Riboflavin as Migraine Prophylaxis in Children and Adolescents: A Systematic Review of the Literature

David N. Counts

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Abstract
Background: Migraine headache is a common condition among children and the prevalence increases into adolescence. Multiple studies have shown riboflavin to be an effective and safe agent for migraine prophylaxis in adults but few studies have looked at using riboflavin in children and adolescents. The purpose of this paper was to perform a systematic review of the literature on the use of riboflavin for migraine prophylaxis in the pediatric population including children and adolescents. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group.

Method: An extensive literature search was performed using MEDLINE, CINAHL, Evidence Based Medicine Reviews Multifile, Web of Science, and PubMed. The keyword search terms “migraine” and “riboflavin” were searched individually and in combination. Search results were limited to human studies, articles published in English, and those published from 2000-2011. Studies of adult patients, duplicates, descriptive reviews, and letters to the editor were excluded. This resulted in three studies, which were analyzed in this review.

Results: Two randomized controlled trials (RCT) and one observational study were included. Both RCTs found no significant difference between treatment and placebo groups for migraine frequency, severity, and duration. The observational study showed a significant decrease in migraine frequency and severity.

Conclusion: There is currently low quality evidence supporting the use of riboflavin as migraine prophylaxis in children and adolescents and only a weak recommendation can be made for its use.

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Riboflavin as Migraine Prophylaxis in Children and Adolescents: A Systematic Review of the Literature

David N. Counts

A course paper presented to the College of Health Professions in partial fulfillment of the requirements of the degree of Master of Science

Pacific University School of Physician Assistant Studies

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Faculty Advisor: Robert Rosenow, PharmD, OD
Clinical Graduate Project Instructors: Torry Cobb, DHSc, MPH, PA-C & Annjanette Sommers MS, PA-C
Biography

David Counts was born and raised in the farm country of southeast Washington. His career in medicine began in high school and continued through college as a member of two rural volunteer EMS agencies. He earned bachelor’s degrees from Washington State University in Communication, with an emphasis on organizational communication, and in Psychology. After completing his undergraduate studies he worked for a large cardiology group in eastern Washington analyzing and editing 24-hour cardiac holter monitor reports and participating in implanted pacemaker and ICD home monitoring. He is proud to study at Pacific University and looks forward to practicing medicine in the Northwest. His clinical interests are in family medicine and pediatrics.

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ABSTRACT

Background: Migraine headache is a common condition among children and the prevalence increases into adolescence. Multiple studies have shown riboflavin to be an effective and safe agent for migraine prophylaxis in adults but few studies have looked at using riboflavin in children and adolescents. The purpose of this paper was to perform a systematic review of the literature on the use of riboflavin for migraine prophylaxis in the pediatric population including children and adolescents. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group.

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Conclusion: There is currently low quality evidence supporting the use of riboflavin as migraine prophylaxis in children and adolescents and only a weak recommendation can be made for its use.

Keywords: Migraine Disorders, Riboflavin, Pediatrics, Child, Adolescent, Review
INTRODUCTION

Background

Migraine headache is a common condition among children and the prevalence increases into adolescence. Three percent of children aged three to seven experience migraines, increasing to 8-23% for age 11 and above (Lewis et al., 2004). Migraines are more frequent in males less than seven years old, equal among males and females between the ages of seven and eleven, after which girls are three times more likely to experience migraines (Eiland, Jenkins, & Durham, 2007).

Migraine headaches are typically unilateral, pulsating, moderate to severe in intensity, made worse by physical activity and can be associated with nausea and vomiting, photophobia, and phonophobia (International Headache Society, 2005). It is more common for children to experience migraine without aura, 60-85% of cases, than to present with migraine with aura, characterized by reversible focal neurologic symptoms (Lewis, 2009). The International Headache Society (IHS) has developed specific guidelines for the diagnosis of migraine with or without aura (Appendix B, IHS Diagnostic Criteria Summary).

