Pediatric vs. Adult: Are Kids Really Different and What Should We Do About It

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Disclosures

Support – grants, contracts, honoraria
NIH, MRF, CHRF research foundation, Amgen, Curelator, Theranica
NIH – Advisory Board, Common Data Elements; HEAL
Migraine Research Foundation – Advisory Board
Assoc Ed – Headache, Cephalalgia, The Journal of Headache Pain
Advisory Board – Alder/Lundbeck, Amgen, Biohaven, Curelator, Depomed, Dr. Reddy, Impax, Lilly, Teva, Upsher-Smith

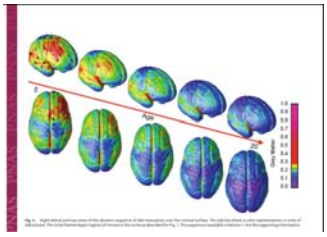
Objectives

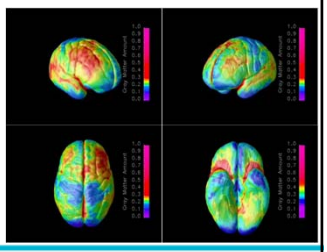
- Explain challenges associated with evaluation and treatment of pediatric/adolescent migraine patients
- Describe how pediatric/adolescent patients present with migraine
- Gain an understanding of the unique design for pediatric/adolescent migraine clinical trials

Evaluation and Treatment Challenges

- Development of the Brain
- Age appropriate assessments

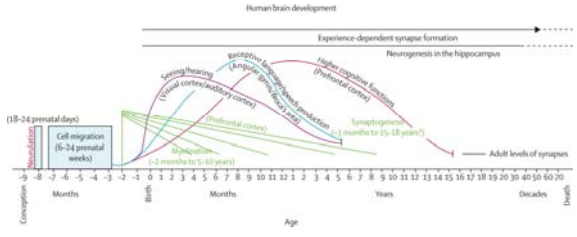
Developing Brain





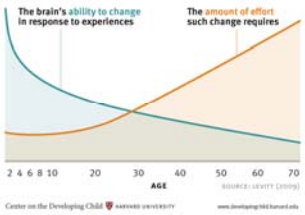
Gogtay et al, PNAS 2004

Developing Brain



Thompson and Nelson, Am. Psychol 2007 & Grantham-McGregor et al., Lancet 2007

Developing Brain - Plasticity



Periodic Syndromes/Episodic Syndromes

Migraine and Migrainous Variants in Pediatric Patients

*Arthur L. Prensky, M.D.**

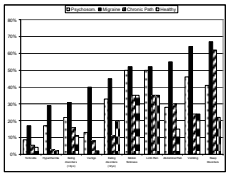
Seminars in Pediatric Neurology, 1976

Children suffer from a number of migraine variants which occasionally pose difficult problems with regard to diagnosis. Many have been mistaken for epilepsy or structural brain disease. The most common of these variants is a "recurrent syndrome" in which children suffer from recurrent abdominal pain with or without nausea and vomiting, cyclic vomiting, associated fever, and autonomic symptoms such as pallor and sweating as well as chest pains and leg cramps. Table 2 com-

Table 2. *A Comparison of Findings in Classical and Common Migraine in Children with the Recurrent Abdominal Syndrome**

	MIGRAINE	ABDOMINAL SYNDROME
Sex	~60% male	~50% male
Headache	100%	43% (0-85%)
Seizures †	8% (3.4-12.3%)	15.1% (0-39%)
Paroxysmal electroencephalogram	<10%	23.2% (7-76%)
Family history		
Seizures	2-3%	10% (0-30%)
Migraine	79% (44-87%)	20.3% (0-66%)

