CHAMP Trial: Design, Outcomes, Context, and Lessons Learned

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Disclosures

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NIH, CHRF research foundation, Curelator
American Headache Society – Board Member
NIH – Advisory Board, Common Data Elements
Migraine Research Foundation – Advisory Board
Assoc Ed – Headache, Cephalalgia, The Journal of Headache Pain
Advisory Board – Amgen, Curelator, Depomed, Impax, Lilly, Teva

Outline

• Why - Background for development of CHAMP
• Who – Clinical Coordinating, Data Coordinating, Sites
• How - Protocol development
• What
  • Baseline Results
  • Study Results
• Where do we go from here
  • Implications on treatment
  • Implications from other studies
Why Migraine

- Migraine prevalence
  - 4% of young children
  - Up to 10.5% of children age 5-15
  - Up to 28% age 15-19
  - Adults 12% (17.1% women, 5.6% men)
- Migraine pathophysiology
  - Migraine as a genetic disease
  - Early intervention may have lifetime implications

- Migraine Impact
  - Up to 200,000 lost school days in US
  - $17 billion (1998) direct and $17 billion indirect cost
  - Individual cost (2006)
    - Direct $127 to $5789
    - Indirect $709 to $4453
  - Chronic Mig vs Episodic Mig (2016)
    - CM – Direct ($5941), Indirect ($3200)
    - EM – Direct ($1705), Indirect ($594)
  - Pharma – CM ($3193), EM ($1296)
  - Potential progression to refractory headaches if not treated

Why Migraine – Global Burden of Disease


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
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

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Why
• Children and Adolescents are impacted by migraine
• There are significant gaps

Who
How
What
Where
Cincinnati Children’s Headache Center

• Established in Oct 1996
  • collaboration between neurology and psychology
• Combined Clinical and Research Program on Pediatric Headache
  • Local, Regional, National and International referral patterns
  • Over 700 different Zip Codes
  • 23 different states
  • Patients from North America, South America and Central America, Asia

A CCHMC partnership (Headache Center; Behavioral Medicine; Neurology; Office for Clinical and Translational Research)

A inter-institution collaboration (CCHMC – Clinical Coordinating Center & University of Iowa - Data Coordinating Center)

A national effort (involving over 40 sites)
CHAMP Study Staff

Principal Investigators
Andrew Hershey, MD, PhD, FAHS
Scott Powers, PhD, ABPP, FAHS
Christopher Coffey, PhD

Study Leadership Team
Linda Porter, MD, NINDS Project Manager
David Dodick, MD, Medical Safety Monitor
Leigh Ann Chamberlin, CCC Project Manager
Dixie Ecklund, DCC Project Manager
Leslie Korbee, CCC Regulatory Manager

*denotes sites that enrolled a participant.
• Why
  • Children and Adolescents are impacted by migraine
  • There are significant gaps
• Who
  • Cincinnati Children's, Univ of Iowa, NIH – NINDS and NICHD,
    • all of our sites.
• How
• What
• Where

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

Study Design

Real World Approach

• Subjects to reflect patients seen in typical headache, neurological and pediatric practice
• Subjects are children and adolescents, ages 8 to 17 years old
• Consistent headache frequency that indicates need for prophylaxis (>4 headaches per month)
• Standardized dosing of most commonly used preventative medication
  • AMI 1 mg/kg/day
  • TPM 2 mg/kg/day


Study Design

Primary and Secondary Outcomes

• Greater than 50% reduction in migraine frequency
• Absolute reduction in monthly migraine frequency
• Reduction in migraine disability
• Tolerability of drug therapies


Inclusion Criteria

1. Diagnosis: Migraine with or without aura (International Classification of Headache Disorders, 2nd Edition (ICHD-II) or chronic migraine (ICHD-III revision))
2. Frequency: Migraine frequency based upon prospective headache diary of 28 days must be ≥ 4. Migraine frequency defined as any migraine during one day in the 28-day baseline period*
   • Migraine frequency is defined as the period from the onset to the stop time of painful migraine symptoms not to exceed 24 hours with the clock starting at midnight. If painful symptoms last longer than 24 hours, this is considered a new and distinct migraine headache. If painful symptoms recur within 24 hours of initial onset, this is considered part of the initial migraine episode and would be counted as one migraine.
3. PedMIDAS: PedMIDAS Disability Score > 10, indicating at least mild disruption in daily activities and < 140, indicating extreme disability that may require more comprehensive, multi-component therapy
4. Age: Females or males 8-17 years, inclusive

Exclusion Criteria (1)

