relatively minor
703 consideration in the overall management of patients with possible SAH, when this is coupled with patient dislike of
704 a dreaded "spinal tap," shared mutual patient-physician decision making becomes important. In a survey study of
705 ED patients that were presented with the theoretical clinical scenario of an acute ED headache concerning for SAH
706 with the risks and benefits of LP versus CTA explained, 79.2% of patients preferred CTA to exclude SAH.[72]

707

708 Additional Concerns with CTA Testing

709 The most consequential concern of replacing CTA with LP is that a discovery of an aneurysm may not in
710 fact be the cause of the headache and may represent an incidental finding that potentially leads to an unnecessary
711 endovascular or neurosurgical procedure. Although the risk for this in ED headache patients suspected of SAH is
712 unknown, it has been estimated that 2% of the general population have asymptomatic cerebral aneurysms at
713 baseline.[73] One approach to identify these false positive CTA cases would be to perform LPs on all positive
714 CTAs.[74]

715 Another significant concern of the use of CTA would be the increased radiation exposure. During the
716 performance of a cranial CT, an adult is typically dosed approximately 2 mSv of radiation. Adding a CTA to a CT
717 would double this exposure. In addition to the cancer risk, patients who undergo head and neck CT may have an
718 increased risk for cataract development.[75]

719 Another concern with CTA are significant alternative diagnoses that would have been found on LP and
720 missed on CTA. Migdal et al[76] reported on 302 patients who were evaluated for possible SAH and had a LP after a
721 negative noncontrast head CT. He found a 10.6% incidence of alternative diagnoses. These included viral
722 meningitis (6.3%), intracranial hypertension (2.0%), bacterial meningitis (1.7%), chemical meningitis (0.3%), and
723 intrathecal hematoma (0.3%).

Finally, an additional theoretical concern is the likely increased usage of testing (especially CTA) after an initial negative head CT and the complications associated with its use. As discussed above, ED headache patients suspected of having a SAH receive an initial noncontrast head CT. If this is negative, many do not have additional testing (LP or CTA). If CTA becomes a viable testing alternative to LP in this situation, there will likely be increased utilization because of the ease for the ED clinician to order this test.

Summary

Emergency department patients presenting with headache in which there is a suspicion for SAH remains challenging. Clinical decision rules may be able to rule out some of these patients; however, the remaining patients will begin an ED based workup.[9] The initial test of choice in these patients is an unenhanced head CT. This may rule out SAH, especially if performed within 6 hours of symptom onset.[8] If the noncontrast head CT is negative, there remains a small risk (approximately 1%) of having a consequential SAH.[46,48,76,77] If the clinician continues to have concern regarding a significant SAH a LP or CTA are viable options.

Unfortunately, there are few studies that directly compare CT/LP versus CT/CTA in ED patients with this scenario. The 1 quality study that does directly compare these diagnostic workup options is limited by low numbers of study subjects with sensitivity point estimates having wide CIs.[51] Therefore, one is left with comparing the pros and cons of CT/LP versus CT/CTA to address this clinical question.

As enumerated above, the main positive for LP is that it is very sensitive for detecting SAH. If the test is negative, the patient has completed their workup. Unfortunately, there are a number of limitations with its use. These include a very low testing yield, a high rate of traumatic tap, high rates of uninterpretable LP test results, physician time to perform the procedure, patient preference, and the high rate of post-LP headache.

For CTA, the main positive is that many of the negatives associated with the performance of a LP can be avoided. In addition, CTA appears to be an excellent test for detecting cerebral aneurysms. The major disadvantage of using the CTA diagnostic strategy is that this test diagnoses aneurysms and not bleeding. The aneurysm may be an incidental finding and may lead to unnecessary invasive cerebral procedures. In addition, CTA exposes the patient to additional radiation risk and decreased LP diagnosis of certain medical diseases.[73]

Weighing all the available evidence and the pros and cons of CT/LP versus CT/CTA, in the adult ED patient who is still considered to be at risk for SAH after a negative noncontrast head CT, CT angiography of the head appears to be a reasonable alternative to LP to safely rule out SAH.

Future Research

Studies directly comparing CT/LP versus CT/CTA are limited. Only 1 quality study was identified in the literature search for this critical question.[51] In addition, this study was limited by the low number of patients with SAH. Additional studies with larger numbers of SAH cases need to be performed to directly compare these 2 diagnostic algorithms.