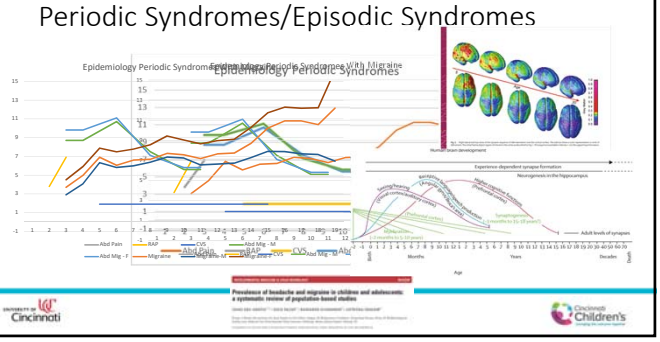
Periodic Syndromes/Episodic Syndromes



Symptom	*Psychosom.*	*Migraine*	*Chronic Path*	*Healthy*
Vomiting	46%	64%	24%	24%
Abdominal Pain	28	55	30	15
Motion Sickness	50	52	35	35
Limb Pain	50	52	35	35
Vertigo	13	40	8.1	2.2
Hyperthermia	17	29	2.7	2.2
Torticollis	8.7	17	5.4	4.3
Sleep Disorders	41	67	62	22
Eating disorders (<2yo)	33	45	11	20
Eating disorders (>2yo)	22	31	16	11

Lanzi et al, Ital. J. Neurol. Sci., 1997

Periodic Syndromes/Episodic Syndromes



Age appropriate assessments

- Patient is the child, not the parent
  - Parent likely to have headaches
    - may not recognize that they are migraine
    - Personal experience generates bias
    - Need to limit parental responses ("you will have a chance to answer")
  - Interviews need to be developmentally appropriate for the age
    - Impact of developing brain
    - Experienced interviewer
    - Potential use of drawings, visual tools
    - Semi-structured interview process

Age appropriate assessments

- Children are in general healthy
  - Adults have co-morbid illness, less likely in children
  - Chronic diseases common in children
    - Allergy, asthma, anxiety, depression, obesity
  - Episodic syndrome role
- School will impact timing, disability, treatment availability
  - PedMIDAS has demonstrated kids not trying to get out of school, but leave social activities and home activities first

Migraine in Pediatrics

Classification of Headache

International Classification of Headache Disorders – 3rd Edition

- **Migraine without aura**
- **Migraine with aura**
  - Migraine with typical aura
  - Migraine with brainstem aura
  - Hemiplegic migraine
  - Retinal migraine
- **Chronic migraine**
- **Complications of migraine**
  - Status migrainosus
  - Persistent aura without infarction
  - Migrainous infarction
  - Migraine aura-triggered seizure
- **Probable migraine**
  - Without aura
  - With aura
- **Episodic syndromes that may be associated with migraine**
  - Recurrent gastrointestinal disturbance
    - Cyclical vomiting syndrome
    - Abdominal migraine
  - Benign paroxysmal vertigo
  - Benign paroxysmal torticollis

Migraine Without Aura (1.1)

International Classification of Headache Disorders – 3rd Edition

- **At least 5 attacks**
- **Last 4 - 72 hours untreated**
  - **Sleep included in duration**
  - **2 - 72 hours in children under 18 years old**
  - *1-72 if diary confirmation (removed)*

Migraine Without Aura (1.1)

International Classification of Headache Disorders – 3rd Edition

- **Two of four characteristics**
  - Unilateral location
  - Pulsating quality
  - Moderate or severe intensity
  - Aggravated by routine physical activity

Migraine Without Aura (1.1)

International Classification of Headache Disorders – 3rd Edition, Cephalalgia 2013

- **One of two associated symptoms**
  - Nausea and/or vomiting
  - Photophobia and phonophobia
- **Not attributed to another disorder**

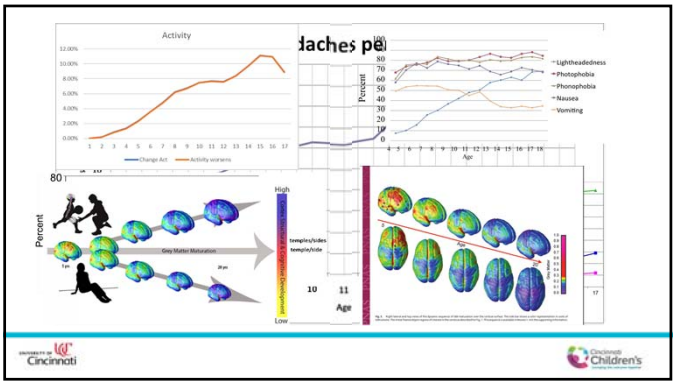
Migraine Without Aura (1.1)

