Drug Discovery and Development: NICHD Investments

Council Sept 18, 2015

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Topics

- Drug Development and NICHD: Unmet Medical Needs
- Pediatrics
- Women
- Contraception

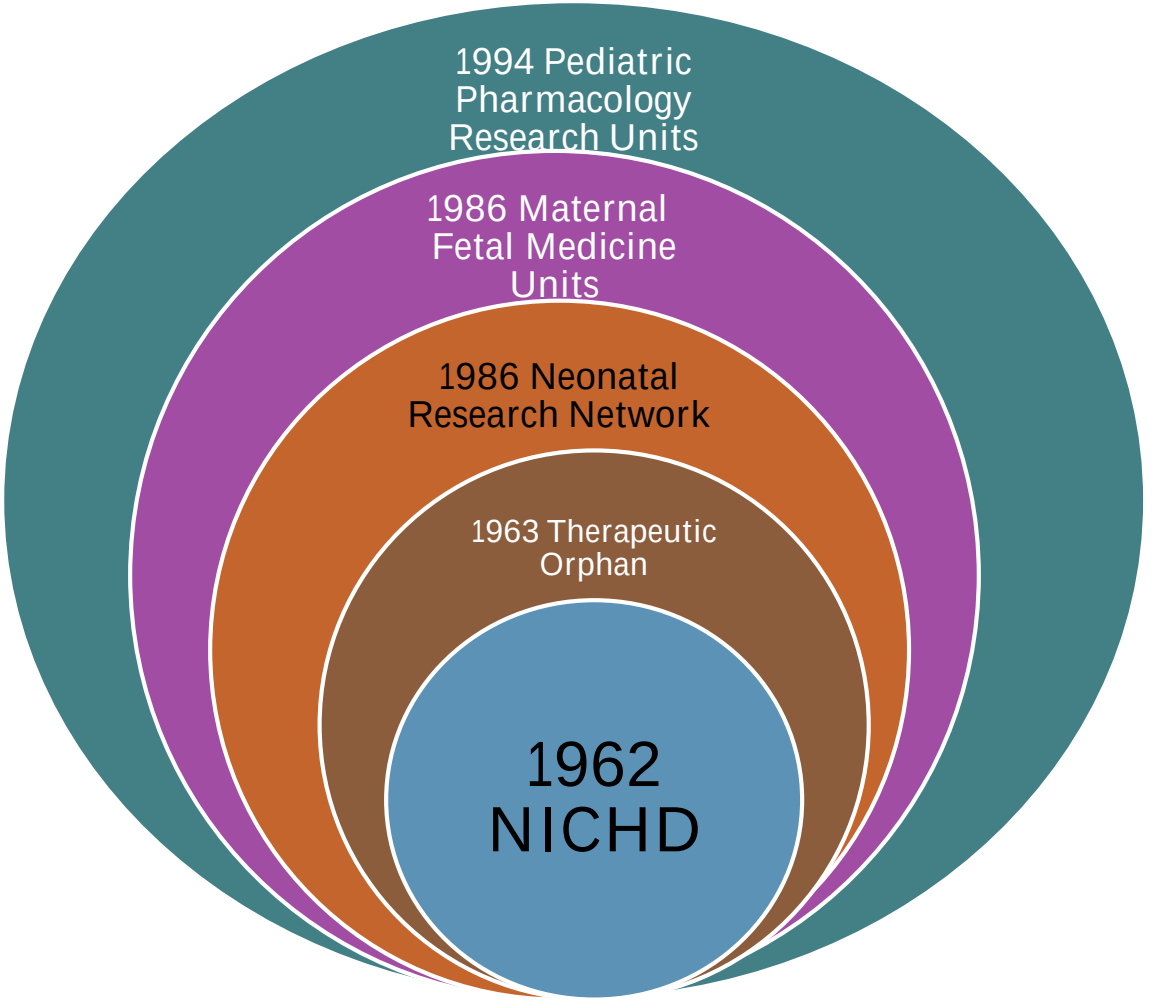
The Writing Life | SEPTEMBER 14, 2015 ISSUE

Omission

Choosing what to leave out.