Few studies exist considering symptomatic or prophylactic treatment of pediatric migraines. Lewis et al. (2004, p. 2215) said, “For a clinical problem so prevalent in children and adolescents, there is a disappointing lack of evidence from controlled, randomized, and masked trials.” Current treatments include ibuprofen and acetaminophen that are effective for acute treatment of pediatric migraine (Damen et al., 2005; Lewis et al., 2004). Damen et al. (2005) concluded nasal-spray sumatriptan to be effective and safe in children and Lewis et al. (2004) concluded it is effective and
safe in adolescents. A drug company sponsored study concluded nasal-spray zolmitriptan was well tolerated and effective in acute treatment of adolescent migraines (Lewis, Winner, Hershey, & Wasiewski, 2007). In 2004, Lewis et al. stated that the use of oral triptans could not be supported or refuted, but subsequently stated the safety of their use has been demonstrated in children (Lewis, 2009). The small number of studies performed in this field limit generalizations of therapy effectiveness.

Prophylactic treatment should be considered when migraine headaches have significant impact on the patient’s life despite acute treatment, for frequent headaches, contraindication to, failure of, or overuse of acute therapy, adverse events with acute treatment, at the patient’s preference, or in the presence of uncommon migraine conditions such as migraine with prolonged aura (Silberstein, 2000). The goal of preventive treatment is to reduce the frequency, severity, and duration of migraine episodes, to improve responsiveness to acute treatment, and to improve functioning and reduce disability.

There are currently no medications with an FDA approved indication for migraine prophylaxis in children but several medications are used off-label (Eiland et al., 2007). Current reviews are inconsistent in concluding the effectiveness of these agents, demonstrating the need for further research. Multiple reviews concluded that flunarizine is probably effective for preventive therapy but the drug is not available in the United States (Damen et al., 2005; Eiland et al., 2007; Lewis et al., 2004). The same reviews were inconsistent in their conclusions regarding the use of trazodone, pizotifen, amitriptyline, topiramate, cyproheptadine, and valproic acid. There is general agreement, however, that few studies of high quality exist in this area.
A number of supplements have been used for migraine prophylaxis, including riboflavin (vitamin B2). A precursor for two coenzymes needed for the transfer of electrons in mitochondrial oxidation-reduction reactions, riboflavin has been shown to reduce symptoms in patients with mitochondrial dysfunction (Boehnke et al., 2004; Schoenen, Jacquy, & Lenaerts, 1998). Riboflavin has also been shown in multiple trials to be effective for migraine prophylaxis in adults. A randomized controlled trial (RCT) conducted on adults with a three-month therapy period showed a decrease in frequency of migraine as a result of taking riboflavin 400mg daily compared to placebo (Schoenen et al., 1998). This trial showed a number needed to treat of 2.3. Another study in adults at a specialized outpatient headache clinic showed that taking riboflavin 400mg daily decreased migraine frequency and duration, and decreased the need for acute treatment (Boehnke et al., 2004).

Purpose of the Study

The purpose of this paper is to perform a systematic review of the literature on the use of riboflavin for migraine prophylaxis in the pediatric population including children and adolescents. The quality of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group.

METHOD

An extensive literature search was performed using MEDLINE, CINAHL, Evidence Based Medicine Reviews Multifile, Web of Science, and PubMed, accessed through the Pacific University Library. The keyword search terms “migraine” and “riboflavin” were searched individually and in combination which returned 242 articles.
Search results were limited to human studies, articles published in English, and those published from 2000-2011, lowering the total to 139 articles. Studies of adult patients, duplicates, descriptive reviews, and letters to the editor were excluded. This resulted in three studies pertaining to the use of riboflavin in children and adolescents for migraine prophylaxis which will be analyzed in this review.

RESULTS

High-Dose Riboflavin for Migraine Prophylaxis in Children: A Double-Blind, Randomized, Placebo-Controlled Trial – MacLennan et al. (2008)

MacLennan et al. (2008) conducted a double-blind randomized controlled trial with 48 subjects ages five to 15 years with 24 males and 24 females. The trial was performed in Australia and participants were recruited primarily from school newsletters. The intervention was riboflavin 200mg taken once daily, compared to placebo. The treatment period was 12 weeks. The primary endpoint was a decrease of 50% or greater in frequency, defined as the number of migraines per four weeks, and showed no significant difference between the groups (placebo 14/21 (66.6%) vs. riboflavin 12/27 (44.4%); p = .125). The response rate between riboflavin and placebo was identical when calculated by the number of days with migraine.