Another potential area of exploration is identifying patients that may not need additional testing (LP or CTA) after a negative noncontrast head CT. Identifying risk factors for significant SAH and developing pretest probabilities for individual patients may better inform clinicians and patients on whether to proceed with these tests.

Another potential diagnostic pathway in this clinical scenario is the use of CTA only no noncontrast Head. This approach may decrease time and radiation exposure. Studies addressing the safety, risks, and benefits of this alternative strategy are warranted.

Finally, the most significant negative issue regarding the use of CTA is the potential for finding an incidental cerebral aneurysm. Studies looking at differentiating a clinically significant aneurysm from an incidental one would be useful. One such strategy might be the performance of LP after CTA identifies a cerebral aneurysm.

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Appendix A. Literature classification schema.*

Design/ Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series	Case series	Case series

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome, including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

Appendix C. Likelihood ratios and number needed to treat.*

LR (+)	LR (–)	
1.0	1.0	Does not change pretest probability
1–5	0.5–1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Figure 1.

Ottawa SAH Rule[13] (PENDING COPYRIGHT PERMISSION)

Investigation required if the patient presents with 1 or more of the following criteria:

- Symptoms of neck pain or stiffness
- Age >40yrs
- Witnessed loss of consciousness
- Onset during exertion
- Thunderclap headache (peak pain instantly)
- Limited neck flexion upon examination

1056 **Evidentiary Table.**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Perry et al [9] (2013)	II for Q1	Prospective multicenter cohort study from 2006 to 2010; 10 Canadian EDs	Patients ≥16 y old; nontraumatic headache reaching maximum intensity in <1 h; headache duration of <14 days; GCS 15; outcome was SAH; outcome determined by CT, LP, or proxy outcome of follow-up phone call, coroner records	2,131 patients enrolled out of 2,736 eligible; 1,767 received CT; 833 received LP; 132 with SAH (6.2%); investigate if ≥1 high-risk variable present (1) age ≥40 y, (2) neck pain or stiffness, (3) witnessed loss of consciousness, (4) onset during exertion, (5) thunderclap headache (instantly peaking pain), (6) limited neck flexion on examination; rule identified all 132 of the SAH cases; the sensitivity, specificity, LR+ and LR- were 100.0% (95% CI 97.2% to 100%), 15.3 (95% CI 13.8 to 16.9), 1.17 (95% CI 1.15 to 1.20), 0.024 (95% CI 0.001 to 0.39), respectively	Low loss to follow-up; appropriate spectrum of disease; extremely poor sensitivity; age ≥40 y would include a lot of people being worked up for SAH

1057 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Carpenter et al[13] (2016)	II for Q1	Meta-analysis and systematic literature review	Meta-analysis up to June 2015 evaluating historical features, physical examination findings, CSF and CT, and clinical decision rules for SAH	5,022 publications identified; 122 full-text review; 22 included; mean SAH prevalence 7.5%; neck pain LR+ 4.1; neck stiffness LR+ 6.6; negative CT <6 h, LR- 0.01; 95% CI 0.0 to 0.04); negative >6 h, LR- 0.07 (95% CI 0.01 to 0.61) CSF RBC <1,000, LR- 0.21 (95% CI 0.03 to 1.7)	9 of the 22 studies were retrospective; search did not include abstracts or unpublished data; 2 hospital-based studies included which are not ED patients
	III for Q4		Adult ED patients with acute headache; outcome: pooled sensitivity, specificity, and likelihood ratios for various CSF criteria to diagnose SAH	Pooled sensitivity and specificity of "RBC >1000 x 106/L" were 0.76 (95% CI 0.60 to 0.88) and 0.88 (95% CI 0.86 to 0.90), respectively; pooled sensitivity and specificity of spectrophometric xanthochromia were 1.0 (95% CI 0.59 to 1.0) and 0.95 (95% CI 0.93 to 0.96), respectively; pooled sensitivity and specificity of visible xanthochromia were 0.71 (95% CI 0.56 to 0.83) and 0.93 (95% CI 0.91 to 0.94), respectively	There were only two studies which examined "RBC >1000 x 106/L" and spectrophometric xanthochromia criteria
Perry et al[14] (2017)	III for Q1	Prospective multicentre cohort from January 2010 to January 2014; 6 Canadian university affiliated tertiary-care hospital EDs	Validation study of Ottawa SAH Rule used in: patient ≥16 y; nontraumatic headache reaching maximum intensity in <1 h; headache duration of <14 days; GCS 15; outcome was SAH; outcome determined by CT, LP, or proxy outcome of follow-up phone call, coroner records	1,153 patients enrolled out of 1,743 eligible; 590 missed eligible; 1,004 of those enrolled received CT; 452 of those enrolled received LP; 67 (5.8%) with SAH in physician enrolled patients; 33 (5.6%) with SAH in missed eligible; sensitivity of 100% (95% CI 94.6% to 100%), specificity of 13.6% (95% CI 13.1% to 15.8%)	Selection bias because of enrollment; variance between assessing physician and the control site; width of the l CI in a worrisome disease; potential for incorporation bias because it is unclear if the person making the determination of SAH was blinded to the rule elements

