Drug Discovery and Development: NICHD Investments

Council Sept 18, 2015

Anne Zajicek, MD, PharmD
Chief, Obstetric and Pediatric Pharmacology and Therapeutics Branch
Topics

• Drug Development and NICHD: Unmet Medical Needs
• Pediatrics
• Women
• Contraception
Omission

Choosing what to leave out.

BY JOHN MCPHEE
Children’s Participation in Research

Science + Advocacy + Pediatricians → Legislation

NOT Ethical → NOT Ethical NOT TO
Market Failure and the Poverty of New Drugs in Maternal Health


- After thalidomide and diethylstilboestrol, risk of teratogenicity has led to understandable caution in developing drugs for pregnancy and including women in clinical trials, but this has meant increased off-label use, with 75% of pregnant women taking at least one drug for which safety data are unavailable [2]. A greater problem is the dearth of drugs developed specifically for obstetric conditions.

- No new classes of drug have been developed for the big diseases of preeclampsia, fetal growth restriction, postpartum haemorrhage, and miscarriage [3,4]. The mainstays of the 2007 obstetric formulary (magnesium sulfate, α-methyldopa, hydralazine, β-blockers, aspirin, and nifedipine) hark back to an earlier era.
Table 2

Comparison of the Obstetric Drug Pipeline with that of a Mainstream Area (Cardiovascular) and that of a Neglected Disease (Amyotrophic Lateral Sclerosis)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Obstetric</th>
<th>Cardiovascular</th>
<th>ALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-clinical</td>
<td>3</td>
<td>303</td>
<td>16</td>
</tr>
<tr>
<td>Phase I</td>
<td>5</td>
<td>104</td>
<td>7</td>
</tr>
<tr>
<td>Phase II</td>
<td>5</td>
<td>163</td>
<td>7</td>
</tr>
<tr>
<td>Phase III</td>
<td>3</td>
<td>73</td>
<td>4</td>
</tr>
<tr>
<td>Pre-registration</td>
<td>1</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>17</strong></td>
<td><strong>660</strong></td>
<td><strong>34</strong></td>
</tr>
</tbody>
</table>

ALS, amyotrophic lateral sclerosis
Why NICHD is Developing Drugs: Unmet Medical Needs

• Lack of perceived financial incentive and risk for pharma
  ▫ Pediatrics
  ▫ Obstetrics
  ▫ Contraception
Branches Involved Include

- **Contraceptive Discovery and Development Branch**
- **Intellectual and Developmental Disabilities Branch**
- **Pregnancy and Perinatology**
  - Neonatal Research Network
  - Maternal-Fetal Medicine Units Network
- **Maternal and Pediatric Infectious Disease Branch**: registration trials for anti-retrovirals
- **Pediatric Trauma and Critical Illness Branch**: 
  - Collaborative Pediatric Critical Care Research Network (CPCCRN)
- **Obstetric and Pediatric Pharmacology and Therapeutics Branch**
  - Research in Pediatric Developmental Pharmacology Network
  - Obstetric Pharmacology Research Centers
  - Best Pharmaceuticals for Children Act: Pediatric Trials Network
Steps in Drug Development

- Target confirmed
- Hits identified
- Crystalize target protein
- Medicinal chemistry to optimize specificity
- Confirmation of activity in animal models
- Early Preclinical toxicology (genotoxicity, acute toxicity)
- GMP Chemical scale-up
- Clinical batch formulation
- IND preparation
- First in human clinical results
- GMP Large scale (kg) drug synthesis
- GMP Large scale clinical batch manufacture
- Repeat dosing → → clinical evaluation
Cooperative Research and Development Agreement (CRADA)

- Partnership between NIH and a pharmaceutical company to produce a commercially available product
- Timeline: 1981-2010 (FDA approval)
Obstetric and Pediatric Pharmacology and Therapeutics Branch

- Grants in basic pharmacology, development of drug targets
- Pre-clinical models of drug response
- Pharmacogenomics
- Small clinical trials
- Pharmacoepidemiology
- Formulations development
**Pediatric Legislation**