1. Continuous migraine defined as unrelenting headache for a 28 day period
2. Weight less than 30 kg or greater than 120 kg
3. Unwilling to avoid taking non-specific acute medications such as NSAIDs (e.g., ibuprofen), more than 3 times per week, or migraine specific acute medications such as triptans more than 5 times per month
4. Currently taking other prophylactic anti-migraine medication within a period equivalent to 2 weeks of that medication before entering the screening phase, or the use of Botulinum toxin (Botox®) within 3 months of entering the screening phase
5. Subjects who have previously failed an adequate trial of AMI or TPM for prophylaxis of at least 3 months duration at doses recommended for migraine relief because of lack of efficacy or adverse events
6. Current use of disallowed medications/products: opioids, antipsychotics, antianxiety, barbiturates, benzodiazepines, muscle relaxants, sedatives, tramadol, nutraceuticals, SSRI, or SSNRIs

Exclusion Criteria (2)

7. Known history of allergic reaction or anaphylaxis to AMI or TPM
8. Abnormal findings on ECG at baseline, particularly lengthening of the QT interval greater than or equal to 440 msec
9. Subject is pregnant or has a positive pregnancy test
10. Subject is sexually active and not using a medically acceptable form of contraception
11. Diagnosis of epilepsy or other neurological disease
12. History of kidney stones
13. Inability to swallow pills after using behavioral techniques if indicated between screening visit and baseline visit
14. Any and all other diagnoses or conditions which in the opinion of the site investigator, would prevent the patient from being a suitable candidate for the study or interfere with the medical care needs of the study subject

Subject Selection

• 675 subjects
• Migraine without or with aura by ICHD-II
• Frequency allows
  • Episodic (>4 headaches per month)
  • Chronic (>14 headaches per month)
• Continuous disallowed
• Ages 8-17 years
• Up to 40 research sites across the USA
Study Design

Flow of Events

- Dosage increases at 2 week intervals
- For standard titration, final dose starts at week 8
- Modification allowed for tolerability
  - Options
    - Hold dose (no maximum number)
    - Decrease dose (allowed once)
    - Resume titration as tolerated
  - If modification occurs, final dose starts at week 10

Termination Plan

Dosage Titration Plan
Definitions

• Headache Frequency
  • Headache Day – any headache in 24 hour period midnight to midnight
  • Headache Episode – any headache, start to headache free
• Migraine Day – any headache with ICHD Migraine characteristics in 24 hour period
  • Migraine Episode – any migraine from start to headache free

Primary Outcome

• A ≥ 50% reduction in headache frequency from the 4 week baseline period to the last 4 weeks of this 24-week trial
• Headache frequency is defined as the number of days with headache for a given 4 week period
• A 20 percentage point difference from placebo in this reduction effect is considered clinically meaningful by pediatric headache experts.

Secondary Outcomes

• Reduction in migraine disability score on PedMIDAS (Time Frame: end of the week baseline period to the last 4 weeks of the 24-week trial)
• Safety and tolerability of amitriptyline and topiramate (Time Frame: visit 2 until the last 4 weeks of the 24-week trial)
• Occurrence of treatment-emergent serious adverse events (Time Frame: visit 2 to the last 4 weeks of the 24-week trial)
• Reduction in absolute migraine frequency (Time Frame: 4 week baseline period to the last 4 weeks of the 24-week trial)
Simulation – Odds of significant result

<table>
<thead>
<tr>
<th>Decision (%)</th>
<th>Probability of Picking Water (%)</th>
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<tbody>
<tr>
<td>PROI Rate (%)</td>
<td>AMI Rate (%)</td>
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*If a single drug is "best," the correct answer is thought to be selected if the final decision is for either that drug or both drugs.


• Why
  • Children and Adolescents are impacted by migraine
  • There are significant gaps

• Who and Where
  • Cincinnati Children's, Univ of Iowa, NIH – NINDS and NICHD,
  • all of our sites.

• How
  • NIH sponsored, U01 – Multi-site study
  • Childhood and Adolescent Migraine Prevention Study - CHAMP

• What
• Where

Baseline Results

CHAMP results

• Primary - ≥ 50% reduction in headache frequency (day)
  • 28 days prior to randomization vs 28 days prior to end of treatment phase
• Secondary
  • Headache Disability – PedMIDAS, compare randomization to end of treatment
  • Tolerability – whether or not subject completed entire 24 weeks
• Additional Secondary
  • Absolute reduction in headache frequency
  • Side effects

CHAMP results – Consort

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
Primary (>50% distribution)

Results - Secondary

- PedMIDAS
- Tolerability

Secondary - Additional

- Headache Frequency
- Side Effects

CDI (Child Depression Index)
Baseline, Visit 5, Visit 8
CHAMP Results

- Simulations
- Follow-Up
  - 3, 6, 12 months
  - 18, 24, 36 months
- Genomics
  - RNASeq
  - DNASeq
- Adherence
- Trajectory
- Process
- Migraine Characteristics
- Predictors of response

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• What
  • Primary results – all three arms treated headaches, but no difference
  • Side effects in topiramate and amitriptyline, but not placebo
• Where

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?
Expectation of Response
Cormier et al, Pain 2016

Where do we go from here?
• What will you do Monday when you treat your headache patients?
• What are the other options?
• What does this say about the adult studies?

Thank you