International Classification of Headache Disorders – 3rd Edition, Cephalalgia 2013

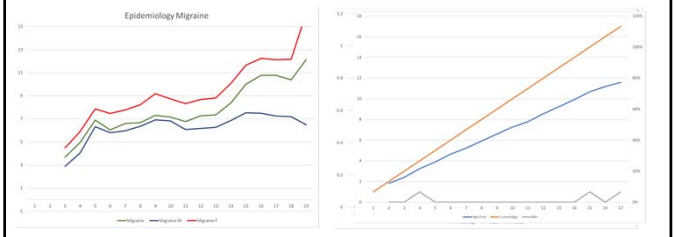
- Pediatric specific Notes/Comments
  - Duration shorter (2-72 hours under 18 years old
  - Location more often bilateral
    - Often frontotemporal
  - Photophobia and Phonophobia can be inferred by parental observation
- No other pediatric specific comments
  - Aura can be bilateral in children, but not in criteria or comments

Changes in Character with Age

- 5659 patients headache characteristics compared
- Age 4 to 18, mean 11.95 ± 3.53
- Analysis of diagnostic criteria across the developmental ages
- McKenzie Miller, summer student



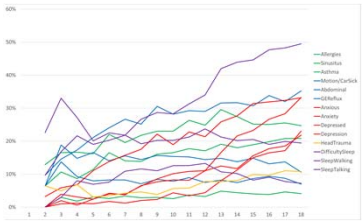
Migraine Epidemiology

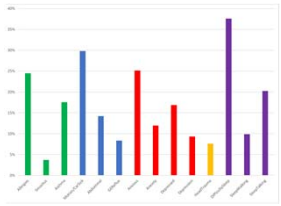


Why Migraine – Global Burden of Disease

GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, Lancet, Oct 8, 2016

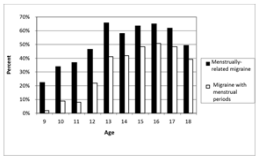
Co-Morbid

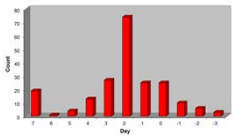




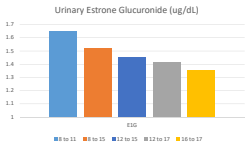
Menstrual Effects

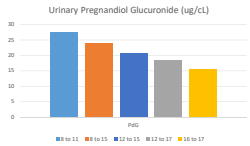
- Is Puberty the Reason?
- Reviewed Headache Center Database
  - 896 girls, age 9 to 18
  - Clinically asked
    - Had first period
    - Headaches worsen with periods
    - Monthly pattern of worsening headaches



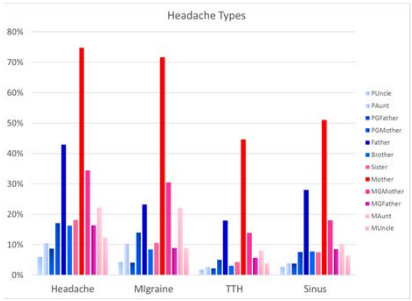


Pubertal Urinary Menstrual Level Changes





Family History



Migraine Twin Children

Svensson et al, *Cephalalgia* 1999

- 1480 Swedish twins
  - Born between Apr 1985 and Dec 1986
  - 8 to 9 year olds
  - Clinical Dx based on ICHD-I

	N	Twin pairs −/−	+/−	+/+
MZ Boys	178	146	21	11
DZ Boys	183	142	36	5
MZ Girls	164	127	24	13
DZ Girls	200	155	38	7
DZ Un	314	227	80	7
Total	1039	797	199	43

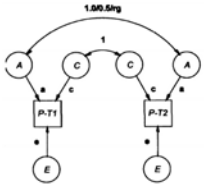


Table 5. Estimates of components of variance in 8 to 9-year-old boys and girls.

