



Svensk Neuropediatrisk Förening -  
Utbildningsdagar 2018

## Huvudvärk och Migrän hos Barn

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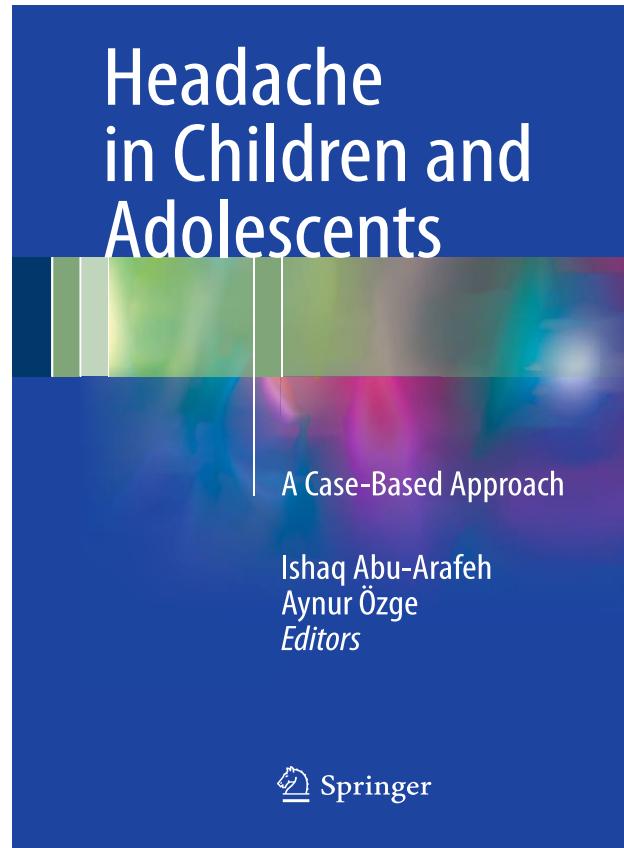
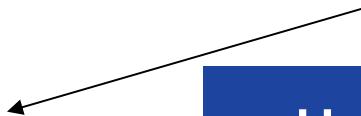
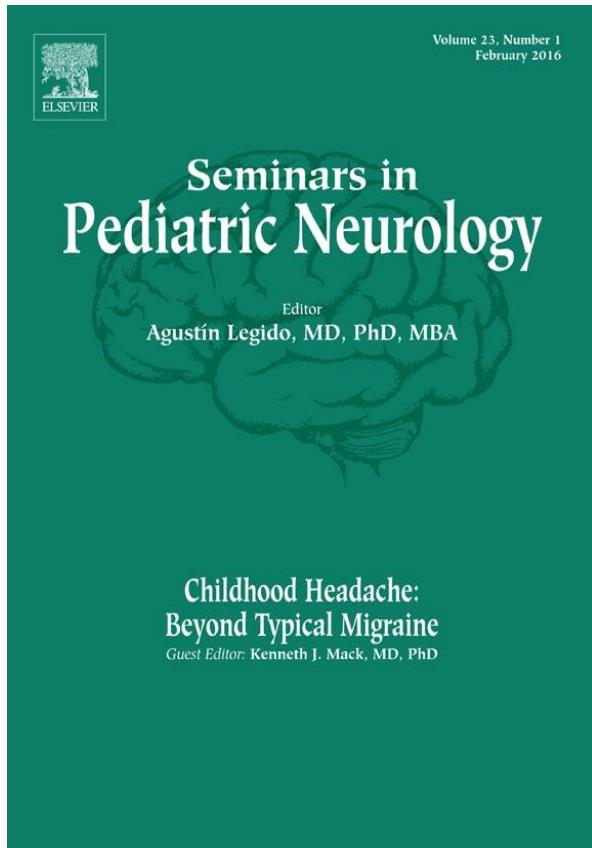
**Important developments in the last 5-10 years:**

- 1) Epidemiology
- 2) Diagnostics
- 3) Treatment: current practice
- 4) Closure





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## Huvudvärk och Migrän hos Barn

Important developments in the last 10 years:

