

**National Institute of Child Health and Human Development  
National Institutes of Health  
BPCA Annual Prioritization Meeting  
December 5–6, 2006  
Marriott Bethesda North Hotel and Conference Center  
Bethesda, MD**

This annual meeting was sponsored by the Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (DHHS).

**DAY 1**

**Introductions**

*Donald R. Mattison, M.D., Captain, U.S. Public Health Service; Senior Advisor to the Directors of NICHD and CRMC; Chief, OPPB, CRMC, NICHD, NIH, DHHS*

Dr. Mattison welcomed the participants to the fifth annual Best Pharmaceuticals for Children Act (BPCA) prioritization meeting, and he thanked them for their roles in implementing BPCA. This year has been a watershed year for the project, which sunsets at the end of fiscal year 2007. In the past annual meetings, participants developed lists of drugs that could be studied and discussed changes in the formulations of pediatric drugs. NICHD, together with the Food and Drug Administration (FDA), established a series of drug priorities. Preclinical and clinical trials have been implemented to study many of these drugs. This meeting presents progress reports on these studies, addresses gaps in pediatric therapies, and describes alternative approaches to treating pediatric conditions. The early phase of BPCA implementation focused on specific drugs. The new phase has shifted to a disease-based approach. BPCA will focus on the frequency of pediatric conditions and determine those that most frequently bring children into the health care system. This new approach will also focus on the drugs that are most frequently prescribed to treat pediatric conditions. The goal of these efforts is to provide a snapshot of the pediatric drugs used in order to develop a comprehensive view of pediatric therapeutic needs, with the ultimate goal of appropriate labeling for the safe and efficacious use of pediatric drugs. This meeting describes the progress in achieving these goals, as well as opportunities for additional studies and future needs.

**Welcome**

*Duane Alexander, M.D., Director, NICHD, NIH, DHHS*

Dr. Alexander welcomed the meeting participants and thanked them for their advice, wisdom, and involvement in BPCA. He acknowledged the hard work of NICHD and FDA representatives and experts in pediatrics and pediatric research. This meeting is a landmark event because of the change in BPCA methodology and new approach to prioritization. BPCA activities began by developing a list of drugs prioritized by their importance in treating pediatric diseases and conditions. The importance of the listed drugs was based on expert opinion. In its new approach

to prioritization, BPCA will assess the frequency of pediatric conditions and the frequency of drugs prescribed for these conditions. This assessment will be empirically based and will focus on both on- and off-patent drugs. BPCA is entering the fifth year of its legislative mandate, and the project will sunset if the legislation is not reauthorized. How BPCA can or should be modified under renewed legislation is already being discussed. Those involved in these discussions recognize the achievements so far and the continuing benefits of this important program. The topics presented at this annual meeting are of enormous interest to all who are concerned with child health, and the study updates demonstrate the tremendous progress made in BPCA's first 4 years. This progress would not have been possible without the valuable advice and contributions of the pediatric experts and NICHD and FDA personnel involved with BPCA.

### **Goals for the Meeting**

*Perdita Taylor-Zapata, M.D., Pediatric Medical Officer, OPPB, CRMC, NICHD, NIH, DHHS*

Dr. Taylor-Zapata briefly reviewed the history of BPCA, including the history of the priority list of off-patent drugs and the prioritization process for these drugs. Prioritization was based on frequency of drug use, severity of disease condition, and health benefit of the drug. The priority list of off-patent drugs evolved from the BPCA legislation, which directed the Secretary of the DHHS, acting through the Director of the NIH and in consultation with the Commissioner of the FDA and experts in pediatrics and pediatric research, to develop and prioritize a list of "off-patent" drugs for which pediatric studies are needed. The Director of NIH delegated to the Director of NICHD, the authority and responsibility to establish and conduct pediatric drug development activities as set forth in the legislation. The activities within BPCA for drug development fall into three general categories: (1) identifying those drugs needing study; (2) submitting written requests from the FDA to the drug manufacturers; and (2) conducting pediatric studies deemed necessary for those drugs as directed by the written requests and if manufacturers decline to do these studies, referring the drug to NIH to conduct the necessary studies. The initial list was published in the January 2003 *Federal Register* and was updated in August 2003.

Upon review of the BPCA listing process, and after the results of outreach to experts, NICHD in consultation with FDA, began to modify the prioritization process to a condition- or therapeutic class-based approach for 2006–2007. This approach allows comparisons of drugs within a therapeutic class (on- and off-patent) and gives a broader description for the availability and use of these drugs in children. It also allows BPCA to obtain focused expertise in therapeutic areas that will subsequently provide more insight into feasibility and study designs. From the advice of pediatric experts at the scientific meeting in November 2005, along with the outreach conducted by NICHD, the prioritization working group:

- Discussed and recommended drugs and conditions for listing in 2006
- Developed an extensive list of organizations and experts to receive information about the process and to provide input
- Contacted several experts in the respective fields of interest to obtain input on the scientific gaps in knowledge
- Incorporated information on issues such as the frequency of use of off-labeled and off-patent drugs in pediatrics and issues surrounding study design in pediatric drug trials.

Dr. Taylor-Zapata listed the following goals for this 2006–2007 prioritization meeting:

- Provide updates on currently funded projects
- Describe outreach outcomes
- Review projects developed under BPCA
- Review current conditions and drugs under consideration for priority listing
- Discuss future directions for BPCA.

Issues and challenges to consider include:

- What is our ultimate goal?
  - Improving pediatric therapeutics and the advancement of science
  - Need more dialogue on what is acceptable for a label change
- How do we determine the best approach for studying a drug and/or condition?
  - Is there the role for on-patent drugs? Head-to-head comparisons?
- Once a drug, condition, or indication is determined, how do we prioritize which drugs in that particular category are important?
  - What is the health impact (frequency of disease, severity of disease)?
  - Are there feasibility issues?
  - Role of NIH institutes, centers, and initiatives
  - Role of experts and outreach
- How do we determine which drugs, conditions, and indications are important to study and translate study findings into label changes?

These are some of the questions to consider for the current and future implementation of BPCA.

## **Updates of BPCA Preclinical and Clinical Studies**

### **Use of Oral Baclofen for Treatment of Spasticity of Cerebral Palsy in Children: Baclofen Efficacy and Safety Trials (BEST)**

*Janice Brunstrom, M.D., Director and Assistant Professor, Pediatric Neurology Cerebral Palsy Center, Washington University School of Medicine*

There is a need for improved use of baclofen in children with cerebral palsy (CP):

- Oral baclofen is widely used for the treatment of spasticity in children with CP.
- No standardized dosing strategy (starting doses, rates of escalation, maximal doses)
- Very little published pharmacokinetic (PK) or pharmacodynamic (PD) data in children
- Heterogeneous patient population
- Adverse events do matter.