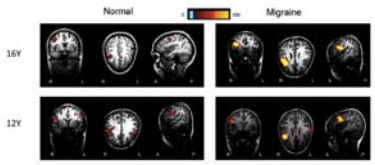
	a^2	c^2	e^2
Estimate	0.70	0	0.30
95% CI	0.54–0.82	-	0.18–0.46

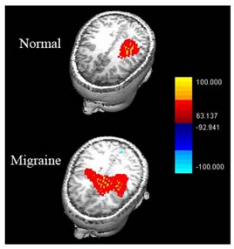
a^2 = Additive genetic effects (heritability); c^2 = shared environmental effects; e^2 = nonshared environmental effects.

MEG

- Migraineurs frequently note that it is hard to think during an acute attack
- MEG can measure cortical function
  - Finger tapping (200 trials, randomly presented clicks in right or left ear to tap fingers)
  - Mis-matched negativity
- Compared subjects with acute migraine seen in the acute headache unit vs. controls

Movement-evoked Magnetic Fields (MEFs) in Children with Migraine (left)



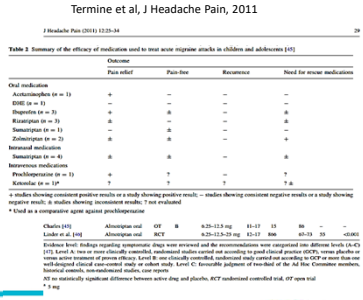


Treatment

Gaps in Prevention

- Very limited number of studies in pediatric and adolescent headaches
- Translation from adults studies may be problematic
  - Are they really generalizable
- Prevention does not only mean medication

Termine et al, J Headache Pain, 2011



J Headache Pain (2011) 12:23–34 29

Table 2 Summary of the efficacy of medication used to treat acute migraine attacks in children and adolescents [45]

	Outcome			
	Pain relief	Pain-free	Recurrence	Need for rescue medications
Oral medication				
Acetaminophen (n = 1)	+	–	–	–
ESME (n = 1)	–	–	–	–
Ibuprofen (n = 3)	+	±	–	±
Rizatriptan (n = 3)	±	–	–	±
Sumatriptan (n = 1)	–	±	–	–
Zolmitriptan (n = 2)	±	±	–	+
Intranasal medication				
Sumatriptan (n = 4)	±	±	–	±
Intravenous medications				
Prochlorperazine (n = 1)	+	?	–	?
Ketorolac (n = 1)*	?	?	?	? ±

+ studies showing consistent positive results or a study showing positive result; – studies showing consistent negative results or a study showing negative result; ± studies showing inconsistent results; ? not evaluated

* Used as a comparative agent against prochlorperazine

Charles [43]	Almotriptan oral	OT	B	6.25–12.5 mg	11–17	15	86	–	–
Linder et al. [44]	Almotriptan oral	RCT		6.25–12.5–25 mg	12–17	866	67–73	33	<0.001

Evidence level: findings regarding symptomatic drugs were reviewed and the recommendations were categorized into different levels (A–C) [47]. Level A: two or more clinically controlled, randomized studies carried out according to good clinical practice (GCP), versus placebo or versus active treatment of proven efficacy. Level B: one clinically controlled, randomized study carried out according to GCP or more than one well-designed clinical case-control study or cohort study. Level C: favourable judgment of two-third of the Ad Hoc Committee members, historical controls, non-randomized studies, case reports

NS no statistically significant difference between active drug and placebo, *RCT* randomized controlled trial, *OT* open trial

* 5 mg

Gap Identification

- Survey given to Pediatric-Adolescent Section
- Assessed current status of prevention
- Asked what is "Clinically meaningful"
- What they are currently using

- Sample questions
  - #3 Meds used
    - AMI, Cypro, VPA, Prop, TPM, Other
  - #4 Dose of this medication
  - #5 How long to tell if work
  - #6 Effectiveness level
    - >50% reduction HF
    - <1/week
    - >50% reduction in disability
    - Ease of admin
    - Cost
    - Other
  - #7 % reduction that would impact practice