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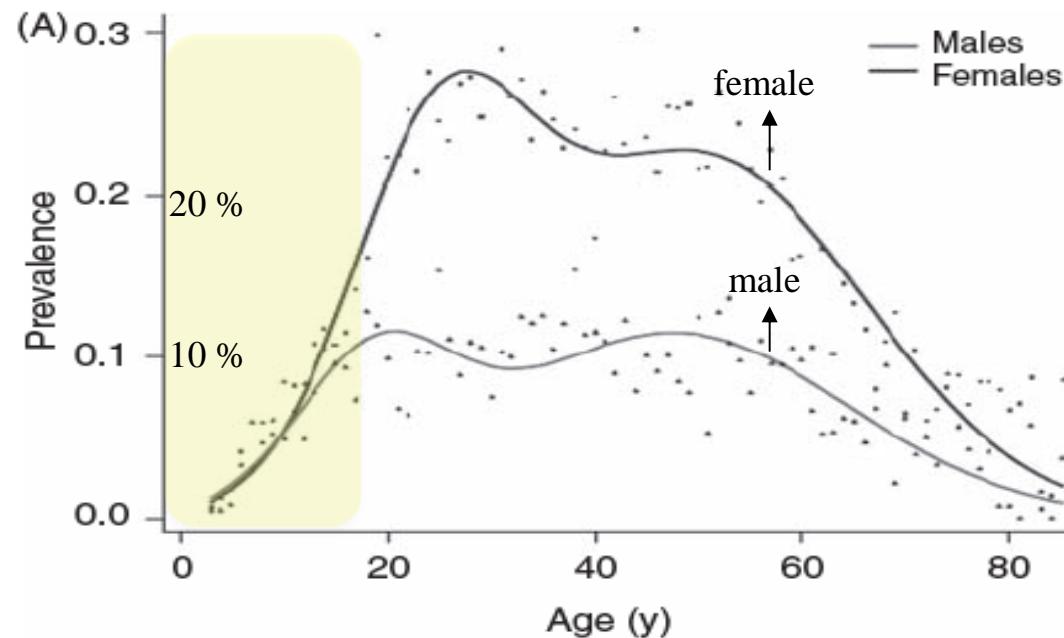


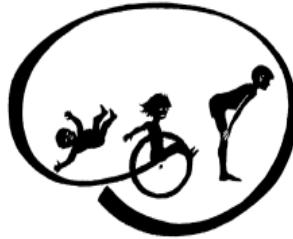


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## Huvudvärk och Migrän hos Barn

One-year period prevalence of migraine  
(Victor et. al., *Cephalgia* 2010)





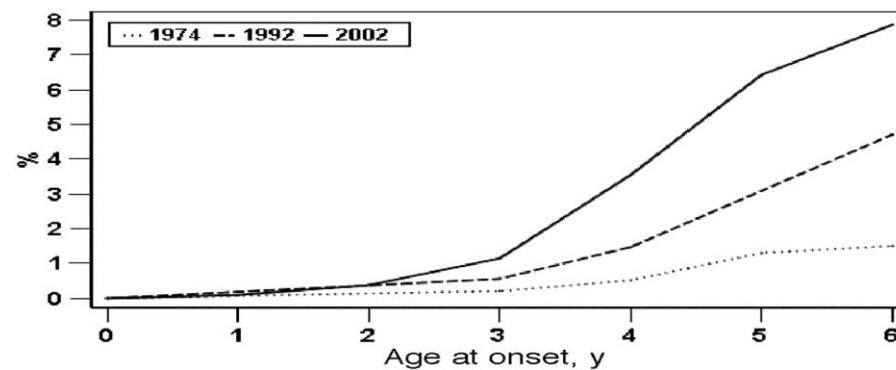
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### Huvudvärk och Migrän hos Barn

Sweden from 1955-2002 In 7-15 yrs age (*Laurell et al, 2004*): Increase in headache prevalence

Finland from 1974-2002 in 7 yrs age (*Antilla et al, 2006*): Risk for frequent headache doubled and for migraine tripled

**Cumulative incidence of migraine**





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# Huvudvärk och Migrän hos Barn

### Younger Age of Migraine Onset in Children Than Their Parents: A Retrospective Cohort Study

Tal Eidritz-Markus, MD<sup>1</sup> and Avraham Zeharia, MD<sup>1</sup>

Journal of Child Neurology  
2018, Vol. 33(1) 92-97  
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DOI: 10.1177/0883073817739197  
[jcn.sagepub.com/home/jcn](http://jcn.sagepub.com/home/jcn)

SAGE

**Table 2.** Age at Onset of Migraine in Children and Parents.

Child-parent pairs	Age onset migraine, y	P value*
Children with a history of paternal migraine	10.0 ± 4.5	<.001 ↑
Fathers	22.2 ± 10.6	
Children with a history of maternal migraine	9.86 ± 4.067	<.001 ←
Mothers	21.01 ± 11.48	

#### Abstract

Migraine is known to run in families and has long been considered a strongly heritable disorder. We sought to investigate the age of onset of migraine between successive generations. Our retrospective cohort included 102 children with migraine who were referred to a pediatric headache clinic and their affected parent(s). Age at migraine onset was significantly lower in the children with a history of maternal or paternal migraine than in their mothers or fathers ( $P < .001$ ). In conclusion, data on parental history of migraine showed that children with migraine were significantly younger at first appearance of the disease than their affected parents.