The secondary outcome, migraine severity, showed no change for either group. Migraine duration could not be calculated for most subjects due to inconsistent headache diaries. When it could be calculated, an increase in mean duration was seen in both groups (placebo 259 to 316 minutes; riboflavin 275 to 315 minutes). There was a decrease in the placebo group for the mean number of days with nausea and vomiting but no decrease was seen in the riboflavin group (placebo 25 to 7 days; riboflavin 35 to
38 days). The mean number of migraine attacks requiring symptomatic treatment with analgesics decreased in both groups. One patient in the treatment group had a new onset of tension headaches and one patient in the placebo group had diarrhea accompanied by other viral symptoms. Four participants in the treatment group noted a change in their urine color. The authors concluded that “riboflavin was not more effective than placebo when given for migraine prophylaxis” (MacLennan et al., 2008, p. 1303).

Riboflavin Prophylaxis in Pediatric and Adolescent Migraine – Condo, Posar, Arbizzani, and Parmeggiani (2009)

Condo, Posar, Arbizzani, and Parmeggiani (2009) performed a retrospective study that appears to be a case-control design with an internal control. There were 41 participants ages eight to 18 with 16 males and 25 females. The study was performed in Italy at an outpatient child neurology and psychiatry unit of a university hospital. Inclusion criteria included “resistant migraine with failure of previous prophylactic therapy” (Condo et al., 2009, p. 362). The study participants were chosen at random to receive riboflavin 200mg daily or riboflavin 400mg daily and participants chose the treatment length to be 3, 4, or 6 months. Phase I was a three month baseline period. Phase II was a three month treatment period and phase III was a three month follow-up period after the cessation of riboflavin. Fourteen patients took riboflavin for four months and 11 patients took it for six months. To account for these patients the last three months of treatment were evaluated and phase II was further divided into phase IIa (2\textsuperscript{nd}, 3\textsuperscript{rd}, and 4\textsuperscript{th} month) and phase IIb (4\textsuperscript{th}, 5\textsuperscript{th}, and 6\textsuperscript{th} month).
Mean migraine frequency, the primary endpoint, was significantly decreased in phase II (21.7 ± 13.7 vs. 13.2 ± 11.8; p < 0.01) and in phase III (21.9 ± 14 vs. 8 ± 9; p < 0.01) when compared to baseline. Phase IIa also showed a significant decrease in frequency (23.4 ± 12.2 vs. 8.9 ± 9.4; p < 0.01) but phase IIb did not show a significant change (19.3 ± 13.4 vs. 11.4 ± 9.6; p > 0.05).

There was a significant decrease in migraine intensity, a secondary endpoint, in phase II (2 ± 0.5 vs. 1.6 ± 0.8; p < 0.01) and phase III (2 ± 0.5 vs. 1.4 ± 0.9; p < 0.01) when compared to baseline. There was no significant change in migraine intensity in phase IIa (1.8 ± 0.4 vs. 1.3 ± 0.9; p > 0.05) or phase IIb (2.1 ± 0.4 vs. 1.9 ± 0.8; p > 0.05).

The secondary endpoint of increased response to symptomatic therapy showed 77.1% (27/35) of patients reported an increased efficacy in their acute treatment during riboflavin therapy. Five patients (12.5%) did not need acute treatment during the treatment or follow-up phases. There was no significant difference found between migraine frequency and intensity responders (those with at least 50% improvement) and semi-responders (those with 25-50% improvement) between riboflavin 200mg or 400mg, migraine types, and age of headache onset. There were a significant number of males in the intensity-responder group (p < 0.05) and a significant number of patients under the age of 12 in the frequency-responder group (p < 0.05).

One patient reported vomiting and another reported increased appetite; in both instances the authors did not credit this to the riboflavin treatment. Some patients reported a discoloration of their urine. The authors concluded riboflavin “might be a safe, well-tolerated, and effective” (Condo et al., 2009, p. 365) migraine prophylactic
agent for children and adolescents but they also recognized further research needs to be performed on this topic.

Medium-Dose Riboflavin as a Prophylactic Agent in Children with Migraine: A Preliminary Placebo-Controlled, Randomised, Double-Blind, Cross-Over Trial – Bruijn et al. (2010)

Bruijn et al. (2010) performed a double-blind, cross-over, RCT in the Netherlands. Forty two patients, ages six-13, 24 males and 18 females, were recruited primarily by referral from their general practitioner. They compared riboflavin 50mg once daily to placebo. The study began with a four week baseline period, followed by a 16 week treatment period with some participants receiving riboflavin and the balance receiving placebo. This was followed by a four week washout period and then another 16 week treatment period with those previously taking placebo then taking riboflavin and vice versa. There were no significant differences between the two groups in regards to migraine frequency (p = 0.44), intensity (p = 0.18), and duration (p = 0.15). A significant reduction in the frequency of tension-type headaches in the riboflavin group was found (p = 0.04). No adverse outcomes were reported during the study. The authors concluded that riboflavin 50mg once daily had no effect on migraine prophylaxis in children. They also concluded riboflavin may have a prophylactic effect on headaches that may represent mild migraine or tension-type headaches in children with migraines.