BY JOHN MCPHEE

NICHD Timeline



Children's Participation in Research

NOT Ethical → NOT Ethical NOT TO

Market Failure and the Poverty of New Drugs in Maternal Health

Nicholas M Fisk* and Rifat Atun. PLoS Med. 2008 Jan; 5(1): e22.

- 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

PMC full text: PLoS Med. 2008 Jan; 5(1): e22.
Published online 2008 Jan 22. doi: 10.1371/journal.pmed.0050022

Table 2

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

Indication	Obstetric	Cardiovascular	ALS
Pre-clinical	3	303	16
Phase I	5	104	7
Phase II	5	163	7
Phase III	3	73	4
Pre-registration	1	17	0
Total	**17**	**660**	**34**

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

1997 FDA Modernization Act

- 6 months additional exclusivity for pediatric studies

2002 Best Pharmaceuticals for Children Act

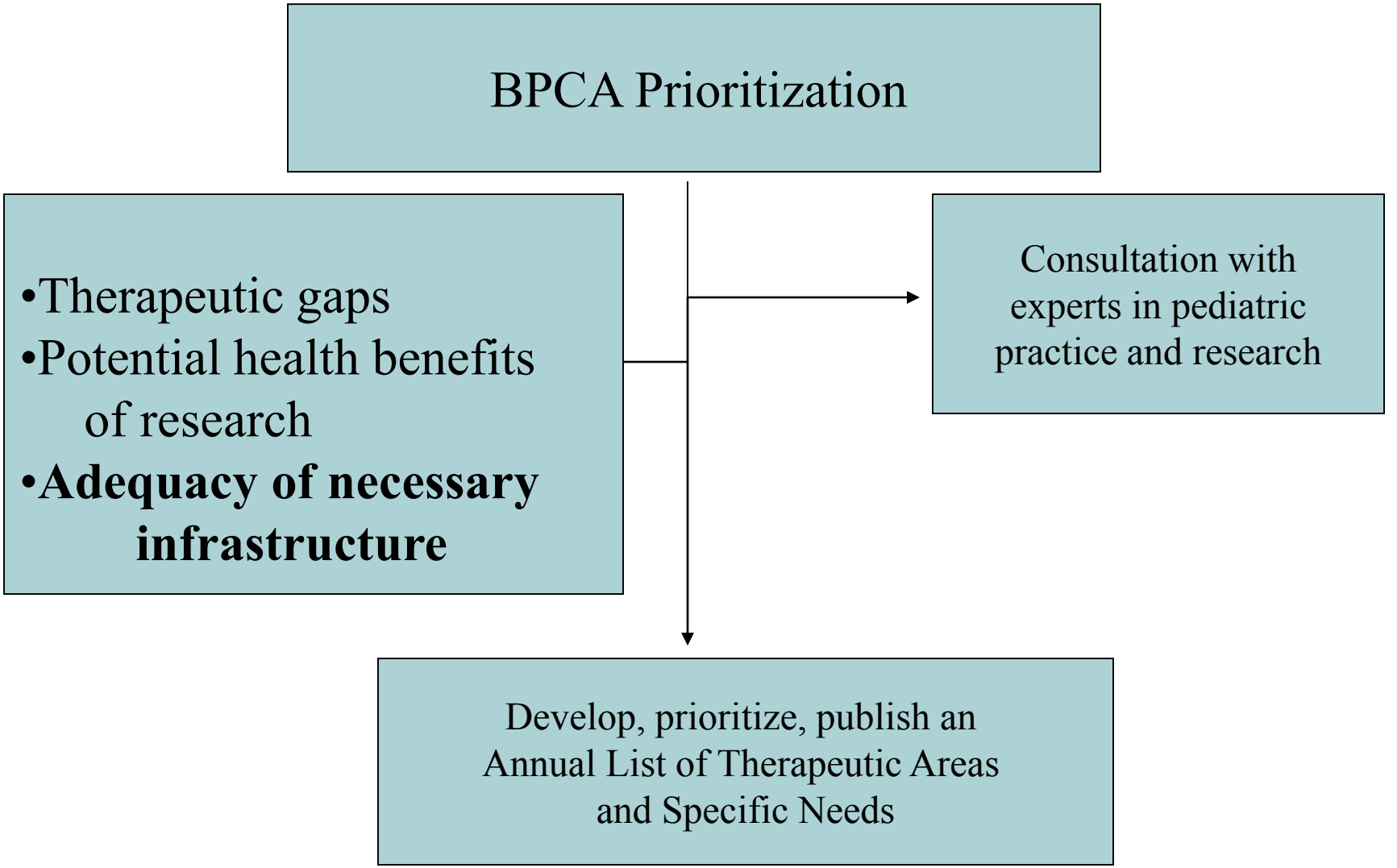
- 6 months additional exclusivity
- Role for NIH