CP is more than just a motor disorder. It includes:

- Abnormal control of movement and posture
- Nonprogressive brain injury of early onset
- Abnormal tone (e.g., hypertonia, spasticity, dystonia)
- Persistent primitive reflexes (startle, tonic neck reflex)
- Disuse atrophy of muscles

- Secondary deformities (e.g., bony torsion, hip dislocation, muscle contracture, scoliosis)
- Variable presentations (e.g., CP subtypes, functional ability).

Other difficulties in children with CP include problems with vision; hearing; epilepsy; speech and language; swallowing and drooling; respiratory infections including pneumonia; poor feeding, malnutrition, and growth failure; bowel and bladder impairments; impaired bone metabolism, osteopenia, and fractures; learning difficulties and school troubles; emotional and behavioral issues; and pain. BEST includes three phases:

- Phase 1 (months 1–12)
  - Retrospective chart review of safety study
  - Pediatric pharmacokinetic study
- Phase 2 (months 13–28)
  - Randomized control trial for efficacy and safety
- Phase 3 (months 29–52)
  - Safety follow-up study.

The goals of the retrospective chart review of safety study of phase 1 are to:

- Describe the characteristics of the pediatric population using oral baclofen to manage the spasticity of CP
- Estimate the subject population size needed to result in a sample of 100 children using oral baclofen continuously for 1 year or more (in preparation for the safety study)
- Describe the safety and effectiveness of oral baclofen in 200 pediatric subjects with CP (under the assumption that this will include 100 subjects on oral baclofen for 1 year)
- Describe treatment course and reason for treatment changes (from oral baclofen to other therapies, additional therapies, etc.), withdrawal, and adverse events (AEs) associated with treatment and withdrawal
- Provide any information detailed in the charts that may support the effectiveness of oral baclofen for reducing spasticity and improving function or care, and that can be used to help guide development of the randomized control trial for safety and efficacy (phase 2)
- Provide any information detailed in the charts regarding subject characteristics that may help distinguish subjects who respond favorably to oral baclofen from those subjects who do not respond favorably (i.e., characteristics that may correlate with increased risk of side effects or increased risk of no improvement on baclofen) in preparation for the safety and efficacy trial.

The design of the retrospective chart review of safety study of phase 1 is as follows:

- Subjects with CP ages 2–16 years while receiving oral baclofen who have been followed at the study site for at least 1 year
- Approximately 200 subjects
- Seven study sites
- Start date: November 27, 2006
- Estimated finish date: March 2007
- Data collection timeframe
  - Minimum = 1 year of data
  - Maximum = 5 years of data

- Prebaclofen data: up to 6 months before start of oral baclofen
- Baclofen data: entire time on oral baclofen up to 4.5 years or until November 27, 2006
- Postbaclofen data
  - Up to 6 months after discontinuation or start of taper withdrawal
  - For subject treated with oral baclofen for <4.5 years who stopped taking oral baclofen prior to the start date of the chart review study
- Chart review data elements
  - Inclusion/exclusion
  - Demographics
  - Medical, surgical, seizure history
  - Prior medications
  - Comorbid conditions (e.g., kidney, bladder, oral motor, gastrointestinal [GI] motility, gastroesophageal reflux disease)
  - Diagnostic studies: imaging, electroencephalograms (EEGs)
  - Motor disorder: GMFS, MACS, spasticity, dystonia, limbs affected, and severity
  - Concomitant medications (e.g., tone, seizures, GI, behavior, renal)
  - Concomitant surgery, therapies
  - Positive events (e.g., reduced spasm or pain; improved sleep, bladder control, feeding tolerance, ease of movement, speech, tremor, clonus)
  - Oral baclofen dosing data
  - Laboratory data: renal function, liver, other
  - Negative events on baclofen or during baclofen taper or after stopping baclofen (e.g., seizures, weakness, confusion, hypertonia, urinary retention)
  - Retrospective AEs.

The goals of the pediatric PK study of phase 1 are to determine (1) the PK of oral baclofen in pediatric patients and investigate the relationship between plasma concentrations of oral baclofen and clinical measures of spasticity and (2) the optimal dose range and interval for administration of oral baclofen for the use in the randomized clinical trial (RCT) of efficacy and safety.

The design of the pediatric PK study is as follows:

- 84 subjects recruited from seven sites
- Open label, multiple dose, ascending dose trial
- Three age groups: 2–6 years, 7–11 years, 12–16 years
- 2.5 mg TID up to 20 mg TID or QID (or to maximum tolerated dose)
- Biweekly pharmacodynamic assessments during escalation phase
- Pharmacokinetic evaluation at steady state after reaching maximum tolerated dose or assigned dosage level (PK on blood and urine along with PD measurements at specific times before and after dose)
- PD measures: spasticity, pain, sedation, physiological parameters (e.g., heart rate, blood pressure, respiratory rate, pulse oximetry), range of motion testing, strength testing, and video assessments.

Characteristics of the randomized control trial for efficacy and safety (phase 2) are as follows:

- Study purpose
  - Evaluate the efficacy of oral baclofen in children under age 16
  - Describe safety, AEs, and withdrawal experience in children under age 16 using oral baclofen for spasticity of CP
- Primary outcomes
  - Spasticity
  - Gross and fine motor function
- Secondary outcomes
  - Dystonia
  - Strength, balance, endurance
  - Health-related quality of life for child and caregiver
- Study design
  - Double-blind randomized crossover trial (baclofen versus placebo or comparator)
  - 10 weeks each arm
  - Adequate taper and wash out periods
  - Safety assessments every 1–2 weeks by telephone interview or in person (e.g., sedation, seizures, cognitive or behavioral changes, renal toxicity).

The safety follow-up study of phase 3 will describe neurodevelopmental outcomes after 1 year of continuous treatment with oral baclofen for spasticity of CP.

### **BPCA Off-Patent Drug Study—Lithium for the Treatment of Pediatric Mania: Collaborative Lithium Trials (COLT)**

*Robert Findling, M.D., Director, Division of Child and Adolescent Psychiatry, University Hospitals of Cleveland, Case Western Reserve University*

A series of pediatric lithium studies is needed because:

- Lithium is one of the most widely used treatments for bipolar disorder in adults.
- Although investigations over the years have served to further document the efficacy of lithium in the treatment of adult bipolar disorder, its efficacy and safety in youths has not been established.
- Although FDA “grandfathered” the indication of lithium for bipolar disorder in children who are 13 years and older, there are no studies to support such an indication for lithium in pediatric mania.
- Despite its role as one of psychiatry’s most important treatments, there is not even a single placebo-controlled trial of lithium for the treatment of mania in children and adolescents, despite an acute need to find effective treatment for this devastating illness.
- Therefore, it is imperative to test lithium’s efficacy and safety in pediatric bipolar.