Gap Identification

- Sample questions
  - #3 Meds used
    - AMI, Cypro, VPA, Prop, TPM, Other
  - #4 Dose of this medication
  - #5 How long to tell if work
  - #6 Effectiveness level
    - >50% reduction HF
    - <1/week
    - >50% reduction in disability
    - Ease of admin
    - Cost
    - Other
  - #7 % reduction that would impact practice

Pediatric Headache Prevention Clinical Trial

#7 What % reduction in headache frequency in

Answer Options		Response Frequency	Response Count
2 weeks	10%	3.6%	4
4 weeks	20%	7.1%	8
6 weeks	30%	29.5%	33
8 weeks	40%	16.1%	18
10 weeks	50%	42.0%	47
12 weeks	60%	1.8%	2
	answered question		112
	skipped question		65
	answered question		73
	skipped question		104

Guidelines

- Trial Guidelines
- Acute Treatment
- Preventive Treatment

Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society

Special Articles

Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention

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Acute Treatment Guidelines

- Focus on Early Treatment
- Choose most appropriate route based on attack
  - Formulation may also be important
- Provide counseling on lifestyle factors
  - Including triggers
- Discuss Medication Overuse

Acute Treatment Guidelines

US FDA approved for
- Children
- Adolescents

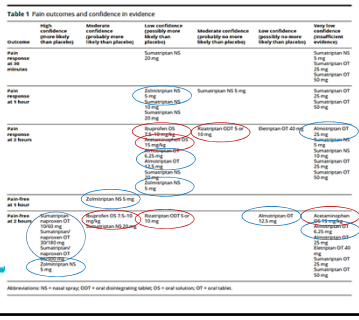


Table 1 Pain outcomes and confidence in evidence

Outcome	High confidence (more likely than placebo)	Moderate confidence (probably more likely than placebo)	Low confidence (possibly more likely than placebo)	Moderate confidence (probably no more likely than placebo)	Low confidence (possibly no more likely than placebo)	Very low confidence (insufficient evidence)
Pain response at 30 minutes			Sumatriptan NS 20 mg			Sumatriptan NS 5 mg Sumatriptan OT 25 mg Sumatriptan OT 50 mg
Pain response at 1 hour			Zolmitriptan NS 5 mg Sumatriptan NS 10 mg Sumatriptan NS 20 mg	Sumatriptan NS 5 mg		Sumatriptan OT 25 mg Sumatriptan OT 50 mg
Pain response at 2 hours			Ibuprofen OS 20–30 mg/kg Sumatriptan OS 15 mg/kg Sumatriptan OT 4.25 mg Sumatriptan OT 4.5 mg Sumatriptan NS 20 mg Zolmitriptan NS 5 mg	Sumatriptan ODT 5 or 10 mg	Eletriptan OT 40 mg	Almotriptan OT 6.25 mg Sumatriptan NS 5 mg Sumatriptan NS 10 mg Sumatriptan OT 25 mg Sumatriptan OT 50 mg
Pain-free at 1 hour		Zolmitriptan NS 5 mg				
Pain-free at 2 hours*	Sumatriptan–naproxen OT 10/60 mg Sumatriptan–naproxen OT 30/180 mg Sumatriptan–naproxen OT 85/500 mg Zolmitriptan NS 5 mg	Ibuprofen OS 7.5–10 mg/kg Sumatriptan NS 20 mg	Sumatriptan ODT 5 or 10 mg		Almotriptan OT 12.5 mg	Acetaminophen 65–75 mg/kg Almotriptan OT 6.25 mg Sumatriptan OS 25 mg Eletriptan OT 40 mg Sumatriptan OT 25 mg Sumatriptan OT 50 mg

Abbreviations: NS = nasal spray; ODT = oral disintegrating tablet; OS = oral solution; OT = oral tablet.

Headache
© 2019 American Headache Society
ISSN 0017-8748
doi: 10.1111/head.13629
Published by Wiley Periodicals, Inc.