<table>
<thead>
<tr>
<th>Act</th>
<th>Key Points</th>
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<tbody>
<tr>
<td><strong>1997 FDA Modernization Act</strong></td>
<td>• 6 months additional exclusivity for pediatric studies</td>
</tr>
<tr>
<td><strong>2002 Best Pharmaceuticals for Children Act</strong></td>
<td>• 6 months additional exclusivity</td>
</tr>
<tr>
<td></td>
<td>• Role for NIH</td>
</tr>
<tr>
<td><strong>2003 Pediatric Research Equity Act</strong></td>
<td>• Pediatric study requirement for new drugs</td>
</tr>
<tr>
<td></td>
<td>• For same indication as in adults</td>
</tr>
</tbody>
</table>
Best Pharmaceuticals for Children Act

- **Section 409I**
  - Generally applicable to drugs *lacking* patent exclusivity
  - NIH responsibility:
    - Prioritization
    - Sponsorship of pediatric clinical trials
    - Submission of clinical trials data to FDA for consideration of label change
BPCA Prioritization

- Therapeutic gaps
- Potential health benefits of research
- Adequacy of necessary infrastructure

Consultation with experts in pediatric practice and research

Develop, prioritize, publish an Annual List of Therapeutic Areas and Specific Needs
Pediatric Trials Network
BPCA Labels

- Pralidoxime
- Propylthiouracil (black box - hepatic failure)
- Mercy TAPE Device (device to estimate body weight)
- Sodium Nitroprusside
- Meropenem - gestational age dosing
- Docket numbers assigned
  - lorazepam for status epilepticus (Exception from Informed Consent)
  - ampicillin
BPCA Progress

- 14 FDA submissions for 21 products
- Labels Anticipated 2016-17
  - Lisinopril
  - Lithium
  - **Hydroxyurea (NHLBI Baby HUG)**
  - Diazepam
  - Vincristine
  - Actinomycin-D
  - Isotretinoin (neuroblastoma)
  - Fluconazole
  - Acyclovir
Illustrative Cases
Does Dopamine Improve Blood Pressure in Premature Neonates?

Design: Factorial design comparing dopamine and hydrocortisone to increase blood pressure in premature infants with hypotension.

Question:
- BP a surrogate marker for clinical outcome in neonates?
Evolving blood pressure dynamics for extremely preterm infants

Gestational age-specific changes in the systolic (a), diastolic (b) and mean (c) arterial blood pressure 50th percentile curves over the first 24h.

FIGURE 3

Center variation in the rate of antihypotensive therapy administration, frequency of low BP, and incidence of hospital survival.
Do Anesthetics Cause Neurocognitive Problems in Children?

• What is normal neurocognition in children requiring surgery at an early age?
• How do you measure a change pre- and post-anesthesia?
• What are the key outcome measures?
• How is anesthesia exposure measured? Are there other confounding exposures occurring during anesthesia?
• Should neuroapoptosis findings pre-clinical models be extrapolated to humans?
How does Lorazepam Compare with Diazepam for Treating Pediatric Status Epilepticus?

• How do we get informed consent from parents in a medical emergency?
• Is it possible to pre-consent likely study patients?
• What is Exception from Informed Consent for Emergency Research? (21CFR 50.24)
• How do we implement community consultation?
• Is “not better” a failed study?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age 3 mo to &lt;3 y</th>
<th>Age 3 to &lt;13 y</th>
<th>Age ≥13 y</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diazepram</td>
<td>Lorazepam</td>
<td>Diazepram</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>48/72 (66.7)</td>
<td>38/62 (61.3)</td>
<td>44/55 (80.0)</td>
<td>49/60 (81.7)</td>
</tr>
<tr>
<td>Efficacy (per-protocol population)</td>
<td>35/48 (72.9)</td>
<td>32/48 (66.7)</td>
<td>36/43 (83.7)</td>
<td>44/50 (88.0)</td>
</tr>
</tbody>
</table>
Does Hydroxyurea Improve Clinical Outcomes in Young Children with Sickle Cell Disease?