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## Huvudvärk och Migrän hos Barn

# Chronic migraine is also common in children and adolescents

0.6% (1 in 165) of 5-12 year-olds have chronic migraine<sup>1</sup>

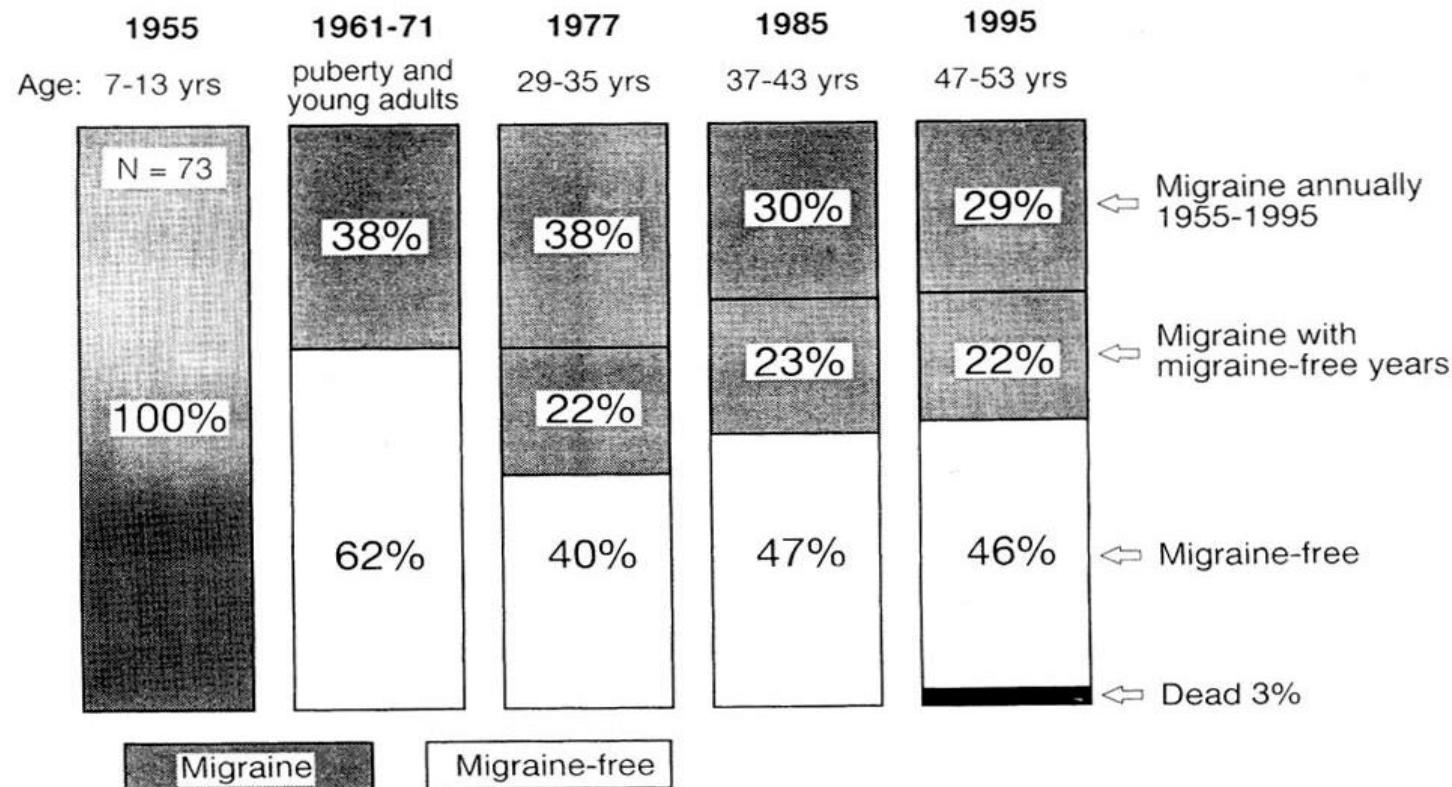
0.8-1.8% (1/125 to ~1/50) of 12-17 year-olds<sup>2</sup>

Socioeconomically disadvantaged children are at higher risk for chronic migraine (**OR 4.2, 95% CI 1.5-11.7**)<sup>1</sup>

Children with migraine miss more school and perform more poorly in school than children without migraine<sup>1</sup>



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### Huvudvärk och Migrän hos Barn

**The prognosis of pediatric headaches--a 30-year follow-up study.** Dooley JM, Augustine HF, Brna PM, Digby AM. Pediatr Neurol. 2014 51:85.

Monitored a group of patients since diagnosis in 1983, using a standardized telephone interview.

Follow-up for 28 of 60 patients (47%). Over the 30 years since diagnosis, 8 patients (**29%**) reported a complete resolution of headaches. The type of headache varied over the 30-year time interval with only three patients maintaining the same headache type at all four time periods of 1983, 1993, 2003, and 2013. Only one patient used prescription medication as the primary method for controlling headaches. The most commonly used intervention was nonprescription analgesia, self-relaxation and/or hypnosis, and precipitant avoidance.