2003 Pediatric Research Equity Act

- Pediatric study requirement for new drugs
- For same indication as in adults

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

http://www.cpj.ca/content/depth-global-economic-crisis-peeling-onion

Does Dopamine Improve Blood Pressure in Premature Neonates?

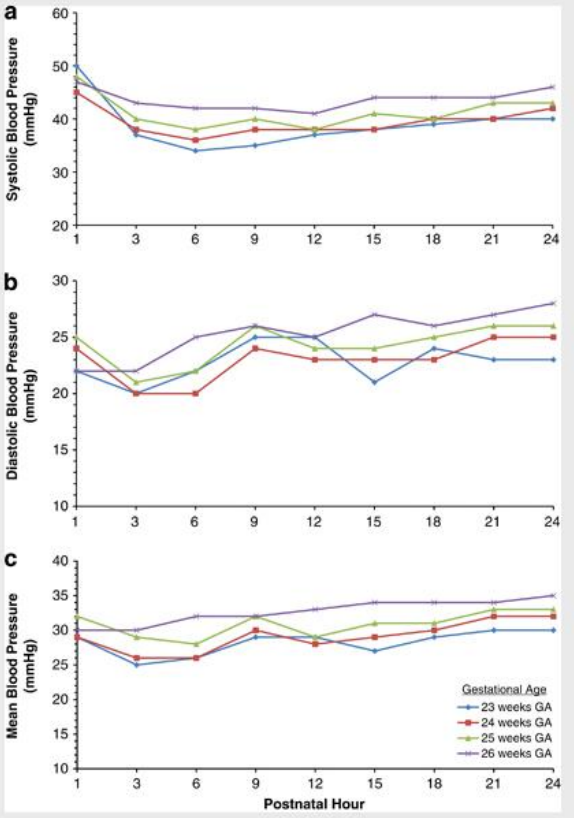
Design: Factorial design comparing dopamine and hydrocortisone to increase blood pressure in premature infants with hypotension.

Question:

- BP a surrogate marker for clinical outcome in neonates?

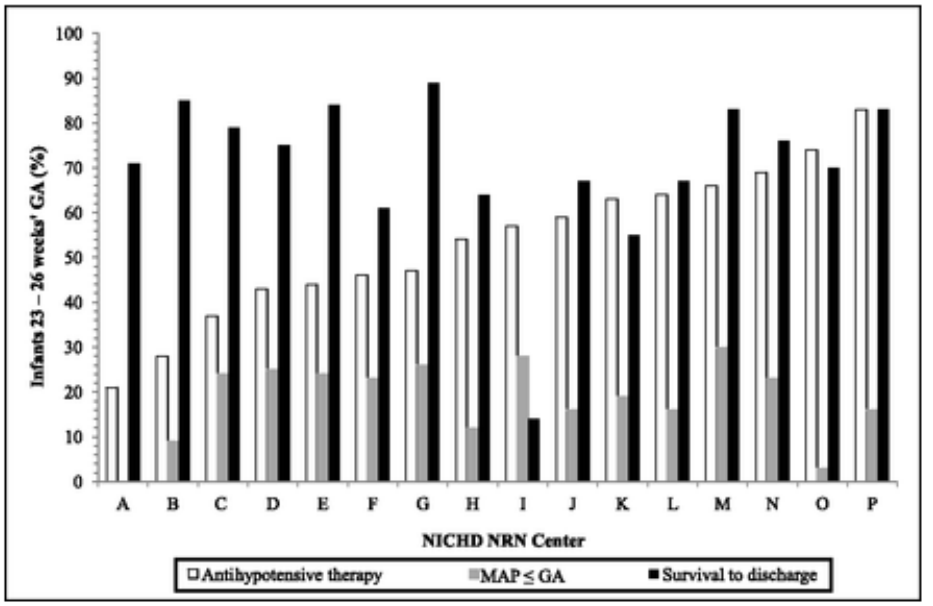
Evolving blood pressure dynamics for extremely preterm infants