- **Design:** RCT hydroxyurea vs placebo in children 9-17 months of age with a diagnosis of sickle cell disease
- **Outcomes:**
  - Kidney, spleen perfusion
  - Hospitalization, acute chest syndrome, pain crises, dactylitis
- **Formulation**
### Hydroxyurea Treatment Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
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<tbody>
<tr>
<td>1. Educate all patients with SCA and their family members about hydroxyurea therapy. <em>(See consensus treatment protocol on page 145).</em> <em>(Consensus–Panel Expertise)</em></td>
</tr>
<tr>
<td>2. In adults with SCA who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period, treat with hydroxyurea. <em>(Strong Recommendation, High-Quality Evidence)</em></td>
</tr>
<tr>
<td>3. In adults with SCA who have sickle cell-associated pain that interferes with daily activities and quality of life, treat with hydroxyurea. <em>(Strong Recommendation, Moderate-Quality Evidence)</em></td>
</tr>
<tr>
<td>4. In adults with SCA who have a history of severe and/or recurrent ACS, treat with hydroxyurea.* <em>(Strong Recommendation, Moderate-Quality Evidence)</em></td>
</tr>
<tr>
<td>5. In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life, treat with hydroxyurea. <em>(Strong Recommendation, Moderate-Quality Evidence)</em></td>
</tr>
</tbody>
</table>
| 6. In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia). *(Strong Recommendation, High-Quality Evidence for ages 9–42 months; Moderate Recommendation, Moderate-Quality Evidence for children >42 months and adolescents)*.  
Note: The panel intentionally used the term “offer” realizing that patients’ values and preferences may differ particularly considering treatment burden (e.g., laboratory monitoring, office visits), availability of drug in a liquid form, and cost. Therefore, the panel strongly encourages shared decisionmaking and discussion of hydroxyurea therapy with all patients. |

Does Betamethasone Reduce Respiratory Complications in Late Preterm Neonates?
Antenatal Late Preterm Steroids (ALPS)

**Aim:** To determine if ACS between $34^0 - 36^6$ weeks gestation with anticipated delivery in the late preterm period reduces need for neonatal respiratory support

**Design:** Double-masked placebo-controlled trial of antenatal corticosteroids vs placebo in late preterm period (34-37 weeks)

**Sample size:** 2,800 women
Antenatal Late Preterm Steroids (ALPS)

- Trial **halted November 2012** due to manufacturing problems
- **Finding pharmacy** with appropriate manufacturing and distribution licenses with the ability to manufacture placebo: **2 RFAs and 7 months**
- Another **5 months** to work out a **formula for the placebo** (the placebo used by the previous pharmacy was not stable in large batch)

- Trial was restarted in **November 2013**
- Recruitment ended 6/2015: **2,831**
Does Oxytocin Improve Behavior in Children with Autism?

Study of Oxytocin in Autism to improve Reciprocal Social Behaviors (SOARS-B)

Figure 2: SOARS-B Study Design

- SCREEN
- PHASE 1: DOUBLE-BLIND
- PHASE 2: OPEN TRMT
- PHASE 3: FU

Min 142 w/Low-functioning
Min 142 w/High-functioning
Screen
Stratified Randomization

*Indicates genetic sample taken. Primary outcome assessed at bolded time points.
SOARS-B Study

• Outcome measures in children
  ▫ Aberrant Behavior Checklist-Social Withdrawal subscale (ABC-SW): parent reported questionnaire focusing on the core social and communication symptoms of autism

• Importation of oxytocin and manufacturing of nasal spray
  ▫ Device
  ▫ Drug
    • Placebo
    • Active drug
Quantitative Measures of Success

• Publications
• Practice guidelines
• Labels

• Commercially available products: need for NIH CRADA with a manufacturer
Other Measures of Success

- A wider range of validated pediatric and obstetric outcome measures in various therapeutic areas
- More studies successfully completed, with full recruitment and statistical power, and auditable and replicable data
Issues

- Disconnect between basic and clinical pharmacology
  - Need for development of *clinically relevant* drug targets
  - Mechanisms of on-target vs off-target effects, particularly in OB (malformations)
- Need for rationale for extrapolation from
  - *in vitro/pre-clinical models to humans*
  - *juvenile animals to children*
  - *adults to children*
- Need for clinically relevant outcome measures
  - Agreed-upon normal values
  - Short- vs long-term outcomes
Issues (continued)

- Need for COG-like model of patient care, with opt-out clinical trial enrollment for observational and interventional studies
- Shortage of trained physicians capable of designing and performing regulatory-level clinical trials (T32)
- Need for investigator understanding and implementation of
  - Good Clinical Practice
  - Good Laboratory Practice
  - Good Manufacturing Practice
- Need for new clinical trial designs for small populations, incorporating validated database/electronic health records data
- Need for formulations
  - Clinical-trial specific formulations manufacturing
  - Flexible, palatable, easy to swallow dosage forms
Questions?