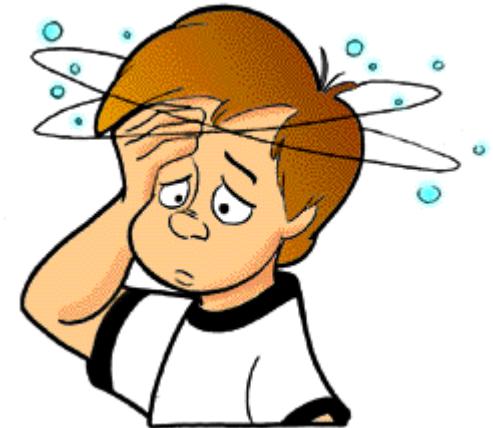


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## Huvudvärk och Migrän hos Barn

Important developments in the last 10 years:

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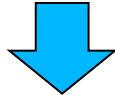


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## Huvudvärk och Migrän hos Barn

The International Classification of  
Headache Disorders  
2<sup>nd</sup> Edition

1<sup>st</sup> revision (May, 2005)



Headache Classification Committee of the International Headache Society (IHS)

The International Classification of Headache Disorders,  
3rd edition (beta version)

Cephalgia

33(9) 629–808

! International Headache Society 2013

Erasmus MC





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## Huvudvärk och Migrän hos Barn Pediatric Migraine: ICHD-III (beta)

- A. At least five attacks fulfilling criteria B-D
- B. Headache attacks lasting 2-72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following four characteristics:
  - 1. unilateral location (**more often bilateral in children<sup>1,2</sup>**), 2. pulsating quality,
  - 3. moderate or severe intensity, 4. aggravation by or causing avoidance of routine physical activity
- D. During headache at least one of the following:
  - 1. nausea/vomiting, 2. photophobia/phonophobia (**can infer from behavior**)
- E. Not better accounted for by another diagnosis



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## Huvudvärk och Migrän hos Barn

**“Episodic syndromes that may be associated with migraine”**

New terminology in ICHD-III (beta)

Previously “Childhood periodic syndromes”

This new terminology recognizes that some of these syndromes also occur in adults



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## Huvudvärk och Migrän hos Barn

### “Episodic syndromes that may be associated with migraine” (1.6 ICHD-III beta)

Childhood periodic syndromes that are commonly precursors of migraine

Cyclical vomiting  
Abdominal migraine  
Benign paroxysmal vertigo of childhood



ICHD-II !

- 1) Infant colic (A.1.6.4)
- 2) Benign paroxysmal torticollis (1.6.3)
- 3) Benign paroxysmal vertigo (1.6.2)
- 4) Abdominal migraine (1.6.1.2)
- 5) Cyclical vomiting syndrome (1.6.1.1)



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## Huvudvärk och Migrän hos Barn

### “Paroxysmal Fussing in Infancy”: Infant Colic

# Pediatrics

VOLUME 14

NOVEMBER 1954

NUMBER 5

#### ORIGINAL ARTICLES

##### PAROXYSMAL FUSSING IN INFANCY, SOMETIMES CALLED “COLIC”

By MORRIS A. WESSEL, M.D.,\* JOHN C. COBB, M.D., EDITH B. JACKSON, M.D.,  
GEORGE S. HARRIS, JR., M.D., AND ANN C. DETWILER, B.A.  
New Haven, Connecticut

Lay definition: Excessive crying in an otherwise healthy and well-fed infant

“Wessel’s criteria”: Crying for at least

3 hours a day

3 days a week,

for 3 weeks

“Modified” Wessel

1 week

Wessel *et. al.*, Pediatrics 1954



## Huvudvärk och Migrän hos Barn

**Gastrointestinal or feeding related cause is often assumed in infant colic but evidence is generally lacking**

### 1) Intestinal gas?

RCT of simethicone vs. placebo showed no difference<sup>1</sup>

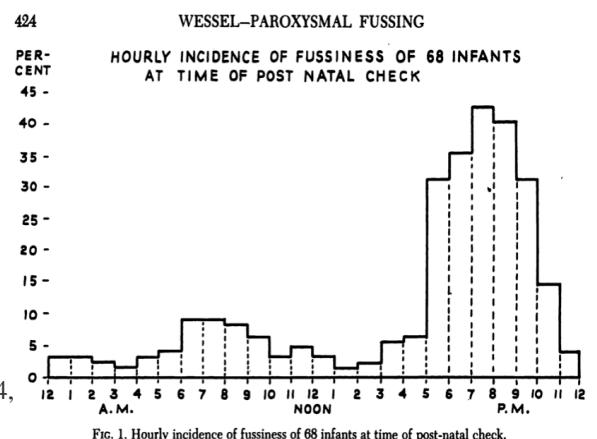
### 2) Milk problem?