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1059 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Blum et al.[15] (2017)	III for Q1	Multicenter study in Switzerland; ED nontraumatic headache; 18 and older; headache <3 months	Prospective, observational cohort ED headache; blood samples drawn and stored for later sampling; treating physicians were blinded to the copeptin levels; follow-up was by phone interview or by primary care provider follow-up; primary outcome was serious cause for headache based on ICHD-II criteria; secondary outcomes were combined death or hospitalization	391patients enrolled; 19% with serious headache; copeptin were higher in secondary headache; AUC 0.70 (95% CI 0.63 to 0.76); copeptin >5.0 pmol/L sensitivity 64.4% and specificity 95.3%; copeptin (OR 2.03, 95% CI 1.52 to 2.70); Age >50 (OR 2.83; 95% CI 1.69 to 4.74); abnormal neurological exam (OR 3.50; 95% CI 1.99 to 6.14); thunderclap onset (OR 4.23; 95% CI 2.38 to 7.52)	Selection bias appears to be an issue with 20% having a serious cause of headache; not every patient received the gold standard; included Bell's palsy and viral meningitis as serious outcomes; copeptin independently associated with serious headache compared with benign headache
Friedman et al[26] (2017)	II for Q2	Randomized double blind study conducted in 2 EDs of Montefiore Medical Center, New York	Eligible patients were adults ≥21 y who presented to the EDs for treatment of migraine rated as moderate or severe in intensity and had not had opioids in the last month; patients were randomized in blocks of 4; participants received hydromorphone 1 mg or prochlorperazine 10 mg plus diphenhydramine 25 mg; the primary outcome was sustained headache relief, defined as achieving a headache level of mild or none within 2 h of medication administration and maintaining that level for 48 h without the requirement of rescue medication; interim analysis was conducted once 48 h data were available for 120 patients	Halted by the data monitoring committee after enrollment of 127 patients; primary outcome achieved in the prochlorperazine arm by 37 of 62 (60%) patients and in the hydromorphone arm by 20 of 64 (31%) participants (difference 28%, (95% CI 12% to 45%, NNT 4, 95% CI 2% to 9%)	Selection bias because of enrollment; variance between assessing physician and the control site; width of the CI in such a worrisome disease; possibility of incorporation bias because it is unclear if the person making the determination of SAH was blinded to the rule elements; there is also concern about the RBC in the CSF criteria that they used

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Friedman et al[27] (2008)	II for Q2	Meta-analysis of randomized controlled trials; objective to determine the efficacy, adverse event profile, and frequency of recurrent headache after treatment with injectable opioids compared with other active agents for the treatment of acute migraine	Article inclusion criteria: injectable defined as administration through intravenous, intramuscular, or subcutaneous routes; acute migraine was defined using criteria established by the International Headache Society's ICHD-II; study was included if a reasonable attempt had been made to include migraine headaches rather than all benign headaches; studies were only included if they presented data on headache intensity within 2 h of treatment; quality of articles assessed with Jadad scores; primary outcome for this analysis was relief of headache within 1 h of medication administration; original authors' definition of relief was used or if not reported; use of rescue medication; if neither outcome was available, authors transformed change in VAS into a dichotomous outcome; secondary outcomes: relative risk for each of the primary efficacy analyses, functional disability after medication administration, recurrence of the headache after initial treatment and adverse effects associated with medications	Meperidine was significantly less efficacious than dihydroergotamine (OR=0.30 95% CI 0.09 to 0.97) for the treatment of acute migraine, caused more dizziness and sedation, and was less likely to result in return to normal functioning; there was a trend towards decreased efficacy of meperidine versus antiemetics (OR=0.46; 95% CI 0.19 to 1.11) and a higher rate of return to the hospital in those who received meperidine, though the antiemetics caused a higher rate of akathisia; there were no significant differences in efficacy or adverse event profile between meperidine and ketorolac (OR=1.75; 95% CI 0.84 to 3.61)	Many assumptions were used to combine results from lack of uniformity in outcome assessment among articles; heterogeneity hindered combination of some results; likely that individuals with non-migraine headache were enrolled trials; could not explore the effect of study level predictors such as dose of meperidine or co-administered antihistamines on pooled results due to limited numbers of articles retrieved