DISCUSSION

Surprisingly little research has been performed on the topic of riboflavin for migraine prophylaxis in children and adolescents. Two RCTs and one observational study are analyzed in this review. Both RCTs show no change in migraine frequency,
severity, and duration (Bruijn et al., 2010; MacLennan et al., 2008). In an observational study, Condo et al. (2009) showed a significant reduction in migraine frequency and severity. The small body of evidence and conflicting results makes it difficult to determine a clear clinical recommendation.

Limitations of the Studies

*MacLennan et al. (2008)*

This study has a relatively small sample size of 48 patients and did not meet the proposed sample size of 56, 28 patients in each group. The authors state a best case scenario analysis was performed and showed if the additional patients in the placebo and treatment groups failed placebo and responded to riboflavin, respectively the results would give a response rate of 14/28 placebo and 13/28 riboflavin.

The authors used strict inclusion and exclusion criteria based on IHS diagnostic criteria which resulted in 44 patients being excluded from the study. They point out that because of these strict criteria the patients in their study may not be representative of all children with migraine headaches.

The placebo response rate in this study was high, 66%, a common problem in studies of migraine prophylaxis in children. The authors state, “Studies using a predetermined reduction in headache frequency as an outcome measure have found placebo response rates between 10% and 50%” (MacLennan et al., 2008, p. 1304). A review of 95 studies on acute therapy of migraine in adults showed the response rate was significantly lower in placebo-controlled trials (Eikermann & Diener, 2003) and MacLennan et al. (2008) suggest future research utilize a cross-over design or large sample size to counter this. MacLennan et al. (2008) point out that even an ineffective...
treatment could show a response of 50% or more, in an open label study, simply as a result of placebo effect.

Condo et al. (2009)

This observational study presents several limitations that call the positive results into question. The most significant limitation is the absence of a placebo control group which makes it impossible to measure a placebo response rate. As suggested by MacLennan et al. (2008) this study design could show a response rate of 50% or greater for an ineffective treatment. Condo et al. (2009) stated they believed it would have been unethical to use a placebo since their patients suffered from severe and resistant migraine headaches and had come to a tertiary care center for treatment. The authors also made recommendations to all patients about “immediate symptomatic pharmacologic intervention” (Condo et al., 2009, p. 364) during the riboflavin treatment phase which could have increased the placebo response rate. There does not appear to be any attempt at blinding patients or researchers to therapy which further weakens the validity of the study.

Since their study was conducted at a university specialty clinic and their inclusion criteria included “resistant migraine with failure of previous prophylactic therapy” (Condo et al., 2009, p. 362) they were potentially treating a sicker population than MacLennan et al. (2008) and their results may not easily extrapolate to the average pediatric patient with migraine headaches.

The relatively small sample size of 41 patients may affect the precision of the study.
The largest limitation to this study is their use of riboflavin 50mg as the treatment dose. Doses of 100-300mg daily have been successfully used to treat mitochondrial diseases in children and doses of 100-200mg daily have been recommended for study in children by trials conducted on adults (Bruijn et al., 2010). It appears the authors were planning to use one of these doses but a study of adults was released close to the beginning of their trial that showed a significant reduction in migraines in both the treatment and placebo groups (Maizels, Blumenfeld, & Burchette, 2004). In this trial the treatment was high-dose (400mg) riboflavin combined with magnesium and feverfew and the placebo included riboflavin 25mg to control for change in urine color. This caused Bruijn et al. (2010) to change the protocol for their study and use what they refer to as a medium-dose riboflavin treatment. This change of protocol based on the results of Maizels et al. (2004) is questionable due to several factors that make the validity of their study suspect. Patients were allowed to take concurrent prophylactic treatment, a smaller dose of the treatment medication was used as placebo, only 52 patients were randomized while the power estimate called for 120, the trial was stopped early, and there was a 44% placebo response rate. Maizels et al. (2004) admit it cannot be determined if the similarity of response between placebo and treatment groups is due to an actual effect or a placebo effect. In the discussion of their results, Bruijn et al. (2010) stated, “If one assumes that children have a much higher metabolic rate than adults, the maximum dosage of riboflavin in children should be even higher than in adults to obtain a similar effect” (Bruijn et al., 2010, p. 1432).
There was no upper limit of headaches per month in the exclusion criteria but a separate analysis showed there were no significant differences in treatment response of those with a high versus a low migraine frequency.