Breast milk or formula: no difference<sup>3</sup>

No evidence for lactose intolerance<sup>4</sup>

Cow's milk protein allergy may play a role in a subset of infants<sup>5, 6</sup>

**Colic tends to occur in the evening, but infants eat around the clock**





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## Huvudvärk och Migrän hos Barn

# Infant Colic

Alternate hypothesis:

Could excessive crying be the result of excessive sensitivity to stimuli (i.e. an expression of migraine genetics in the developing brain)?

ICHD-III beta Infant Colic Diagnostic criteria (A.1.6):

- A. Recurrent episodes of irritability, fussing or crying from birth to 4 months of age, fulfilling criterion B
- B. Both of the following:
  - 1. Episodes last for  $\geq 3$  hrs/day
  - 2. Episodes occur on  $\geq 3$  d/wk for  $\geq 3$  wks
- C. Not attributable to another disorder





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## Huvudvärk och Migrän hos Barn

### Infant Colic and Migraine

In two retrospective studies, children with migraine were more likely to have had “colic” in infancy<sup>1, 2</sup>, however retrospective study designs allows potential for recall bias.

Infants with a maternal history of migraine were more than twice as likely to have colic (cross-sectional study).

29% vs. 11%: PR 2.6 (1.2-5.5, p=0.02, n=154)

<sup>1</sup>Jan and Al-Buhairi, *Clin Pediatr*, 2001

<sup>2</sup>Bruni et. al., *Cephalgia* 1997

<sup>3</sup>Gelfland et al, *Neurology* 2012

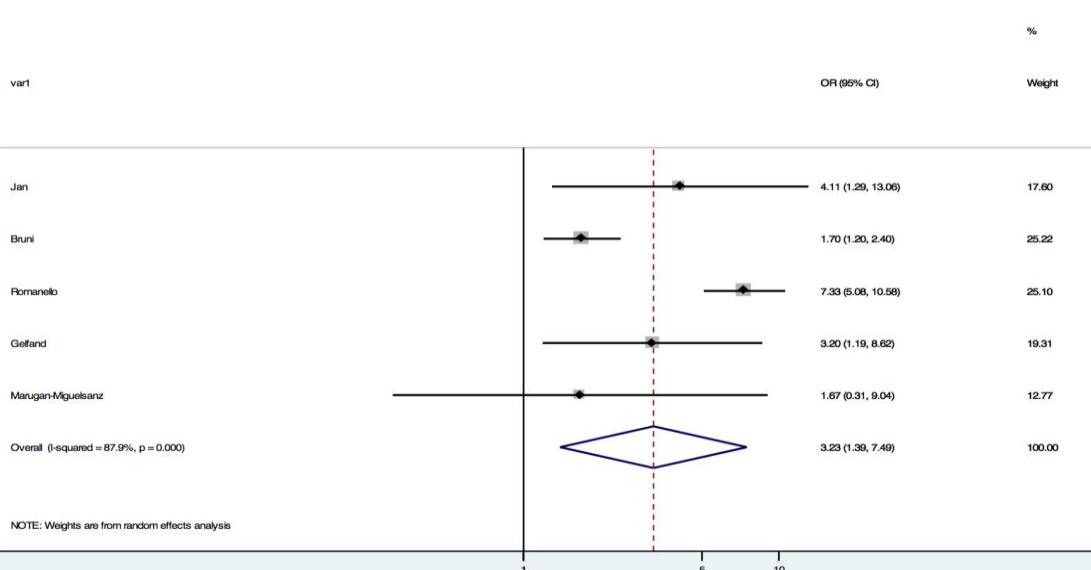


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### Huvudvärk och Migrän hos Barn

**Meta-analysis: Odds of migraine are ~3x higher if baby has colic**

Random Effects Model



Gelfand *et. al.*, *Cephalgia*, 2015



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### Huvudvärk och Migrän hos Barn

### Prospective study showing association between infant colic and adolescent migraine without aura

Prospective population-based cohort study in Finland designed to look at family competence

Collected colic data on babies born 1986

At age 18, collected migraine data

Table 2. Predictors to migraine without and with aura symptoms.

	Migraine without aura				Migraine with aura			
	Univariate		Multivariate		Univariate		Multivariate	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
<b>Infantile colic</b>	<b>2.4</b>	<b>1.4–4.2</b>	<b>2.7</b>	<b>1.5–4.7</b>	0.97	0.5–2.0	0.96	0.5–1.9
Short-tempered, (often vs. sometimes/never), age 3	3.1	1.4–6.5	1.8	0.7–5.2	0.9	0.2–3.4		
High CBCL external score, age 3–15	1.8	1.1–3.1	1.4	0.7–2.9	0.7	0.4–1.4		
Female sex	1.5	0.9–2.5			3.0	1.8–5.1	2.4	1.3–4.1
Sleep disturbances, age 18	1.8	0.8–3.9			2.9	1.7–4.9	1.7	0.9–3.3
High YSR internal score, age 18	1.8	0.9–3.8			3.1	1.9–5.1	1.7	0.9–3.1
Weekly back pain, age 18	1.2	0.8–2.2			2.1	1.3–3.2	1.6	0.96–2.5
SOC score below median, age 18	1.4	0.8–2.2			1.7	1.1–2.6	1.2	0.7–2.0
Mother's migraine	1.4	0.7–2.7			1.1	0.7–1.9		
Father's migraine	1.1	0.3–3.3			1.3	0.6–3.2		

CI: confidence interval; CBCL: Childhood Behavior Checklist; YSR: Youth Self-Report; SOC: sense of coherence.  
Risk ratios (RR) from modified Poisson regression for defined migraine type compared to no migraine (18).