Guest Editorial

New Guidelines: Interpretation, Application and the Future

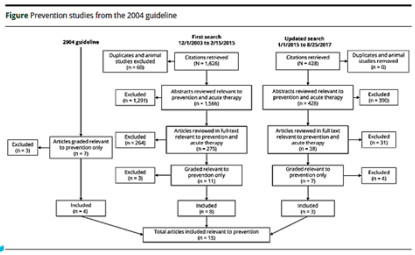
	Children	Adolescents	Treatment
First line	x	x	Ibuprofen OS (10 mg/kg)
Second line		x	Sumatriptan/naproxen OT (10/60, 30/180, 85/500 mg), zolmitriptan NS (5 mg), sumatriptan NS (20 mg), rizatriptan ODT (5 or 10 mg), or almotriptan OT (6.25 or 12.5 mg)
Third line		x	Try an alternate triptan, if 1 triptan fails to provide pain relief, to find the most effective agent to reduce migraine symptoms
If prominent nausea/vomiting	x	x	Offer additional antiemetic treatments

Prevention Guidelines

- Majority fail to demonstrate superiority to placebo
- Lifestyle and behavioral factors may influence frequency
- Assessment and management of comorbid disorders
- Shared decision-making with patients and caregivers with discussion of limitation of evidence

Prevention Guidelines Process

Figure Prevention studies from the 2004 guideline



Prevention Guidelines

US FDA approved for
- Children
- Adolescents

Table Outcomes and confidence in evidence

Outcome	High confidence (more likely than placebo)	Moderate confidence (probably more likely than placebo)	Low confidence (possibly more likely than placebo)	Moderate confidence (probably no more likely than placebo)	Low confidence (possibly no more likely than placebo)	Very low confidence (insufficient evidence)
Decreased frequency of migraine or headache days	Amitriptyline (1 mg/kg/d) combined with CBT	Topiramate (100 mg/d or 2–3 mg/kg/d) or Cimarizine (1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg)				DVPX ER (250 mg/d, 500 mg/d, or 1,000 mg/d) Amitriptyline (1 mg/kg/d) Flunarizine (5 mg/d) Nadolol (10–20 mg, 3 times a day) OnabotulinumtoxinA (74 U IM or 155 U IM)
Decreased headache severity		Cimarizine (1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg)				
At least a 50% reduction in headache frequency	Amitriptyline (1 mg/kg/d) combined with CBT		Propranolol (20–40 mg, 3 times a day) Timolol (1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg)			Topiramate (100 mg/d or 2–3 mg/kg/d) DVPX ER (250 mg/d, 500 mg/d, or 1,000 mg/d) Amitriptyline (1 mg/kg/d) OnabotulinumtoxinA (74 U IM or 155 U IM)
Decreased migraine-related disability		Amitriptyline (1 mg/kg/d) combined with CBT			Topiramate (100 mg/d or 2–3 mg/kg/d)	Amitriptyline (1 mg/kg/d)

Abbreviations: CBT = cognitive behavioral therapy; DVPX ER = extended-release divalproex sodium.

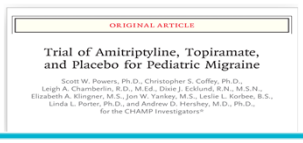
CHAMP Study Goals

- **Outcome for Aims 1-3 – reduction in migraine frequency and disability**
  - **Aim 1: Determine if amitriptyline (AMI) is superior to placebo**
  - **Aim 2: Determine if topiramate (TPM) is superior to placebo**
  - **Aim 3: Determine superiority for AMI vs TPM**
- **Aim 4: To prospectively and systematically determine the safety and tolerability profiles of AMI, TPM and placebo**

Protocol - Hershey, et al, Headache 2013

CHAMP results –

Protocol - Hershey, et al, Headache 2013
Baseline - Powers, et al, Headache 2016
N Engl J Med 2017; 376:115-124 January 12, 2017 DOI: 10.1056/NEJMoa1610384
http://www.nejm.org/doi/suppl/10.1056/NEJMoa1610384/suppl_file/nejmoa1610384_appendix.pdf
https://clinicaltrials.gov/show/NCT01581281