A request for proposals (RFP) was issued in February 2005 for a study of lithium in the treatment of pediatric mania, and the contract was awarded in September 2005. As outlined in the written request, the key objectives of the study include:

- Development of evidence-based dosing strategies for lithium in children and adolescents

- A thorough characterization of the pharmacokinetics/biodisposition of lithium in pediatric patients
- A randomized, placebo-controlled study that will examine the acute efficacy of lithium in children and teenagers with mania
- A randomized trial that will examine the efficacy of lithium as a maintenance treatment for children and adolescents with bipolar 1 disorder
- A meticulous and comprehensive characterization of short- and long-term safety of lithium in children and adolescents.

The COLT group was developed to meet the goals delineated in the written request, RFP, and statement of work. The goals are to comprehensively study lithium in pediatric mania leading to labeling changes. The COLT team consists, in part, of eight academic sites, each with unique strengths. The COLT group will ensure the successful implementation and execution of the studies in a timely fashion. Expected average enrollment is at least one subject per site per month. Several factors were considered in choosing the COLT sites:

- **Expertise in clinical trial design and execution.** All COLT sites have a demonstrated/established track record of expertise and of successful recruitment of children and adolescents with serious psychiatric illnesses into RCTs. The expertise of all of the COLT principal investigators (PIs) will ensure that the studies are performed in a methodologically rigorous manner and that only diagnostically appropriate youths participate in these studies.
- **Safety.** Each of the COLT site PIs has demonstrated expertise and experience in the management of pediatric patients with symptoms of mania under the auspices of clinical trials. Children and adolescents with mania may have safety considerations related to aggressive behavior and suicidality. Therefore, as a result of having only expert physicians serve as COLT PIs, the risk to subjects will be minimized.
- **Academic accomplishment.** All COLT PIs are generally acknowledged to be scientific leaders in child and adolescent psychiatry. All COLT PIs have numerous peer-reviewed publications. All have NIH funding for bipolar disorder or clinical trial research in the seriously mentally ill pediatric population.
- **Collaboration.** The COLT team has demonstrated its ability to work collaboratively based on the weekly and twice weekly telephone conferences that were held in order to prepare for this proposal. The COLT PIs have all worked together on one or more previous projects:
  - Pediatric Bipolar Collaborative Mood Stabilizer Trial (PBC)
  - Treatment of Early Onset Schizophrenia Spectrum Disorder (TEOSS)
  - Divalproex Sodium and Risperidone in Pediatric Bipolar Disorder
  - Stanley Medical Research Institute Early Intervention Initiative (EII).

To comprehensively examine lithium in the treatment of pediatric patients, a series of two inter-related, multiphase studies will be conducted. These studies were tailored to specifically collect the data requested in the solicitation materials from the NICHD in a safe, ethical, and methodologically rigorous fashion. Dr. Findling presented detailed algorithms depicting the designs of COLT Study 1 and COLT Study 2. There are several unique opportunities in these studies:

- Psychometrics
  - Assessment domains are broad
    - Mood, aggression, anxiety, family functioning/family burden
    - Suicidality
  - Instrument development
    - Child Mania Rating Scale
- InstaRead System assessment
- Psychosocial intervention
  - Effectiveness
- Neuropsychological testing
  - Cognitive effects
- Adjunctive medications
  - Effectiveness and safety.

COLT somatic safety assessments include the following:

- Chemistry profile: sodium, potassium, chlorine, carbon dioxide, blood urea nitrogen (BUN), creatinine, and random glucose
- Complete blood count (CBC) with differential
- Prothrombin time (PT)/partial thromboplastin time (PTT) and fibrinogen
- Lithium serum level
- Red blood cell/plasma lithium ratio
- Urine toxicology screen
- Urinalysis
- Thyroid function tests/thyroid antibodies
- Renal function tests
- Serum pregnancy test
- Pregnancy and lithium
- Electrocardiogram (ECG)
- EEG
- Physical examination.

COLT AE assessments include:

- Subjects and their guardians will be directly queried about the presence of AEs or outcomes throughout the COLT trials.
- First step: spontaneous reporting as the result of open-ended queries about the development of AEs
- Second step: proactive elicitation methods
  - Side Effects Form for Children and Adolescents (SEFCA; Klein and Slomkowski, 1993) supplemented by specific items from the UKU Side Effect Rating Scale (Lingjærde et al., 1987) and the Safety Monitoring and Uniform Report Form (SMURF) (Greenhill et al., 2004) in order to elicit AEs from subjects and their families.



## Use of Lorazepam for the Treatment of Pediatric Status Epilepticus: Preliminary PK Results

*James Chamberlain, M.D., Chief, Division of Emergency Medicine, Children's National Medical Center*

Lorazepam is the preferred drug to treat seizures. Its use in adults may be safer than its use in children, but there is no safety data for children. In this presentation, Dr. Chamberlain provided preliminary PK results of a study comparing pediatric patients with and without status epilepticus and introduced a second study to compare lorazepam and diazepam treatment for seizures. Both studies involved research in emergency department (ED) settings. The challenges to ED research are the chaotic and unpredictable clinical environment and obtaining informed consent. The purpose of study 1 was to determine lorazepam PK in pediatric patients with and without status epilepticus. The study design was as follows:

- Cohort 1: pediatric patients with status epilepticus receiving lorazepam for clinical indication
  - 1A: preconsented from neurology practices and ED patients
  - 1B: consent in ED at time of seizure
  - 0.1 mg/kg to a maximum of 4 mg/kg
  - Some clinicians capped at 2 mg/kg
  - Sparse sampling
- Cohort 2: scheduled, volunteer visit to clinical research center (CRC)
  - 0.05 mg/kg to a maximum of 2 mg/kg
  - Intensive sampling.

Study 1 PK sampling strategy was as follows:

- Cohorts 1A and 1B (four postdose samples)
  - 0, 5–10 minutes\*, 30 minutes–2 hours\*, 6–8 hours, 24–36 hours *or*
  - 0, 15–20 minutes\*, 3–6 hours\*, 10–14 hours, 36–48 hours
- Cohort 2 (12 postdose samples)
  - 0, 5 minutes\*, 15 minutes, 30 minutes, 1 hour, 2 hours\*, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours\*, 48 hours.