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## Huvudvärk och Migrän hos Barn

### Infant Colic: Safe, age-appropriate treatment

Time to apply what we know  
about helping children with  
migraine to trying to help  
babies with colic

Behavioral interventions: Turn off  
lights, quiet room

Paracetamol/acetaminophen?

Troublesome crying in infants: effect of advice to  
reduce stimulation

“...reduce stimulation  
from loud music, rattling  
toys, etc...”

Mckenzie *Arch Dis Childhood* 1991



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# Huvudvärk och Migrän hos Barn

## Occipital Headache in Children: Still a Red Flag?

Retrospective study

Children 5-18 years

Emergency department visit because  
of headache

314 patients in 2 years

35 occipital headache

26 % with viral infection, 10 %

migraine, nobody with brain tumor

**Table 4.** Comparison of Occipital and Other Headaches: Imaging and Final Diagnosis.

	Occipital headache (n = 39)		Other headaches (n = 275)		$\chi^2$	P
	n	%	n	%		
CT/MRI					1.72	.19
Yes	13	33	65	24		
No	26	67	210	76		
Final diagnosis					21.6	.07
Viral	10	26	87	32		
Sinusitis	0	0	16	6		
Meningitis	0	0	7	2.5		
Migraine	4	10	33	12		
TTH	3	8	11	4		
Idiopathic intracranial hypertension	0	0	5	2		
Trauma	6	15	11	4		
Other	12	31	95	34.5		

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; TTH, tension-type headache.

Genizi et al, *Journal of Child Neurology*,  
2017



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**Important developments in the last 5-10 years:**

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### INTRODUCTION

#### How was evidence assessed?

- 1) Strong: multiple ( $\geq 2$ ) high quality (HQ) randomised controlled trials (RCT) with generally consistent findings
- 2) Moderate: 1 HQ RCT or  $\geq 2$  low quality (LQ) RCT's with generally consistent findings
- 3) Limited: 1 LQ RCT
- 4) No evidence or insufficient or conflicting evidence



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## Migraine in Children and Adolescents: Acute Pharmacological Treatment

Acute Treatment Therapies for Pediatric Migraine: A Qualitative Systematic review: Patniyot et al, Headache 2015.

- **ibuprofen** and acetaminophen **orally** are evidence based (EB) effective compared with placebo (ibuprofen > acetaminophen, *strong evidence for ibuprofen* (2 HQ studies), *moderate* for acetaminophen (1 HQ study)
- prochlorperazine iv is probably effective (1 LQ study, *limited*),
- no evidence for valproic acid, propofol or magnesium



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## Migraine in Children and Adolescents: Acute Pharmacological Treatment

Acute Treatment Therapies for Pediatric Migraine: A Qualitative Systematic review: Patniyot et al, Headache 2015.

- triptans:

- \* almotriptan orally probably effective (1 HQ RCT, 12-17 year, placebo controlled, *moderate evidence*)
- \* **rizatriptan 10 mg** orally EB (evidence based) effective children 12-17 year (2 HQ studies, *strong evidence*)
- \* rizatriptan 5 mg children 6-12 year: *conflicting evidence*



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## Migraine in Children and Adolescents: Acute Pharmacological Treatment

Acute Treatment Therapies for Pediatric Migraine: A Qualitative Systematic review: Patniyot et al, Headache 2015.

- triptans (continued):

\* **zolmitriptan 5 mg nasal spray** children 12-17 year EB effective  
(2 HQ studies, *strong evidence*)

\* **sumatriptan nasal spray 10 mg** children 12-17 years EB effective  
(3 HQ studies, *strong evidence*)

- sumatriptan/naproxen orally: *moderate evidence* (1 HQ study)

Erasmus MC  
*Ezafus*



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## Migraine in Children and Adolescents: Acute Pharmacological Treatment

Acute Treatment Therapies for Pediatric Migraine: A Qualitative Systematic review: Patniyot et al, Headache 2015.

- DHE (dihydroergotamine): *insufficient evidence*
  - \* one study, 1994, retrospective, iv DHE, considered safe and effective
  - \* one study, 1997, RCT, placebo-controlled, oral DHE, small group, appears superior to placebo, statistical significance not reached
  - \* one study, 2009, retrospective, iv DHE, considered effective



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## Migraine in Children and Adolescents: Acute Pharmacological Treatment

Drugs for the Acute Treatment of Migraine in Children and Adolescents: Billinghurst et al, Cochrane Database Systematic Review 2016.