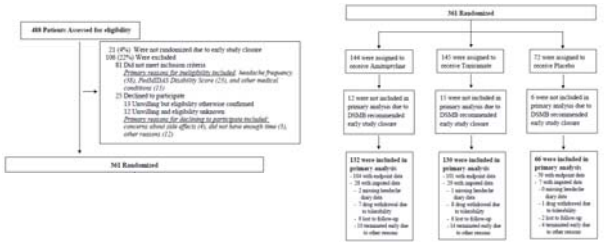


ORIGINAL ARTICLE

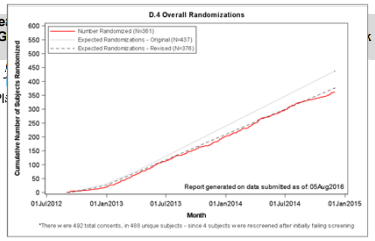
Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine

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*

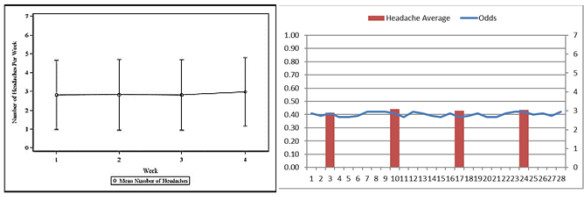
CHAMP results – Consort



CHAMP - Supplementary



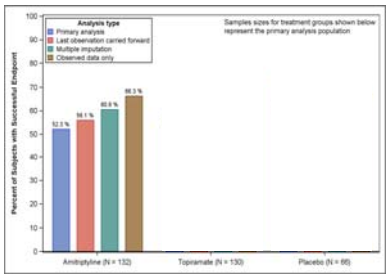
Baseline Results



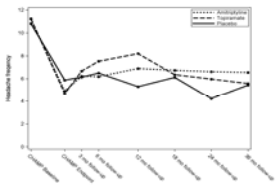
Baseline - Powers, et al, Headache 2016

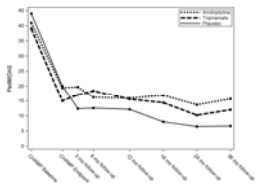
Primary (>50%)

- Primary – all subjects without data considered failures
- Last Observation Carried Forward – most recent visit with 28 day calendar
- Multiple Imputation – methods with multiple chains
- Observed data – all subjects with baseline and last 28 days



Long Term Follow-up

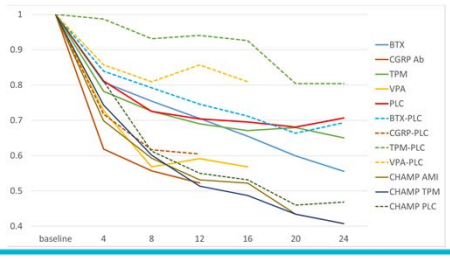




Placebo

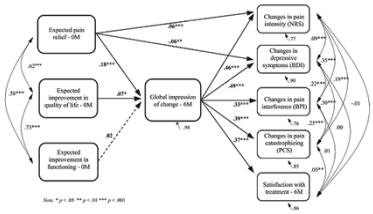
(or is it really expectation)

Is there a placebo problem



Expectation of Response

Cormier et al, Pain 2016

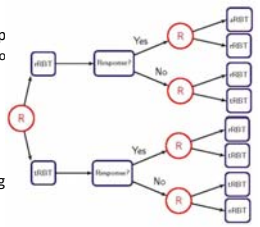


Where do we go from here?

- Children and adolescents with real world migraine get better
  - 50 to 70% with a >50% reduction in headache frequency
  - Mean frequency at end down to almost 1 per week
  - Thus, multidisciplinary care works
- Biochemical effect of medication is not the reason
- Is the reason expectation of response?
- What do we do with the 30-40% that don't get better?

Where do we go from here?

- Traditional RTC model
  - Doesn't work because of high level of Exp
    - By the time studies done in kids, already "pro
  - Modifications
    - Placebo run in
    - Placebo run in with survival curve
    - Cross over
- New Models
  - SMART design (Sequential, Multiple Assig



Headache
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ISSN 0017-8748
doi: 10.1111/head.12795
Published by Wiley Periodicals, Inc.