\*Free and total concentrations. Reduced sampling in subjects with body weight <8 kg.

Study 1 enrollment was as follows:

- Written request: at least 24 patients, about equally distributed among three age groups
- Study plan: 36 patients with sparse sampling, 24 patients with intensive sampling (CRC patients)
- Actual enrollment to date with PK data available: 50 sparse, 15 intensive.

Characteristics of the lorazepam preliminary PK analyses include:

- Data from August 2006:  $\geq 95$  percent complete and clean
  - Cohort 1,  $n = 50$
  - Cohort 2,  $n = 15$
- 331 samples evaluable (6 excluded)
- Non-compartmental Analysis (Cohort 2)

- Population PK
  - Base model
  - Covariate analysis deferred for the final data set.

Study 1 results indicate the following lorazepam population PK parameters:

- Parameters similar between cohorts 1 and 2
- No apparent drug interactions
- Age effects appear to be consistent with allometric scaling
- Having a maximum dose of 4 mg/kg will limit the “age” differences on exposure from 0.1 mg/kg.

Lorazepam protein binding characteristics were as follows:

- Similar among cohorts
- No concentration-dependent binding
- No age effects
- One subject with unusually high free fraction (also high CLt but “normal” CLu).

Dr. Chamberlain presented a graph of lorazepam blood concentrations (ng/mL) over time (0–12 hours) for the proposed dosing of 0.1 mg/kg  $\pm$  0.05 mg/kg. The results indicated that the minimum dose for seizure suppression in this study is consistent with minimum dose seen in adults following dosing of 0.1 mg/kg. Study 2 will be an RCT comparing diazepam treatment with lorazepam treatment. There will be 120 patients in each arm. The study will involve 10 EDs and use the Exception from Informed Consent for Emergency Research (21 CFR 50.24). The exception from consent allows research without immediate consent under the following limited circumstances:

- Life-threatening condition with prospect of direct benefit to patient
- Current therapy unproven or unsatisfactory
- Informed consent not feasible within the therapeutic window
- Not otherwise possible to do the research.

Exception safeguards include community consultation, public disclosure, independent data safety monitoring board (DSMB), informed consent whenever possible before and as soon as possible after, and provision of opportunities to opt out.

Dr. Chamberlain compared emergency research with regular emergency clinical care:

- | <u>Regular Emergency Care</u>   | <u>Emergency Research</u>   |
|---|---|
| • Doctor decides care, not enough time to involve parents   | • Same  |
| • Individual doctor decides on medicine based on his/her belief, even if the evidence is not clear about what is best | • Medicine choice is decided by chance so that patients have an equal chance to get the better medicine |
| • No scientific review or regulation of doctor’s individual practice  | • Rigorous review of the science by the nation’s medical and ethics experts                             |

- Normal clinical care
- Enhanced safety monitoring and oversight

## Use of Sodium Nitroprusside in Infants and Children

*Gregory Hammer, M.D., Associate Director, Pediatric Intensive Care Unit, Stanford University Medical School*

Dr. Hammer reviewed the history of sodium nitroprusside (SNP):

- Discovery: 1850
- Hypotensive effect: 1929
- Therapeutic use: 1955
- Deliberate hypotension: 1962
- Pediatric use: 1968.

Clinical use of SNP includes:

- Hypertensive emergencies
  - Primary hypertension (HTN)
  - Renovascular disease
  - Pheochromocytoma
  - Cerebral hemorrhage
  - Aortic coarctation
- Deliberate hypotension during surgery
- “Controlled normotension” in pediatric intensive care unit (PICU).

Deliberate hypotension is step-wise, elective reduction in blood pressure to decrease blood loss, diminish need for blood transfusion, and improve operating conditions. SNP’s mechanism of action is as follows:

- SNP dissociates, liberates nitric oxide (NO)
- NO activates guanylate cyclase: increasing cGMP
- cGMP inhibits  $Ca^{++}$  entry into vascular smooth muscle cells
- Vasodilation (arterial > venous).

Nitroprusside also releases  $CN^-$  which is converted in the liver to thiocyanate by the enzyme rhodanase, a reaction that requires a sulfur donor such as thiosulfate. Thiocyanate is then excreted by the kidney. In the absence of sufficient thiosulfate,  $CN^-$  can quickly reach toxic levels. SNP metabolism is as follows:

- $SNP + OxyHb \downarrow$ 
  - MetHb
  - NO
  - $CN^- \times 5$
- $CN^-$  converted to thiocyanate by rhodanase (liver)
  - Thiosulfate used as sulfur donor
- $CN^-$  accumulates when sulfur donor (thiosulfate) MetHb depleted
- Inhibition of cytochrome oxidase in mitochondria  $\Rightarrow$  hypoxia).

The results of a study of SNP toxicity of 24 surgical patients younger than 18 years old reported two cases of “tachyphalaxis” and one death from CN<sup>-</sup> toxicity. Two other studies of SNP toxicity in children reported no toxicity. Clinical signs of CN<sup>-</sup> toxicity include:

- Anaerobic metabolism  $\Leftarrow$  hypoxia
  - Central nervous system (CNS) depression
  - Cardiovascular instability
  - Lactic acidosis
  - Increased SvO<sub>2</sub>, decreased A-VdO<sub>2</sub>
- Difficult to identify under general anesthesia
- Has not been systematically studied in children.

Dr. Hammer described the BPCA SNP study written request:

- Randomized, double-blind, parallel-group, dose-ranging trial for controlled blood pressure reduction during surgical and medical procedures
- Objectives:
  - To define onset and offset of blood pressure lowering effects of SNP to obtain adequate instructions for dose titration
  - To construct a PK/PD model of the relationship between SNP infusion rate and changes in blood pressure
- Five pediatric age groups from neonates to <17 years old who need acutely controlled blood pressure for  $\geq 2$  hours; about 200 subjects total
- Patients randomized to one of four initial infusion rates of 0.3–3 mcg/kg/min
  - Infusion rates up- or down-titrated at  $\geq 10$ -minute intervals or until three measurements 2 minutes apart show that vital signs have stabilized
  - Dose further titrated to maximum dose affording optimum blood pressure control (target MAP) defined by investigator.

Written request challenges include:

- Double-blinded: throughout procedure?
  - 30-minute blinded infusion followed by open label period
  - No “titration” during blinded infusion
  - Step-changes x 3 beginning at one-third full rate
  - After stabilization of anesthesia, vital signs
  - Performed preincision or stable stimulus
- Vitals signs/AE documentation: continuous data capture
- PK/PD study:
  - Could we develop SNP assay?
  - Or use CN<sup>-</sup>, thiocyanate as surrogate molecules?