B Batton, L Li, N S Newman, A Das, K L Watterberg, B A Yoder, R G Faix, M M Laughon, B J Stoll, R D Higgins and M C Walsh for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. J Perinatol 2014; 34:301-305.



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

Use of Antihypotensive Therapies in Extremely Preterm Infants. Batton B, Li L, Newman NS, Das A, Watterberg K, et al, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Pediatrics 2013; 131(6):e1865-73.



View larger version:

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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?**

Lorazepam vs Diazepam for pediatric status epilepticus: a randomized trial. Chamberlain JM, Okada F, Holsti M, Mahajan F et al. JAMA 2014; 311(16): 1652-60.

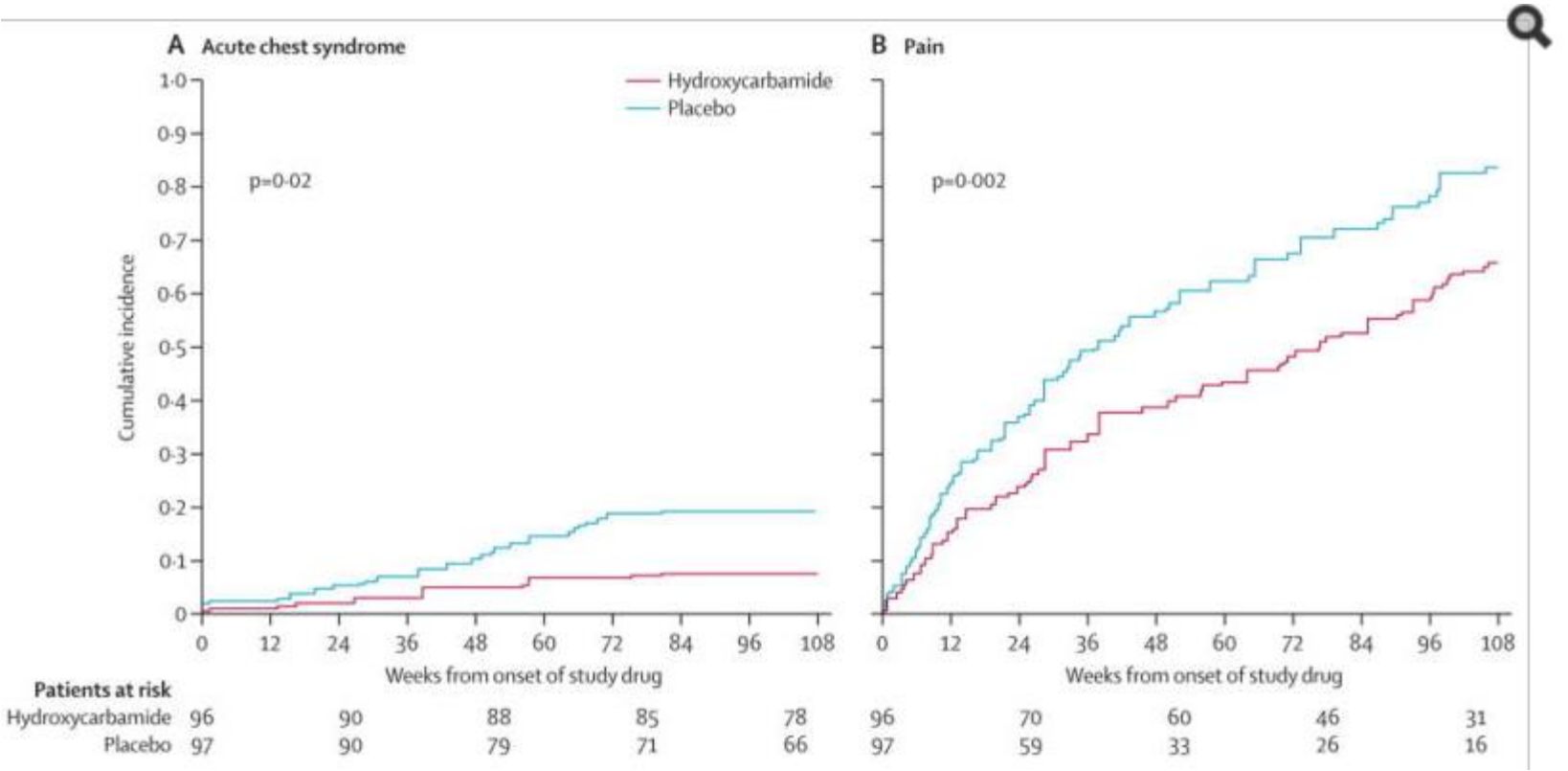
Table 3. Primary and Secondary Efficacy and Safety Outcomes[a]