1061 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Friedman et al[28] (2014)	II for Q2	Emergency department of Montefiore Medical Center, Bronx, NY; randomized, double blind, clinical trial	Adult patients who presented to the ED with acute migraine or acute probable migraine headache as defined by ICHD-II criteria; interventions: (1) valproate 1 g of IV, (2) ketorolac 30 mg IV, (3) metoclopramide 10 mg IV; outcomes: primary 11-point NRS; secondary included a standard four-point pain intensity categorical scale and akathisia; assessed outcomes and adverse events 1 h and 24 h after medications	N=330 randomized; 110 in each arm; 106 in ketorolac, 107 in valproate, and 107 in metoclopramide groups; the primary endpoint showed that those patients randomly allocated to valproate improved by 2.8 points (95% CI 2.3 to 3.3); those receiving metoclopramide improved by 4.7 points (95% CI 4.2 to 5.2); and those receiving IV ketorolac improved by 3.9 points (95% CI 3.3 to 4.5); return to usual activities without impairment; in the valproate arm, 31 of 110 (28%) (95% CI 21% to 37%) replied affirmatively, in contrast to 43 or 110 (39%) (95% CI 30% to 48%) of ketorolac patients, and 57 of 107 (53%) (95% CI 44% to 62%) of metoclopramide patients; metoclopramide arm, 6% (95% CI 3% to 12%) of patients reported being “very restless,” in contrast to only 1% of patients randomized to ketorolac or valproate	Indirectly applicable, no opiate comparison group; mostly women; patients were excluded for concurrent use of one of the investigational medications

1062 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Taggart et al[31] (2013)	III for Q2	Meta-analysis of randomized controlled trials; objective to determine the effectiveness of parenteral ketorolac in acute migraine	Internal validity of the included trials was assessed using the Cochrane Collaboration's Risk of Bias tool, the scale developed by Jadad et al, and the Schulz approach for concealment of allocation; primary outcome was pain relief; several secondary outcomes included: the need for and number of rescue analgesic medications, symptom relief, relapse, and side effects; a subanalysis compared toradol to meperidine	Eight trials were included, involving over 321 (141 ketorolac) patients; the median quality scores were 3 (interquartile range: 2 to 4); there were no baseline differences in 10-point pain scores (WMD=0.07; 95% CI -0.39 to 0.54); ketorolac and meperidine resulted in similar pain scores at 60 min (WMD=0.31; -0.68 to 1.29); however, ketolorac was more effective than intranasal sumatriptan (WMD=-4.07; 95% CI -6.02 to -2.12); while there was no difference in pain relief at 60 min between ketorolac and phenothiazine agents (WMD=0.82; 95% CI -1.33 to 2.98), heterogeneity was high (I^2=70%); side effect profiles were similar between ketorolac and comparison groups	Quality of studies are reported, but each study's deficiencies are not evident, results are only reported in aggregate; used a fixed effects model, and the numbers are low and unstable despite an I-square of 0% for the meperidine comparator groups; not all studies used concealed allocation
Taheraghdam et al[32] (2011)	III for Q2	Emergency ward of Tabriz Iman Reza Hospital, Tabriz, Iran from September 2008 to May 2009; prospective randomized, double blinded, clinical trial	Patients 18 to 65 y; met International Headache Society criteria for migraine episode with and without aura; not receiving steroids or opiate medications; blinded administration of 8 mg dexamethasone or 0.1 mg/kg morphine IV; headache severity measured with VAS 10 cm scale measured at baseline, 10 min, 60 min, 24 h after intervention	N=190 patients; clinically important decreases (>2.2 cm) in both study arms, no significant differences between groups – 0 min 8.49 dexamethasone vs 8.75 morphine, 60 min 2.89 dexamethasone vs 2.33 morphine, 24 h 0.64 dexamethasone vs 1.03 morphine; all had VAS scores ≤1 at 24 h	Less men in the morphine group, 33% vs 41%; many baseline characteristics not reported in a table for detection, but were screening criteria, eg, Migrane Disability Assessment scales; unclear how the 0.1 mg/Kg morphine dose was administered while maintaining blinding; was an equivalent saline placebo given to the control arm; side effects of morphine are much different than dexamethasone; no CONSORT diagram