Research Submission

Cognitive Behavioral Therapy plus Amitriptyline for Children and Adolescents with Chronic Migraine Reduces Headache Days to ≤4 Per Month

John W. Kroner, MS; Andrew D. Hershey, MD, PhD, FAHS; Susmita M. Kashikar-Zuck, PhD; Susan L. LeCates, MSN; Janelle R. Allen, MS; Shalonda K. Slater, PhD; Marium Zafar, PsyD; Marielle A. Kabbouche, MD, FAHS; Hope L. O'Brien, MD; Chad E. Shenk, PhD; Joseph R. Rausch, PhD; Ashley M. Kroon Van Diest, PhD; Scott W. Powers, PhD, ABPP, FAHS

American Pain Society
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PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 18, No 6 (June), 2017: pp 637-644
Available online at www.jpain.org and www.sciencedirect.com

Trajectory of Improvement in Children and Adolescents With Chronic Migraine: Results From the Cognitive-Behavioral Therapy and Amitriptyline Trial

John W. Kroner,* James Peugh,*,† Susmita M. Kashikar-Zuck,*,† Susan L. LeCates,†,‡ Janelle R. Allen,*,‡ Shalonda K. Slater,*,†,‡ Marium Zafar,* Marielle A. Kabbouche,†,‡,§ Hope L. O'Brien,†,‡,§ Chad E. Shenk,*,† Ashley M. Kroon Van Diest,* Andrew D. Hershey,†,‡,§ and Scott W. Powers*,†,§

*Division of Behavioral Medicine and Clinical Psychology, †Division of Neurology, ‡Headache Center, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.
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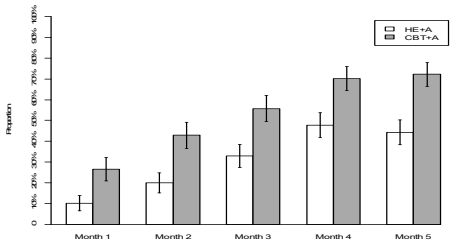
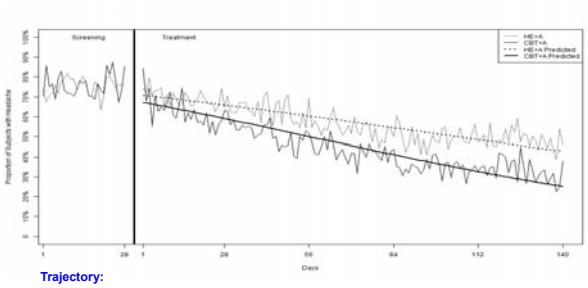


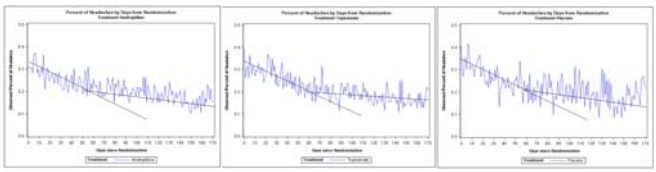
Proportion of patients with 50% or greater reduction in headache days for each month of the 5-month trial



Trajectory:

Proportion of patients in each group that had a headache for each day of the trial

CHAMP Trajectory



Putting it all together – a treatment strategy

- Patients and parents present because headaches are impacting their lives "Need to do something"
- Baseline of CHAMP shows that just because you diagnosis, provide acute treatment, and introduce healthy habits, it's not enough
- Expectation of response is needed
  - Pharmaceutical expectation
  - Cognitive Behavioral Therapy
  - Wait and see
  - "The Expert Effect"

Conclusions

- Migraine is common in children and adolescents
  - Increasing with brain maturation
- Diagnostic criteria are more uniform across the ages with the exception of duration
- Children and Adolescents need to be active participants in the decision making process
  - This may improve expectation and thus response and outcomes
- New and novel study designs are likely needed to advance headache treatment in children and adolescents