	No./Total No. (%)							
	Age 3 mo to <3 y		Age 3 to <13 y		Age ≥13 y		Overall	
Outcome	Diazepam	Lorazepam	Diazepam	Lorazepam	Diazepam	Lorazepam	Diazepam	Lorazepam
Primary Outcomes								
Efficacy	48/72 (66.7)	38/62 (61.3)	44/55 (80.0)	49/60 (81.7)	9/13 (69.2)	10/11 (90.9)	101/140 (72.1)	97/133 (72.9)
Efficacy (per-protocol population)	35/48 (72.9)	32/48 (66.7)	36/43 (83.7)	44/50 (88.0)	7/11 (63.6)	9/9 (100.0)	78/102 (76.5)	85/107 (79.4)

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

Hydroxycarbamide in very young children with sickle cell anaemia: a multicenter, randomised, controlled trial (BABY HUG). Wang WC, Ware RE, Miller ST, et al. The Lancet 2011; 377 (9778): 1663-1672.



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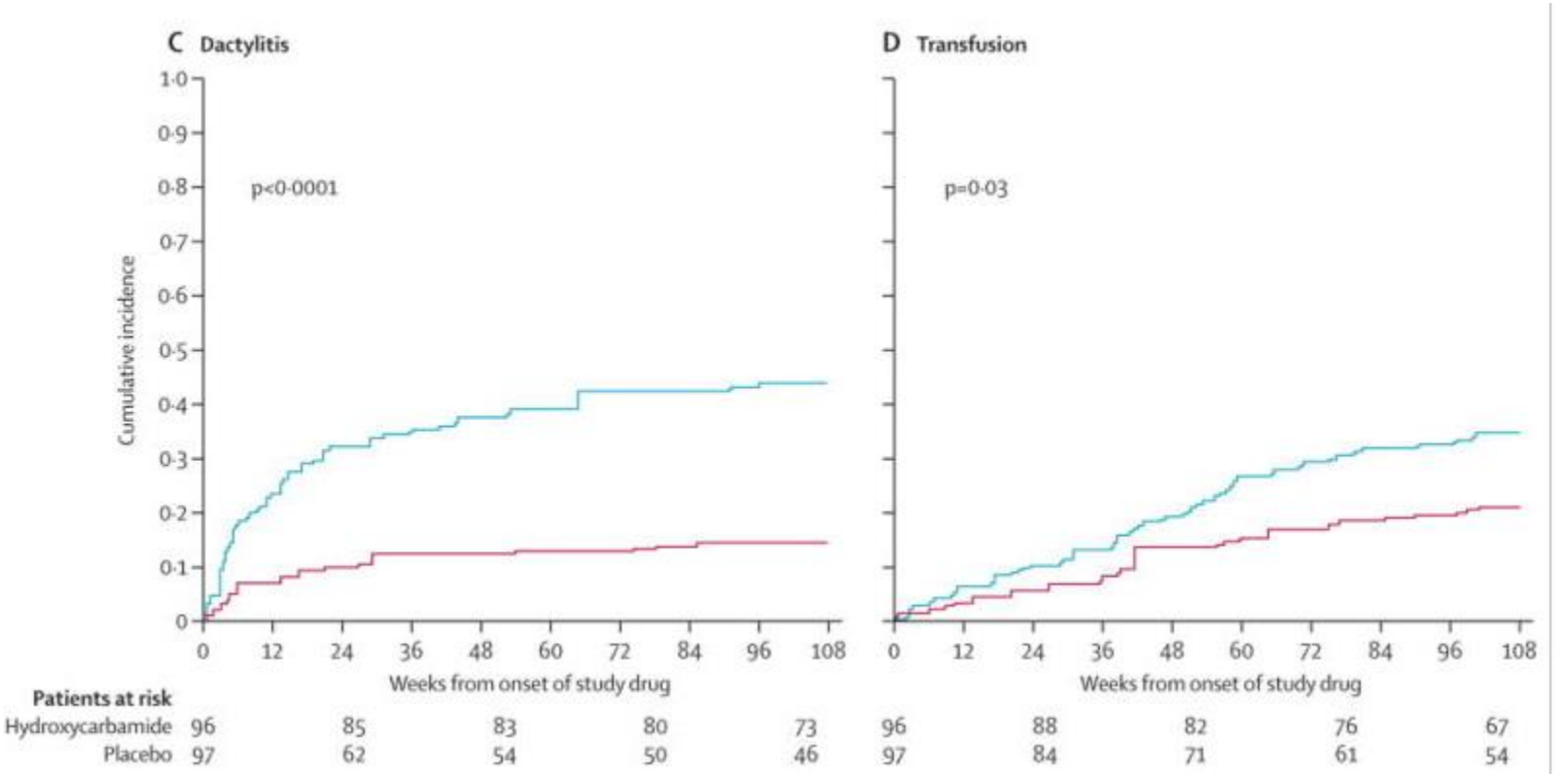
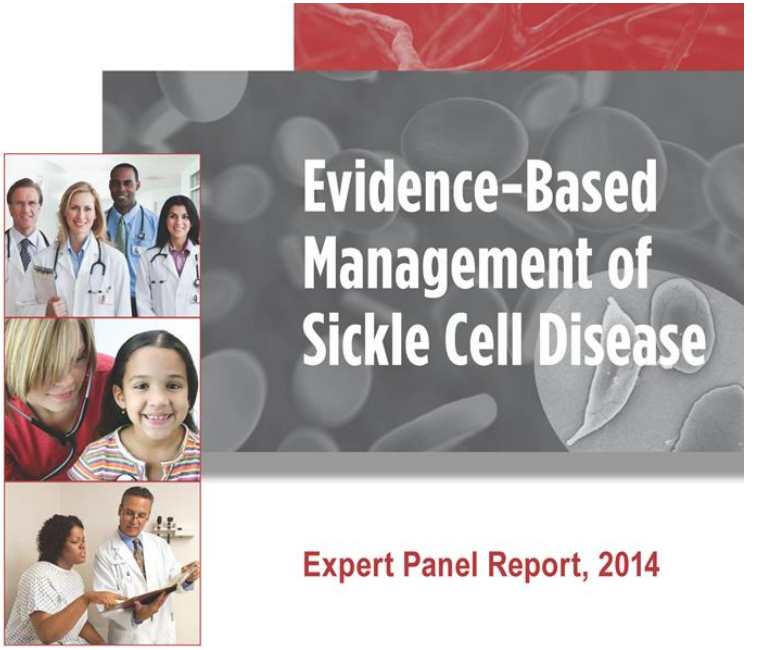