1063 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Orr et al[33] (2015)	III for Q2	Meta-analysis of randomized controlled trials; objective to identify interventions for acute pain relief in adults presenting with migraine to emergency settings	Only studies using either the ICHD-II for migraine; studies graded according to its risk of bias, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions; the final rating of individual studies according to their methodological quality was carried out as per the US Preventive Services Task Force criteria; groups of two or more trials without significant clinical heterogeneity were combined in meta-analyses; odds ratios were calculated for the outcome of interest, with confidence intervals set at 95% for both the individual studies and the pooled odds ratio	Sumatriptan vs placebo: pooled OR for pain relief 8.41 (95% CI 6.96 to 10.16); other findings are consensus recommendations based on heterogeneous literature of good, fair, and, poor quality	Section about opiate medications had poor quality articles with significant heterogeneity; recommendations mostly are without pooled estimates aside from sumatriptan due to heterogeneity and low-quality studies; article methods more aligned with consensus recommendations than a focused meta-analysis article
Orr et al[34] (2016)	III for Q2	Meta-analysis of randomized controlled trials; to provide evidence-based treatment recommendations for adults with acute migraine who require treatment with injectable medication in an emergency department	Used the American Academy of Neurology's risk of bias tool to grade study quality; meta-analysis was performed when there were both a sufficient number of homogeneous studies and uncertainty with regard to the direction, magnitude, or precision of results; sufficient homogeneity required at least two studies to have used the same medication, the same comparator, and the same outcome	Meta-analysis of dexamethasone for preventing headache recurrence after ED discharge: OR=0.60 (0.38 to 0.93); no other meta-analyses performed due to failing to meet the sufficient number of homogenous studies criteria	Section about opiate medications had poor quality articles with significant heterogeneity; recommendations mostly are without pooled estimates aside from dexamethasone due to heterogeneity and low-quality studies; article methods more aligned with consensus recommendations than a focused meta-analysis article

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1065 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Friedman et al[35] (2010)	III for Q2	EDs at Montefiore Medical Center is in the Bronx, NY; Columbia University Medical Center is in Manhattan, NY; and the University of South Alabama is in Mobile, AL; randomized, double blind comparative efficacy trial	Age 18 to 64 y; included patients only if they received parenteral medication for their headache in the ED and if secondary or organic headache was not considered, and were being discharged home; followed all patients by telephone 48 h after ED discharge, but by design, we included in the primary efficacy analysis only those patients who took their medication; included the full spectrum of primary headache patients, including those with "unclassifiable" primary headache; secondary analyses on those classified as migraines using ICHD-II criteria; interventions: naproxen 500 mg or sumatriptan 100 mg orally as discharge medications; outcomes: primary outcome 11-point verbal NRS; before taking the pain medication and 2 h later as recorded in headache diaries; secondary outcomes assessed among migraine patients and functional impairment	N=196; 98 in each arm; 48 with migraine in the naproxen arm, 40 in the sumatriptan arm; within the subset of patients with migraine without aura, the naproxen group had a mean pain improvement over 2 h of 4.3 NRS points and the sumatriptan had a mean improvement of 4.2 points (95% CI for a difference of 0.1 points: -1.3 to 1.5 points); among all primary headache patients, the naproxen group improved by a mean of 4.3 points, whereas the sumatriptan group improved by a mean of 4.1 points (95% CI for difference of 0.2 points: -0.7 to 1.1 points)	Indirectly applicable; no opiate comparison group; majority of patients in this study received a parenteral dopamine antagonist as initial ED treatment for their headache; generalizability of this study to other types of ED treatment may be limited; decision to include only those that required a dose, seems appropriate, yet much attrition occurred from screening to the final included sample; conclusions often state equivalent efficacy, yet the trial was not set up as an equivalence trial