- **ibuprofen orally** more effective than placebo (*low quality evidence*)
- **triptans** are in general superior to placebo without report for serious side effects
- sumatriptan plus naproxen sodium superior to placebo in one study (*moderate evidence*)
- **no evidence for oral DHE**



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## Migraine in Children and Adolescents: Prophylactic Pharmacological Treatment

A Comparative Effectiveness Meta-analysis of Drugs for the Prophylaxis of Pediatric Migraine Headache: El-Chammas K, et al. JAMA Pediatrics 2013.

- **topiramate** and **trazodone** have limited evidence supporting efficacy for episodic migraines
- placebo is effective in reducing headaches
- other commonly used medications (clonidine, flunarizine, pizotifen, propranolol and valproate) have no evidence\*



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## Migraine in Children and Adolescents: Prophylactic Pharmacological Treatment

**Childhood and Adolescent Migraine Prevention (CHAMP) Study: a double blinded, placebo-controlled, comparative effectiveness study of amitriptylline, topiramate, and placebo in the prevention of childhood and adolescent migraine. Hershey AD, Powers SW, CHAMP Study Group. Headache 2013.**

- 361 subjects
- target dose 1 mg/kg amitriptylline and 2 mg/kg topiramate
- titration period of 8 weeks



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# NEJM 10-2016: Powers SW, Hershey AD et al



### Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine

Scott W. Powers, Ph.D., Christopher S. Coffey, Ph.D.,  
Leigh A. Chamberlin, R.D., M.Ed., Dixie J. Ecklund, R.N., M.S.N.,  
Elizabeth A. Klingner, M.S., Jon W. Yankey, M.S., Leslie L. Korbee, B.S.,  
Linda L. Porter, Ph.D., and Andrew D. Hershey, M.D., Ph.D.,  
for the CHAMP Investigators\*

?

### CONCLUSIONS

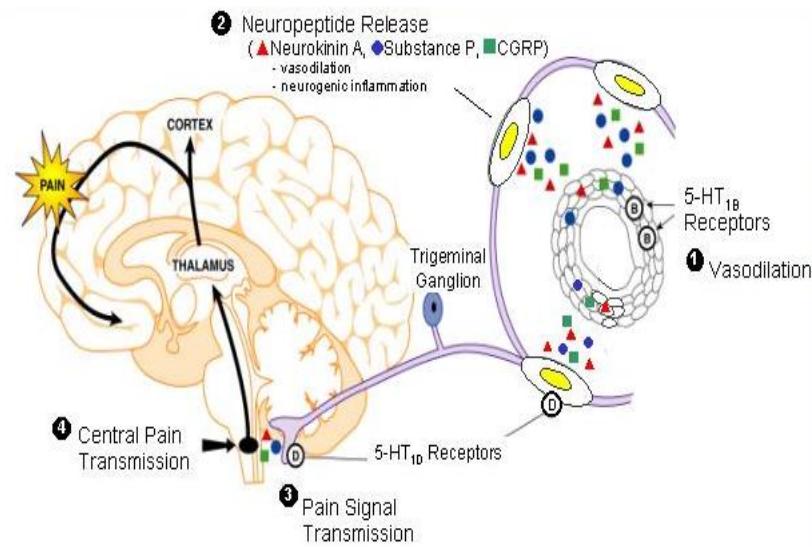
There were no significant differences in reduction in headache frequency or headache-related disability in childhood and adolescent migraine with amitriptyline, topiramate, or placebo over a period of 24 weeks. The active drugs were associated with higher rates of adverse events. (Funded by the National Institutes of Health; CHAMP ClinicalTrials.gov number, NCT01581281).



# Migraine in Children and Adolescents: Prophylactic Pharmacological Treatment

## Anti-CGRP Antibodies

- a number of phase II studies have been published describing efficacy and safety of anti-CGRP antibodies in adults with migraine with promising results
- until now no studies concerning children and/or adolescents with migraine have been published describing development and/or efficacy and safety of anti- CGRP antibodies



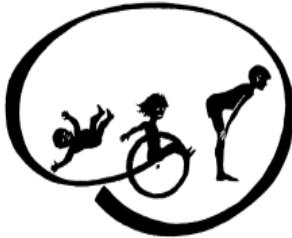


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## Migraine in Children and Adolescents: non-Pharmacological Treatment

**Biofeedback as Prophylaxis for Pediatric Migraine: a Meta-Analysis.** Stubberud et al. Pediatrics 2016.

- systematic search in 5 databases for prospective RCT's
- five studies included, total 137 participants
- biofeedback reduced migraine frequency, duration and intensity significantly compared with waiting-list control
- no adjuvant effect combined with active or other behavioral treatment
- possible bias judgements, further investigation needed



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## Migraine in Children and Adolescents: non-Pharmacological Treatment

**Cognitive Behavioral Therapy plus Amitriptylline for Children and Adolescents with Chronic Migraine Reduces Headache Days to 4 Per Month.** Kroner and Hershey et al. Headache 2016.