https://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines

Hydroxyurea Treatment Recommendations

Recommendations
1. Educate all patients with SCA and their family members about hydroxyurea therapy. (See consensus treatment protocol on page 145). **(*Consensus–Panel Expertise*)**
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. ***(Strong Recommendation, High-Quality Evidence)***
3. In adults with SCA who have sickle cell-associated pain that interferes with daily activities and quality of life, treat with hydroxyurea. ***(Strong Recommendation, Moderate-Quality Evidence)***
4. In adults with SCA who have a history of severe and/or recurrent ACS, treat with hydroxyurea.* ***(Strong Recommendation, Moderate-Quality Evidence)***
5. In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life, treat with hydroxyurea. ***(Strong Recommendation, Moderate-Quality Evidence)***
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.

https://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines

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

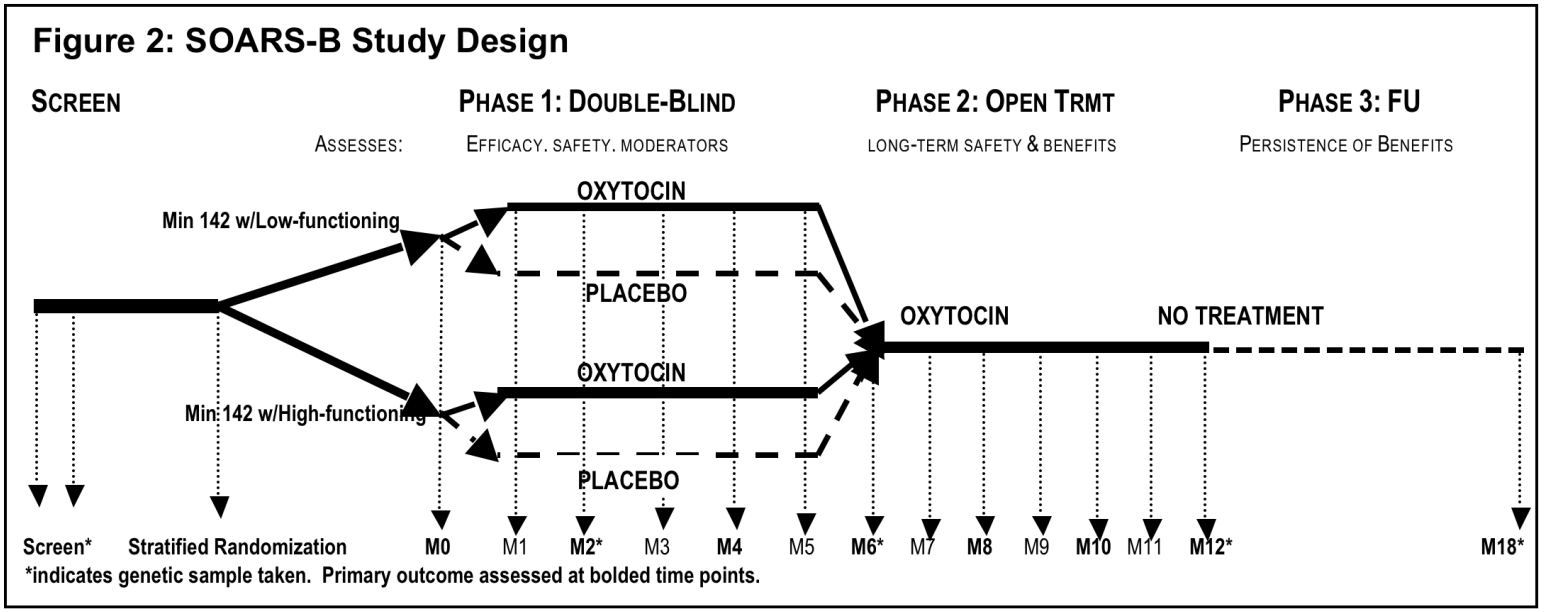
Antenatal Late Preterm Steroids (ALPS)

- 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 **O**xytocin in **A**utism to improve **R**eciprocal **S**ocial **B**ehaviors (**SOARS-B**)



SOARS-B Study

- Outcome measures in children
  - **A**berrant **B**ehavior **C**hecklist-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?