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1067 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Friedman et al[36] (2016)	III for Q2	Emergency department of Montefiore Medical Center, Bronx, NY; randomized, double blind, clinical trial;	Included patients <65 y who presented with an acute moderate or severe headache meeting migraine or probable migraine criteria, as defined by ICHD-II criteria patients enrolled on presentation to the ED, followed for up to 2 h in the ED, and then contacted by telephone 48 h later to determine headache status; interventions: (1) metoclopramide 10 mg and diphenhydramine 50 mg, infused intravenously during 15 min; (2) metoclopramide 10 mg and saline solution placebo, infused intravenously during 15 min; inclusion: adult patients younger than 70 y who had an acute exacerbation of a migraine without aura as defined by the ICHD-II; excluded prolonged duration >72 h or <4 h; intervention: arm 1, metoclopramide 10 mg plus diphenhydramine 25 mg, infused intravenously over 20 min; arm 2, metoclopramide 20 mg plus diphenhydramine 25 mg, infused intravenously over 20 min; arm 3, metoclopramide 40 mg plus diphenhydramine 25 mg, infused intravenously over 20 min; outcomes: primary standard four-point pain intensity categorical scale, “severe”, “moderate”, “mild”, or “none”; secondary: 11-point NRS and a four-point functional disability scale, and akathisia	N=208; 104 in each arm randomized, after loss to follow-up 99 in diphenhydramine, 103 placebo; the primary outcome, sustained headache relief, reported by 40% (95% CI 31% to 50%) randomized to diphenhydramine and 37% (95% CI 28% to 47%) randomized to placebo (95% CI for difference of 3%: –10% to 16%); NRS difference 0.3 (–0.6 to 1.1); functional impairment difference 4% (–8 to 17%); akathisia difference 1% (–6 to 8%)	Indirectly applicable; no opiate comparison group; baseline headache duration longer in the diphenhydramine group (72 h vs 48 h); mostly women in the sample

1068 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Friedman et al[37] (2011)	III for Q2	Emergency department of Montefiore Medical Center, Bronx, NY; randomized, double blind, dose finding study	Inclusion: adult patients younger than 70 y who had an acute exacerbation of a migraine without aura as defined by the ICHD-II; excluded prolonged duration >72 hours or <4 h; intervention: Arm 1, metoclopramide 10mg plus diphenhydramine 25 mg, infused intravenously over 20 min; Arm 2, metoclopramide 20 mg plus diphenhydramine 25 mg, infused intravenously over 20 min; Arm 3, metoclopramide 40 mg plus diphenhydramine 25 mg, infused intravenously over 20 min; outcomes: primary 11-point NRS; secondary included a standard four-point pain intensity categorical scale, "severe", "moderate", "mild", or "none" and a four-point functional disability scale, severe ("cannot get up from bed or stretcher"), moderate ("great deal of difficulty doing what I usually do and can only do very minor activities"), mild ("little bit of difficulty doing what I usually do"), or none, and akathisia; assessed outcomes and adverse events 1 h, 2 h, and 48 h after medication administration	Screened 869 patients with non-traumatic headache for enrollment and randomized 356; 1 h after medication administration the 10 mg metoclopramide group improved by 4.7 NRS points (unadjusted 95% CI 4.2 to 5.2), the 20 mg metoclopramide group improved by 4.9 points (unadjusted 95% CI 4.4 to 5.4), and the 40 mg metoclopramide group improved by 5.3 points (unadjusted 95% CI 4.8 to 5.9); akathisia developed in 33 patients (9%) (95% CI 6% to 12%) and was evenly distributed across the study arms	Indirectly applicable; no opiate comparison group; mostly women; duration of headache was lower in the 40 mg group; all groups received IV diphenhydramine