Dr. Hammer characterized SNP assay development:

- No existing validated assay for SNP in biological fluids
  - Very short half-life in blood (minutes)
- Development of SNP assay in conjunction with SFBC Analytical Labs

- Used ICP-MS (inductively coupled plasma mass spectrometry)
- Unsuccessful in applying assay to blood for quantitation of SNP.

Dr. Hammer characterized CN<sup>-</sup> and thiocyanate assays:

- Worked with SFBC on new assay for CN<sup>-</sup>
  - Stability and reproducibility issues
- Currently using commercial lab (NMS) for CN<sup>-</sup> and thiocyanate assays
  - Modifications to minimize sample volumes
  - Whole blood CN<sup>-</sup> assay because most CN<sup>-</sup> is in red blood cells
  - Spectrophotometric assay, detects >0.1 μg/mL
  - Thiocyanate: plasma and urine
  - Ion exchange chromatography, detects >1 μg/mL.

Assay results to date are:

- No detectable cyanide levels in blood in any subjects
- Low levels of thiocyanate detectable in urine and occasionally in plasma
- Important result showing very low risk of cyanide toxicity in these short-term infusions.

SNP study enrollments by site are:

- Stanford: 58
- Texas: 16
- CHOLA: 11
- Duke: 10
- CHOP: 7
- WVU: 6
- Pitt: 6

SNP study enrollment statistics for Stanford are:

- Screened: 117
- Screened/not interviewed: 44
  - Surgery shorter than scheduled, unable to reach patient, no study personnel available, ward of the court
- Interviewed: 73
  - Enrolled: 57 (78 percent)
  - Refused: 16 (22 percent)
    - Blood draws, blinded infusion.

The infrastructure as Stanford provides a model for success in clinical trials:

- Nonclinical time
- Ph.D. research director
- Trained research coordinators, nurses
  - Departmental “back-stop”
- Web-based system for sharing resources
- Rapid processing by institutional review board (IRB)
- Streamlined research contracting.

## The Lorazepam Sedation Saga

*Jeffrey Blumer, M.D., Professor, Departments of Pediatrics and Pharmacology, Case Western Reserve University*

Among infants and children sedated with intravenous (IV) lorazepam in the intensive care unit, there was a reported 18 percent mortality attributed to the excipients in the parenteral formulation. Lorazepam is used to sedate about 50 percent of the mechanically ventilated infants and children in the United States. The lorazepam knowledge gap includes:

- Optimal mode of administration
  - Intermittent bolus (IB)
  - Continuous infusion (CI)
- Efficacy
  - Effectiveness for sedation of mechanically ventilated infants and children
  - Effectiveness relative to midazolam (a drug labeled for this indication)
- Safety
  - Tolerability of IV lorazepam in children from birth to 18 years of age
  - Safety of the excipients in the parenteral formulation (specifically Ativan<sup>®</sup>)
    - Polyethylene glycol
    - Propylene glycol
    - Benzyl alcohol/benzoate
- PK
  - Lorazepam in critically ill, mechanically ventilated infants and children
  - Lorazepam excipients in mechanically ventilated infants and children
  - Midazolam in mechanically ventilated infants and children.

The Lorazepam for Sedation Study (NICHD-2003-11) is a multicenter, randomized, observer-blinded clinical trial to determine the overall safety of lorazepam administered as a CI or IB and midazolam administered as a continuous infusion for sedation of critically ill, mechanically ventilated pediatric patients. The study's overall approach includes:

- Assembling an investigative team
- Defining a sedation event
- Selecting tools for evaluation
- Developing analytical methodology for drug and excipient measurements
- Establishing a means to assure uniformity of assessments and patient safety across investigative sites
- Integrating all of these elements into a protocol that is minimally intrusive in the patient care routines of the participating sites.

The team includes pediatric critical care specialists, neonatologists, pediatric pharmacologists, pharmacokineticists, critical care nurses, biostatisticians, analytical chemists, toxicologist, and pharmacogeneticist. The study is supported by a group of outstanding research coordinators. The sedation event is divided into three phases: (1) initiation; (2) maintenance, which includes dose titration and optimal sedation; and (3) discontinuation. These phases reflect true clinical practice,



- Efficacy
  - Develop an understanding of the appropriate dosing of lorazepam and midazolam for sedation in the PICU
  - Compare the effectiveness of IB or CI sedation
  - Compare the effectiveness of lorazepam to midazolam for sedation of mechanically ventilated patients in the PICU
- Safety
  - Determine safety profile for lorazepam and midazolam when used to sedate mechanically ventilated infants and children
    - Clinical laboratory
    - Vital signs
    - Mortality
  - Safety profile for the excipients propylene glycol, polyethylene glycol, and benzyl alcohol
    - Clinical laboratory
    - Mortality
- Incidence of tolerance to the study drugs when used in this setting
- Incidence of drug withdrawal when the study drugs are used in this setting
- A safe and effective way to liberate patients from long-term sedation with these study drugs
- PK
  - Describe the biodisposition of the study drugs when used in this setting
  - Describe the biodisposition of the lorazepam excipients propylene glycol, polyethylene glycol, and benzyl alcohol
  - Construct a PK/PD model to guide dosing of the study drugs in the target patient population
  - Determine the feasibility of the sparse sampling strategy used in the study for accomplishing these objectives
- Pharmacogenetics
  - Evaluate the role of genotypic differences in glucuronyl transferase and alcohol dehydrogenase in determining the interindividual differences in the biodisposition of study drugs and the lorazepam excipients.

Secondary study objectives are to:

- Determine:
  - Relative efficacy of three different bolus doses of lorazepam for initiating sedation
  - Tolerability of CI lorazepam and IB lorazepam and CI midazolam as a maintenance sedative
  - Tolerability of lorazepam excipients and their relatedness to lorazepam dose
  - PK of lorazepam and midazolam in the study population
  - PK of lorazepam excipients in the study population
- Compare the incidence of drug abstinence upon discontinuation of the three maintenance regimens.



Exploratory objectives are to:

- Determine whether PK of lorazepam, midazolam, and their metabolites and excipients can be characterized using a sparse sampling strategy
- Evaluate the relationship between level of sedation using COMFORT scale score and the concentration or disposition of sedative agents
- Define the ontogeny of the PK and PD of study drugs
- Determine the role of drug metabolizing enzyme genotypes in the PK of study drugs.