Comparison between the treatment and placebo groups was limited to the last four weeks of each 16 week study period based on the original riboflavin trial of Schoenen et al. (1998) in which the maximal effect was seen in the fourth month. This analysis may miss a potential treatment benefit in the first 12 weeks of therapy.

Similar to the other studies analyzed this trial has a relatively small sample size of 42 patients. This may affect precision but the authors contest their “power estimation was according to standard criteria” (Bruijn et al., 2010, p. 1432).

The pattern of a high placebo response rate making it difficult to prove efficacy in past migraine studies also applies to this study. This potential effect may have been increased by instructions given to all patients to improve sleep quality and duration, eliminate caffeine intake, and decrease television and computer use.

An issue common to all three analyzed studies is the use of the terms “pediatric,” “children,” and “adolescents” without providing clear definitions. While there may be common assumptions about the definition of these terms they should be explicitly defined to ensure it is understood for which population authors are making generalizations or recommendations. Translation provides an opportunity for further confusion of these terms. It is assumed the article by MacLennan et al. (2008) was originally written in English. Condo et al. (2009) did not return personal correspondence regarding this issue. Bruijn et al. (2010) was originally written in English and edited by a native English speaker (J. K. Bruijn, personal communication, April 28, 2010). Bruijn et
al. (2010) based definitions on PubMed MeSH terms where “child” is defined as age six-12. He defined “adolescent” as age 12-18 while PubMed defines it as 13-18. In his opinion, “pediatrics” encompasses birth to age 18, likely a common view. PubMed, however, defines this term as birth to adolescence, further propagating the ambiguity of this vocabulary.

All three studies also considered patients with concomitant headache diagnoses, such as tension type headache, admissible which presents a possible confounder.

GRADE

The GRADE Working Group has developed a tool for rating the quality of evidence and strength of recommendations (Guyatt et al., 2008). This tool provides a GRADE of the quality of evidence which explains how likely future research is to change the effect or confidence in the effect. The GRADEs of high, moderate, low, and very low quality evidence are defined, respectively as,

Further research is very unlikely to change our confidence in the estimate of effect...Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate...Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate...Any estimate of effect is very uncertain (Guyatt et al., 2008, p. 926).

The quality of evidence for each of the studies included in this review has been analyzed and a GRADE has been assigned (Appendix A, Table 1, GRADE Table).
Migraine Frequency

All three studies analyzed, considered the outcome of migraine frequency. The two RCTs showed no significant change while the observational study showed a significant decrease. Following GRADE protocol the RCTs began with a GRADE of high and the observational study began with a GRADE of low. Changes to the GRADE are made based on all three trials but the RCTs and observational trial have been divided out in the GRADE table so changes can be better understood. This outcome GRADE was downgraded one point for study quality and one point for consistency. MacLennan et al. (2008) and Bruijn et al. (2010) both showed deficits in study quality as discussed above. Specifically MacLennan et al. (2008) was downgraded for small sample size and strict inclusion criteria while Bruijn et al. (2010) was downgraded for small sample size, for limiting the comparison to the last four weeks of each treatment period, and for using a 50mg dose in light of the negative results of MacLennan et al. (2008) at a higher dose. The outcome was downgraded for consistency because the three studies do not agree on the results. There were no upgrades to this outcome. The ending GRADE for both the RCTs and the observational study, as well as the outcome in general, was low.

Migraine Severity

All three trials also considered the outcome of migraine severity. The RCTs showed no significant change and started with a GRADE of high while Condo et al. (2009) showed a significant decrease and started with a GRADE of low. This outcome was downgraded one point for study quality and one point for consistency for the same reasons cited for the previous outcome. No upgrades were made to this outcome. The ending GRADE for the RCTs, observational study, and the outcome was low.
Migraine Duration

Only the two RCTs considered the outcome of migraine duration and both showed there was no change. They started with a GRADE of high and were downgraded one point for study quality for the same reasons cited above. The evidence was not upgraded for this outcome. This gave an outcome GRADE of moderate.