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1070 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Friedman et al[38] (2008)	III for Q2	Two academic EDs in discrete neighborhoods of New York City - Montefiore Medical Center and Columbia University; randomized double blind, controlled trial	Adult patients who presented to the ED with a primary headache; any patient with migraine with or without aura, as defined by the International Headache Society's ICHD-II; interventions consisted of administration of 10 mg intravenous prochlorperazine or 20 mg intravenous metoclopramide, both accompanied by 25 mg of intravenous diphenhydramine; administered as an intravenous drip during 15 min; if subjects required more pain medication after 1 h, they were administered rescue medication at the discretion of the treating physician; outcomes: NRS at baseline 30 min intervals; and 4-point functional disability scale, as recommended by the International Headache Society; subjects were contacted by telephone 24 h after ED discharge to ascertain pain status, approval of the treatment, and presence of adverse effects	N=152 patients screened, 97 were eligible and 77 were randomized; mean change in numeric rating scale scores at 1 h were 5.5 and 5.2 in subjects receiving prochlorperazine and metoclopramide, respectively (difference 0.3, 95% CI -1.0 to 1.6); findings were similar at 2 h and 24 h; 18 of 39 (46%) of prochlorperazine and 12 of 38 (32%) of metoclopramide subjects reported adverse events (difference 15%; (95% CI -6% to 36%); 26 of 34 (77%) of prochlorperazine and 27 or 37 (73%) of metoclopramide subjects wanted to receive the same medication in future ED visits (difference 4%, 95% CI -16% to 24%)	Indirectly applicable; no opiate comparison group; imbalances in baseline characteristics; 10% more severe headache in the metoclopramide group; and 10% more were women; generalizability: both arms were mostly women, 85% prochlorperazine, 95% metoclopramide

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1072 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Gaffigan et al[39] (2015)	III for Q2	Emergency Department at Naval Medical Center Portsmouth, Portsmouth, Virginia; double blinded, randomized, controlled trial	Adult patients 18 to 50 y, presenting with their typical migraine headache, were identified by the triage nurse or their assigned provider as potential subjects; those meeting the Modified International Headache Society's criteria for migraine were included; all subjects received 1L NS bolus with 25 mg IV diphenhydramine; interventions: (1) metoclopramide 10 mg IV, (2) haloperidol 5 mg IV, both were given over 2 min outcomes: pain, nausea, restlessness (akathisia), and sedation were each assessed via separate 100 mm nonhatched VAS presented to the subject at 0, 20, 40, 60, and 80 min; and 48 h by phone; primary outcome improvement in pain as reported on the VAS within 80 min of therapy; an absolute difference of 13 mm or more was considered clinically significant	N= 4; haloperidol 31; metoclopramide 33; mean reduction in pain from baseline to the last recorded measure of pain on the 100 mm VAS scale was statistically and clinically significant for both haloperidol- and metoclopramide-treated groups: 57 mm for the haloperidol group and 49 mm for those treated with metoclopramide ($p < 0.01$ for each comparison); when compared to each other, the VAS pain scores for the haloperidol and metoclopramide groups did not differ at baseline, at the last recorded measurement, or in the magnitude of the pre-post treatment change ($p > 0.05$); eight of the 33 subjects in the metoclopramide group (24%) were given rescue medications, compared with only 1 of the 31 subjects (3%) receiving haloperidol ($p < 0.02$); telephone follow-up rates were insufficient 74% haloperidol vs 61% metoclopramide	Indirectly applicable, no opiate comparison group; mostly women; more women in the haloperidol arm 87% vs 76%; outcome was last reported VAS before discharge or at 80 mins after receiving study medication; not at uniform times

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1074 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Singh et al[40] (2008)	III for Q2	Meta-analysis of randomized controlled trials; goal to provide recommendations for patient care regarding the use of dexamethasone for the prevention of headache relapse in patients with acute migraine headache in the ED	Searched MEDLINE, EMBASE, CINAHL, LILACS, recent emergency medicine scientific abstracts, and several prepublication trial registries; trial quality was assessed using the Jadad scale for each reviewed study; primary outcome proportion of migraine patients with self-reported symptoms of moderate or severe headache at 24 to 72h follow-up evaluation; a fixed-effects and random-effects model was used to obtain summary risk ratios and 95% CI for the self-reported outcome of moderate or severe headache on follow-up evaluation	Pooled analysis of seven trials involving 742 patients suggests a modest but significant benefit when dexamethasone is added to standard migraine therapy to reduce the rate of patients with moderate or severe headache on 24h to 72 h follow-up evaluation (risk ratio=0.87, 95% CI 0.80 to 0.95; absolute risk reduction = 9.7%); the treatment of 1,000 patients with acute migraine headache using dexamethasone in addition to standard migraine therapy would be expected to prevent 97 patients from experiencing the outcome of moderate or severe headache at 24h to 72 h after ED evaluation	Indirect evidence, no opiate comparator; included abstracts making it difficult to assess study quality
Perry et al[8] (2011)	II for Q3	Prospective cohort study; 11 EDs in Canada	Adult (>15 y) patients with headache reaching maximum intensity within 1 h and a normal neurological examination who underwent evaluation for SAH; outcome: SAH, defined by positive CT, xanthochromia, or red cells in the final tube of CSF	N=3,132; SAH prevalence=7.7%; overall: sensitivity 93%, specificity 100%; for subgroup with headache onset within 6 h: sensitivity 100% (95% CI 97% to 100%), specificity 100% (95% CI 99.5% to 100%)	Spectrum bias; workup bias; diagnostic bias
Dubosh et al[41] (2016)	III for Q3	Systematic review and meta-analysis	Five studies included; ED patients presenting with nontraumatic headache within 6 h of onset	N=4,440; pooled prevalence of SAH 19%; pooled sensitivity 99% (95% CI 97% to 99%)	Perry J BMJ 2011 accounted for >70% of the cohort; spectrum bias, workup bias, diagnostic bias