Study drugs' characteristics are as follows:

- Lorazepam
  - Each mL of sterile injection contains 2 mg of lorazepam, 0.16 mL polyethylene glycol 400 in propylene glycol with 2 percent benzyl alcohol as preservative
  - 4 mg/mL lorazepam also supplied
- Midazolam hydrochloride (HCl) injection
  - Midazolam HCl is a water soluble benzodiazepine available as a sterile nonpyrogenic dosage form for IV or intramuscular (IM) injection
  - Each mL containing midazolam HCl equivalent 5 mg midazolam compounded with 0.8 percent NaCl.
- Fentanyl citrate injection
  - Each mL contains fentanyl (as the citrate) 50 µg. May contain NaOH and/or HCl for pH adjustment. The solution contains no bacteriostatic, antimicrobial agent, or added buffer.
- Rescue medication is thiopental (each syringe contains 250 mg).

Special protocol conditions include:

- Fentanyl bolus doses
  - Fentanyl 1–2 µg/kg should be administered before anticipated noxious procedures, such as suctioning of endotracheal tube, invasive procedures, etc.
  - Drug should be administered 5–10 minutes before the procedure
- Thiopental rescue
  - Bolus dose thiopental is available as a rescue medication in all study phases
  - May be used when COMFORT scale score during treatment is >26 and patient is at risk for self injury, self-extubation, and/or removal of vascular catheters
  - Dose 1 mg/kg rapid IV bolus.

Inclusion criteria are:

- Males or females from full-term birth ( $\geq 38$  weeks PCA at enrollment) through 18 years of age (up to their 18th birthday)
- Must be expected to require mechanical ventilation  $\geq 8$  hours
- Must be intubated and mechanically ventilated  $\leq 48$  hours
- Must not be expected (in the opinion of the investigator) to require neuromuscular blocking agents; use of neuromuscular blocking agent to facilitate endotracheal intubation is allowed.

Exclusion criteria are:

- Life expectancy <48 hours

- Expected duration of sedation, in the opinion of the investigator, is <8 hours
- Patient history of hypersensitivity to any component of lorazepam, midazolam, fentanyl, and/or thiopental
- Female patient who is pregnant or breastfeeding
- Patient requires medication for sedation or analgesia other than study drugs (analgesics or nonsteroidal anti-inflammatory drugs used as antipyretics are not exclusions).

The patients will be randomized into three arms: (A) lorazepam IB with three subarms for initial bolus dose, (B) lorazepam continuous infusion with three subarms for initial bolus dose, and (C) midazolam continuous infusion. Within each arm, participants will be stratified by age and severity of underlying illness. The initiation phase begins when COMFORT scale score reaches >26 following discontinuation of prestudy sedation. Patients receive bolus doses of benzodiazepine per protocol based on randomized study arm assignment. This phase ends when one of two things occurs:

- Patient attains a COMFORT scale score  $\geq 17$  and  $\leq 26$
- Patient fails to attain the target COMFORT scale score after the three bolus doses.

Critical or near-critical incidents related to inadequate sedation or oversedation for the initial phase include:

- Blood pressure change: mean arterial pressure (MAP)  $\pm 30$  percent from baseline
- Dysrhythmias
- Heart rate change  $\pm 30$  percent from baseline
- Accidental extubation
- Loss of IV access: undersedation
- Apnea
- Tachypnea: respiratory rate >130 percent of baseline
- Oxygen saturation <90 percent in patients without intracardiac shunts
- COMFORT scale score <17 or >26
- Seizures
- Metabolic acidosis
- Death.

Maintenance phase dose titration begins when one of two events occur: (1) target COMFORT scale score is achieved or (2) patient is declared an initiation phase failure. Dose-escalate benzodiazepine every 15 minutes until target COMFORT scale score is achieved. There is no per protocol limit on the number of dose escalations or the total dose of benzodiazepine given. Patients are observed for a minimum of 4 hours. Maintenance phase ends when one of two events occurs:

- Target COMFORT scale score is attained and sustained for 4 hours without benzodiazepine dosage adjustment
- Patient is declared a dose titration portion failure because of inability to achieve target COMFORT scale score.

Maintenance phase optimal sedation begins when patient in the dose titration portion has achieved and maintained the target COMFORT scale score for at least 4 hours.

- A fentanyl infusion, 1 µg/kg/h, will be initiated in all patients
- Patients will continue receiving the dose of benzodiazepine established for that patient during the dose titration portion
  - Dose adjustments will be made per protocol
- Once patients have been stable in the optimal sedation portion of the maintenance phase for 24 hours they will be randomized:
  - Half will temporarily discontinue their fentanyl infusion for 30 ± 6 hours
  - Half will continue with their regimen unchanged
- At 30 ± 6 hours into this randomized subsection of the protocol the fentanyl infusion will be reinitiated at 1 µg/kg/h in the patients in whom it was temporarily discontinued
  - Dosage adjustments may occur during both parts of this portion of the maintenance phase
- Maintenance phase ends when one of the following events occurs:
  - Decision is made to discontinue sedation.
  - More than four dosage adjustments of benzodiazepine are required within a 24-hour period.
  - More than three bolus doses of thiopental are required within 1 hour.
  - Dosage adjustment with fentanyl CI.

Critical or near-critical incidents related to inadequate sedation or oversedation for dose titration and optimal sedation include:

- Organ failure including renal, brain, bone marrow, liver, or cardiac
- Lack of synchronization or inability to maintain mechanical ventilation associated with inadequate sedation
- Blood pressure change: MAP ± 30 percent from baseline
- Dysrhythmias
- Heart rate change ± 30 percent from baseline
- Accidental extubation
- Loss of IV access: undersedated
- Apnea
- Tachypnea: respiratory rate >130 percent of baseline
- Oxygen saturation <90 percent in patients without intracardiac shunts
- COMFORT scale score <17 or >26
- Seizures
- Metabolic acidosis
- Death.

Discontinuation phase begins with decision to transition to extubation

- Patients who receive study drug <72 hours will have their sedatives abruptly discontinued
- Patients who receive study drug ≥72 hours will be randomized to
  - Abrupt discontinuation
  - Tapering regimen (20 percent per day for 5 days)

- Patients will be assessed in two ways
  - Readiness for extubation will be assessed by CROP scoring
  - Abstinence effects related to sedative agents will be assessed using the Finnegan/Modified Finnegan score
- Ends when sedatives have been successfully discontinued for at least 72 hours
- Extubation is not a part of the protocol.
- CROP scoring every 8 hours until a value of  $\geq 0.10$  is attained
  - Attempts to score more frequently are generally confounded by ongoing patient care issues (e.g., feeding, changing diapers, suctioning) that may interfere with accurate scoring.
- Extubation can be performed in patients still receiving sedative agents if the target CROP score is attained.
- Once a patient is extubated he or she will transition to the follow-up phase.