- 135 randomized participants received 20 weeks of treatment with either CBT and Amitriptylline (titration in 8 weeks till 1 mg/kg/day) or Headache Education and Amitriptylline (same dosage)
- 20 weeks post treatment 47% of CBT/A and 20% HE/A < 4 HA/month\*
- 12 months post treatment resp 72% and 52% < 4 HA/month



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## Tension Type Headache in Children and Adolescents: non-Pharmacological Treatment

**Vitamin D Deficiency Mimicking Chronic Tension Type Headache  
in Children.** Prakash et al. BMJ 2016.

- 3 premenarchal girls with chronic tension type headache and generalised body pain
- no response to conventional therapy
- severe vitamin D deficiency and biochemical osteomalacia
- marked improvement after vitamin D therapy



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## Pharmacological and non-Pharmacological Treatment of Headache in Children and Adolescents: General Recommendations

The influence of excessive chewing gum use on headache frequency and severity among adolescents. Watemberg et al. Ped. Neurol 2014.

- 30 patients, ♀>>♂, 6-19 jr, chronic headache (18 migraine, 12 TTH)
- gum chewing for 1 to 6 hours a day
- gum chewing discontinued for 1 month: 26 reported improvement of headache, 19 reported resolution
- after reintroduction gum chewing 20/20 headaches return  
→ temporomandibular joint? aspartam as sweetener? ←





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## Huvudvärk och Migrän hos Barn

Important developments in the last 5-10 years:

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## CORRESPONDENCE

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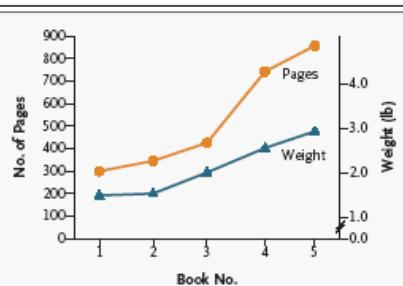
1. Guthell TG, Appelbaum PS. Clinical handbook of psychiatry and the law. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2000.

## Hogwarts Headaches — Misery for Muggles

**TO THE EDITOR:** During the past several months, I have evaluated three children between 8 and 10 years of age who presented with a two-to-three-day history of generalized headaches. In each case, the headache was dull and the pain fluctuated throughout the day. One patient also reported neck and wrist pain. All the patients were afebrile and free of any symptoms suggesting an underlying infectious or neurologic cause. On further questioning, it was determined that each child had spent many hours reading J.K. Rowling's latest book in the Harry Potter series. Two patients read the book lying prone, and the third propped the book on her legs and rested her head on a pillow.

The presumed diagnosis for each child was a tension headache brought on by the effort required to plow through an 870-page book. The obvious cure for this malady—that is, taking a break from reading—was rejected by two of the patients, who preferred acetaminophen instead. In all cases, the pain resolved one to two days after the patient had finished the book.

It is worth noting that I did not witness this phenomenon with any of the previous Harry Potter tomes and that each of Rowling's successive books



**Figure 1.** Page and Weight Inflation in the Harry Potter Series.

To convert values for weight to kilograms, multiply by 0.45.

tion continues as Rowling concludes the saga, there may be an epidemic of Hogwarts headaches in the years to come.

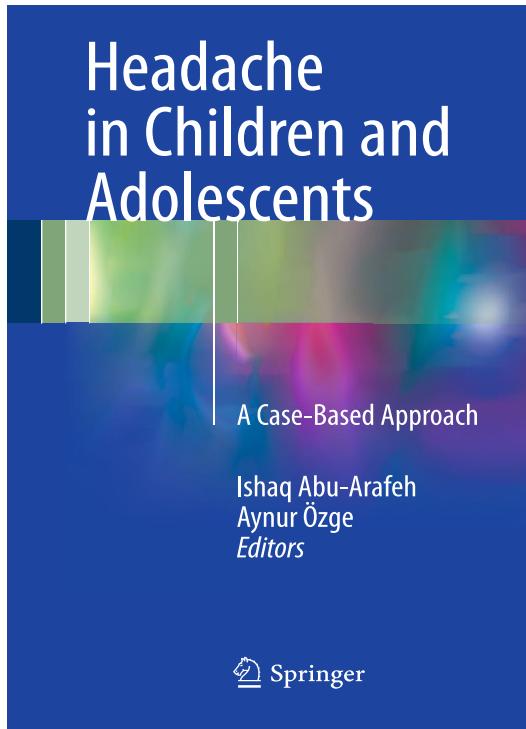
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# Thank you for your attention!



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