The overall GRADE of the quality of evidence for this systematic review is low. The outcomes of migraine frequency and migraine severity have a GRADE of low and the outcome of migraine duration has a GRADE of moderate. There is enough question about the evidence presented that “further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate” (Guyatt et al., 2008, p. 926).

Conclusion

In conclusion, there is currently low quality evidence supporting the use of riboflavin as migraine prophylaxis in children and adolescents and only a weak recommendation can be made for its use. Additionally, high quality RCTs are needed to strengthen the evidence. As recommended by MacLennan et al. (2008) and Bruijn et al. (2010) future research should utilize RCTs with large sample size in a cross-over or parallel group design. If riboflavin is in fact effective for migraine prophylaxis in the pediatric population the appropriate dosage is yet to be determined. Future research should utilize riboflavin 200mg, 300mg, 400mg daily, or a higher dose, alone or in combination. The studies analyzed showed a low rate of adverse events and the relative safety of riboflavin in doses of 100mg to 300mg has been shown in the treatment of mitochondrial diseases (Bruijn et al., 2010). Furthermore, Bruijn et al.
(2010) states we “can now conclude that riboflavin in dosages up to 400mg daily for a period of several months can be safely used in children with migraines” (p. 1433). Future studies on this topic should also consider investigating the use of a weight based dose in the pediatric population.

MacLennan et al. (2008) pointed out that 44 patients were excluded from their study because they did not meet strict IHS diagnostic criteria and thus their participants may not be representative of all children with migraine headaches. Condo et al. (2009) did not specify how many patients were excluded for this reason and Bruijn et al. (2010) stated only two patients were excluded because they did not meet inclusion criteria, which included IHS diagnostic criteria. It is possible this affected MacLennan et al. (2008) more than the others because their recruitment was primarily community based. Nonetheless, this raises a question about using IHS criteria for studies of migraines in children if they are potentially strict enough to exclude the average migraine patient. It is possible that diagnostic criteria used clinically vary from those used in research. Further research could investigate the potential difference between clinical and research diagnostic criteria of migraine with and without aura and possibly consider developing modified criteria for research that more closely matches those used clinically.


APPENDICES
### APPENDIX A

#### Table 1: GRADE Table

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Quantity and type of evidence</th>
<th>Findings</th>
<th>Starting grade</th>
<th>Decrease GRADE</th>
<th>Increase GRADE</th>
<th>GRADE of Evidence by Study Types</th>
<th>GRADE of Evidence by Outcome</th>
<th>Overall GRADE of Evidence</th>
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<td>Low</td>
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<tr>
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<td></td>
<td></td>
<td>1 Obs</td>
<td>Significant decrease</td>
<td>Low</td>
<td>- - - - - 0 0 0</td>
<td>0 0 0</td>
<td>Low</td>
<td>Low</td>
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<tr>
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<tr>
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APPENDIX B
IHS Diagnostic Criteria Summary
(Adapted from IHS, 2005)

Migraine without Aura

A. At least 5 attacks fulfilling B-D
B. Headache attacks lasting 4-72 hours
C. Headache has at least two of the following characteristics:
   a. Unilateral locations
   b. Pulsating quality
   c. Moderate or severe pain
   d. Aggravation by routine physical activity
D. During headache at least one of the following:
   a. Nausea and/or vomiting
   b. Photophobia and phonophobia
E. Not attributed to another disorder

Migraine with Aura

A. At least 2 attacks fulfilling B
B. Migraine aura fulfilling criteria B & C for a sub-form of migraine:
   a. Fully reversible visual symptoms (e.g. spots, or loss of vision)
   b. Fully reversible sensory symptoms (e.g. pins and needles, or numbness)
   c. Fully reversible speech disturbance
   d. At least two of the following fully reversible symptoms without motor weakness
      i. Dysarthria
      ii. Vertigo
      iii. Tinnitus
      iv. Partial hearing loss
      v. Double vision
      vi. Simultaneous visual symptoms in nasal and temporal fields
      vii. Ataxia
      viii. Decreased level of consciousness
      ix. Simultaneous bilateral paresthesias
   e. Homonymous visual symptoms and/or unilateral sensory symptoms
   f. At least one aura symptom develops gradually over more than 5 minutes and/or different aura symptoms in succession over 5 minutes
   g. Each symptom lasts 5-60 minutes
C. Not attributable to another disorder