Critical or near-critical incidents related to inadequate sedation or oversedation in the discontinuation phase include:

- Blood pressure change:  $\text{MAP} \pm 30$  percent of baseline
- Dysrhythmias
- Heart rate change  $\pm 30$  percent of baseline
- Apnea
- Tachypnea: respiratory rate  $>130$  percent of baseline
- Oxygen saturation  $<90$  percent in patients without intracardiac shunts
- Accidental extubation
- Seizures
- Metabolic acidosis
- Death.

Study follow-up includes:

- Follow up conducted upon PICU discharge or 3 days after discontinuation of sedative agents—whichever occurs first
- Perform
  - Physical examination
  - Vital signs and body weight
  - 12-lead ECG
  - Blood chemistries, hematology, and urinalysis
  - Urine aliquots for lorazepam metabolites determination
  - Adverse events
  - Concomitant medications
- Study ends with completion of this phase.

Special protocol conditions are:

- Stopping rule
  - Patients will be evaluated for discontinuation of study sedatives anytime

- New onset metabolic acidosis characterized by a base deficit  $\geq 10$  unexplained by clinical condition and/or
- The presence of an osmolal gap  $>30$
- Doses of benzodiazepine may be reduced temporarily for:
  - Acute evaluation
    - Respiratory function
    - Cognitive function
    - Neurologic function
    - Analgesic requirements
  - Family visits if desired and medically feasible
- Reductions should be limited in time to about 30 minutes.

Emerging trends in results include:

- When an objective scoring tool is used a number of children appear to require no sedation/analgesia during mechanical ventilation.
- Younger children appear to require sedation/analgesia less often than older children.
- Lorazepam appears to demonstrate greater effectiveness than midazolam in initiating sedation ( $P < 0.05$ ).
- Patients sedated with lorazepam appear to require less time to attain target COMFORT scale score than patients sedated with midazolam ( $P < 0.05$ ).
- Optimal sedation portion of maintenance phase
  - There were fewer failures among patients sedated with lorazepam than those sedated with midazolam.
  - There were few patients sedated with either benzodiazepine who required increases in dose during randomization to temporary fentanyl discontinuation.
  - Patients sedated with midazolam required more doses of rescue medication and had more serious AEs than patients sedated with lorazepam.
  - There is no apparent difference in success rate between IB and CI lorazepam.
- Lorazepam excipients
  - No patient has attained the osmolal gap criterion for stopping; there has been no unexplained metabolic acidosis.
  - Propylene glycol and polyethylene glycol concentrations demonstrate wide interindividual variations ( $>10$ -fold).
  - These variations appear to be independent of age and time on treatment (up to 30 days) or renal function.
  - The benzyl alcohol/benzoic acid concentrations are all below the level of quantitation ( $LQ \leq 10$  percent of lowest concentration associated with gasping syndrome in newborns).
- Abstinence reactions appear to be infrequent in patients whose sedation regimens are abruptly discontinued regardless of duration of exposure.
- Most patients achieve objective criteria for extubation before sedatives are discontinued during a tapering regimen.

## **BABY HUG Update: Hydroxyurea Treatment of Sickle Cell Disease**

*Charles M. Peterson, M.D., Division Director, Sickle Cell Disease Coordinator, Blood Diseases Program, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute (NHLBI), NIH*

Dr. Peterson briefly reviewed the history of sickle cell disease:

- Sickle cell diseases are identified: 1910
- Congress passes the National Sickle Cell Anemia Control Act: 1972
- NHLBI establishes Comprehensive Sickle Cell Centers: 1972
- First statewide newborn screening program is implemented: 1975
- PROPS I shows that prophylactic administration of penicillin to children prevents pneumococcal infection: 1986
- MSH trial shows that hydroxyurea treatment reduces painful episodes in severely affected adults with sickle cell anemia: 1995
- NHLBI-supported researchers demonstrate that bone marrow transplantation can provide a cure for young sickle cell patients (ages 3–14 years) who have a matched sibling: 1996
- STOP study shows that frequent blood transfusions can lower rate of stroke by 90 percent: 1996.

From 1910 to 1980, the average lifespan for a person with sickle cell anemia increased slowly from <10 years of age to about 20 years of age. From 1980 to 2000, average life span increased to about 45 years of age.

BABY HUG (Pediatric Hydroxyurea in Sickle Cell Anemia—an international prevention, randomized, double-blind, placebo-control, parallel-assignment, efficacy study) evolved from the HUSOFT Study, characterized by the following:

- Phase I/II pilot study of hydroxyurea for infants with SCD, regardless of disease severity
- Objectives: to determine the feasibility of hydroxyurea administration, and its toxicity, hematologic effects, and effect on spleen function over 2 years
- Hydroxyurea dose 20 mg/kg/day, liquid preparation
- Results: ↑ Hb, ↑ Hb F, ↓ WBC, ↑ spleen function.

Characteristics of the HUSOFT Extension Study included:

- 21 patients completed 2 years of therapy on HUSOFT; all families agreed to participate in the Extension Study
- Extension Study designed to evaluate long-term clinical and hematologic efficacy of hydroxyurea
- Hydroxyurea dose escalated by 5 mg/kg increments to a maximum dose of 30 mg/kg/day
- Cohort completed a total of 4–6 years of hydroxyurea treatment.

The results of the HUSOFT Extension Study were:

- Neutropenia (ANC <1,500): 8 percent of CBCs, usually associated with viral illness
- Severe neutropenia (ANC <500): none
- Severe anemia (Hb <5 g/dL or ↓ >20 percent): four episodes

- No cases of myelodysplasia or cancer
- One splenic sequestration event
- One fatal case of pneumococcal sepsis
- Acute chest syndrome (ACS) 7.5/100 patients per year. (expected 24.5/100 patients per year.)

The conclusions of the HUSOFT Extension Study were:

- Infants with sickle cell anemia can tolerate prolonged liquid hydroxyurea therapy with sustained hematological benefits.
- Toxicities are mild and similar to those in previous studies.
- Hydroxyurea may preserve (or possibly lead to recovery of) splenic function.
- Hydroxyurea was not associated with decreased growth.
- Hydroxyurea was associated with fewer ACS events.
- Randomized studies are needed to define the benefit of hydroxyurea for the prevention of chronic organ damage in young children with sickle cell anemia.