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1076 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Perry et al[48] (2015)	III for Q4	Planned secondary analysis of a prospective, academic, multi-center study of ED patients	Patients with nontraumatic, abrupt-onset headache and GCS 15 who underwent LP and had abnormal CSF (defined as >1 x 10^6/L RBC in final tube or xanthochromia); outcome was aneurysmal SAH; patients not diagnosed with SAH during initial visit were followed up by telephone at 1 and 6 months	15 of 641 patients were diagnosed with aneurysmal SAH; combination of 2000 10^6/L RBC or xanthochromia sensitivity 100% (95% CI 75% to 100%), specificity 91% (95% CI 89% to 93%)	Criterion was not validated in a separate population
Carstairs et al[51] (2006)	III for Q4	Prospective cohort study of ED patients; single academic center	Consecutive adult patients with headache concerning for SAH; all patients underwent noncontrast CT and CTA; patients with normal noncontrast CT also had LP; imaging interpreted by blinded neuroradiologists; DSA was criterion standard for aneurysm	Of 106 patients, 5 patients were diagnosed with aneurysms; CTA identified aneurysms in all 5 patients with one false positive result; 2 of 5 patients with aneurysm seen on DSA and CTA had normal CSF and normal noncontrast CT	Limited by small sample size
El Khaldi et al[52] (2007)	III for Q4	Prospective cohort study of patients with nontraumatic acute SAH diagnosed on noncontrast CT who had CTA and DSA at a single hospital	All patients had CTA, which was interpretated by a single radiologist; DSA (criterion standard) was performed either preoperatively or postoperatively	CTA identified 84 of the 85 aneurysms; there were no false positives seen on CTA among 20 patients had normal DSA	Included patients with SAH seen on noncontrast CT; demographic and clinical characteristics of cohort not reported
Menke et al[53] (2011)	III for Q4	Meta-analysis including prospective and retrospective studies	Patients with suspected cerebral aneurysm who had CTA; reference standard was DSA or intraoperative findings; random effects analysis	Included 45 studies with mean prevalence 86% of nontraumatic SAH; pooled sensitivity 0.97 (CI 0.96 to 0.98), pooled specificity 0.98 (CI 0.96 to 0.99).	Included studies were published between 1995 and 2010 and involved different generation CT scanners (single-row to 64-row)

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Perry et al[54] (2008)	III for Q4	Prospective cohort study of ED patients at 2 academic centers	Patients with nontraumatic, abrupt-onset headache and GCS 15 who were evaluated by CT/LP strategy; structured medical record and telephone follow-up at 3 months	N=592 patients; 61 patients were diagnosed with SAH (55 by CT and 6 by LP); no cases of missed SAH were identified	10% patients were lost to follow-up

AUC, area under the curve; *CI*, confidence interval; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *CTA*, computed tomography angiography; *DHE*, dihydroergotamine; *DSA*, digital subtraction angiography; *ED*, emergency department; *GCS*, Glasgow coma score; *h*, hour; *ICHD-II*, International Classification of Headache Disorders, 2nd Edition; *LP*, lumbar puncture; *LR*, likelihood ratio; *min*, minute; *MRA*, magnetic resonance angiography; *MRI*, magnetic resonance imaging; *mSV*, millisievert; *NNT*, number needed to treat; *NRS*, numeric rating scale; *OR*, odds ratio; *SAH*, subarachnoid hemorrhage; *US*, United States; *VAS*, visual analog scale; *vs*, versus; *WMD*, weighted mean differences; *y*, year.