Dr. Peterson characterized BABY HUG, which is a collaborative study between NICHD and NHLBI. The objectives of the study are to determine whether hydroxyurea can prevent or reduce chronic organ damage in very young children with sickle cell disease. The study's primary objective is to determine hydroxyurea's effect on spleen and kidney function. Secondary objectives are to determine relationships between Hb F and chronic organ damage and to investigate safety regarding growth, neurodevelopment, immunologic responses, and mutagenic effects on DNA.

The BABY HUG study design is as follows:

- Total number of patients:  $n = 200$
- Randomization: 100 patients receive hydroxyurea; 100 receive placebo
- Feasibility and safety pilot trial:  $n = 40$
- Each patient followed for 2 years
- Inclusion criteria
  - Diagnosis of Hb SS or Hb S $\beta^0$  thalassemia
  - Age 9–17 months
  - No severity criteria
- Exclusion criteria
  - Chronic or recent transfusion
  - Height, weight, or head circumference <5th percentile
  - Mental Developmental Index <70
  - Abnormal velocity on transcranial doppler (TCD) ultrasound.

Baseline assessments include:

- Routine history and physical examination
- Anthropometry
- Neurologic examination
- CBC, chemistry, Hb genotype, urinalysis
- Bayley and Vineland neurodevelopmental assessments

- Liver/spleen scan
- Abdominal sonogram
- TCD ultrasound
- Urine concentrating ability
- Renal dithiophosphoric acid (DTPA) clearance
- Hydroxyurea PK.

Primary efficacy endpoints are:

- Spleen: uptake on radionuclide L/S scan
- Kidney: glomerular filtration rate (GFR) using DTPA clearance.

Secondary efficacy endpoints are:

- Hematology: Hb F, Hb, MCV, WBC, platelet count
- CNS: TCD velocities
- Lungs: O<sub>2</sub> saturation
- Hepatobiliary: gallstones, bilirubin level
- Spleen: pit cells, spleen size (ultrasound [U/S])
- Kidney: serum globin, microalbuminuria, kidney size (U/S)
- Clinical events: hospitalizations, ACS, etc.

Safety endpoints are:

- Death, stroke, splenic sequestration
- Growth: height, weight, head circumference
- CNS: neurodevelopment testing, neurological exam
- Mutagenesis: VDJ recombination events, cytogenetics
- Hematology and chemistry values
- Immune system: antibody response to immunization, T cell counts.

Measurement of spleen function at baseline includes:

- Tc-99m sulfur colloid liver-spleen scan
- Qualitative interpretation: spleen to liver uptake (normal, decreased, absent)
- Quantitative: geometric mean total counts
- Pitted erythrocyte counts
- Flow cytometric quantitation of Howell-Jolly bodies (HJB) (micronuclei in mature RBC).

Conclusions of spleen function at baseline are:

- Quantitative evaluation of L/S scan may allow more informative gradation of the decline in splenic function.
- Surrogate measures such as pit count and HJB are highly correlated with L/S scan results.
- Decline of splenic function with age in young children can be assessed by multiple techniques.

Dr. Peterson provided background information on kidney function in sickle cell disease:



- Sickle nephropathy begins early in life
  - Concentrating, acidification defects
  - Glomerular hyperfiltration
  - Proteinuria
- GFR
  - May be an early marker of disease
  - Can be quantitatively measured.

Preliminary GFR data are as follows:

- HUSOFT
  - Estimated GFR using retrospective data:
    - $121 \pm 20$  mL/min/1.73 m<sup>2</sup> at entry
    - $162 \pm 43$  mL/min/1.73 m<sup>2</sup> at exit
  - Change in GFR associated with change in HbF
- HUG KIDS
  - Median GFR >200 at entry and exit.

Current GFR status for BABY HUG is:

- Quantitative GFR measurement is feasible using DTPA.
- GFR is elevated early in life and is increased with older age.
- GFR and (?) the Schwartz equation may be used to measure the renal primary endpoint.

The assessment of urine-concentrating ability in BABY HUG includes:

- Secondary endpoint of renal function
- Osmolality measured on timed overnight second void urine after fluid deprivation (M = 7 h)
- 71 percent able to concentrate urine (urine osmolality > mean serum osmolality + 1 SD)
- Correlation with duration NPO
- Will evaluate whether early hydroxyurea treatment can preserve or restore this function.

Hydroxyurea PK in BABY HUGS is characterized as follows:

- Hydroxyurea clearance predominantly renal
- No PK data published for hydroxyurea in young children with Hb SS
- PK samples collected in conjunction with DTPA clearance measurement after administration of first dose of study drug
- Baseline data show faster clearance and shorter half-life compared with adults
- Will examine relationship of PK to clinical response.

CNS evaluations at baseline include:

- MRI/MRA: 3/23 (13 percent) had silent infarcts; no MRA abnormalities
- Development:
  - Bayley Scales of Infant Development
- TCD: no patients with abnormal TCD velocities.

The BABY HUG timeline is as follows:

- October 2003: first patient enrolled
- January 2005: feasibility and safety pilot study completed (first 40 patients enrolled)
  - No safety concerns noted by DSMB
  - Protocol “streamlined” to reduce central labs, neurology/neuropsychology exams, growth eligibility requirements, and monitoring
- July 2005: NICHD became joint sponsor; four new clinical centers added.

Dr. Peterson described the significance of the BABY HUG study:

- If hydroxyurea prevents spleen/kidney damage, and if hydroxyurea is not associated with significant toxicity, and if results suggest hydroxyurea is associated with decreased pain and ACS, similar to what is seen in school-age children and adults, then hydroxyurea could become part of routine management for all Hb SS patients and hydroxyurea could be prescribed much like penicillin is now prescribed.
- Although the long-term safety of hydroxyurea is still uncertain, the relative value of hydroxyurea compared with (or in addition to) new anti-sickling agents remains to be investigated.
- The relative efficacy and safety of hydroxyurea compared with other treatment modalities such as transplant and chronic transfusion also remains to be determined.

### **Assessment of Ketamine in the Developing Nonhuman Primate (Update)**

*Cheng Wang, M.D., Research Neurobiologist, Division of Neurotoxicology, National Center for Toxicological Research, FDA, DHHS*

Dr. Wang listed the following representative test agents:

- NMDA (N-methyl-D-aspartate) antagonists
  - Ketamine and phencyclidine (PCP)
  - Nitrous oxide
- GABA (gamma-aminobutyric acid) agonists
  - Midazolam
  - Propofol
- Combinations (NMDA antagonists and GABA agonists):
  - Ketamine + midazolam
  - Nitrous oxide + midazolam + isoflurane (triple anesthetic drug protocol)
- Narcotics
  - Fentanyl (control; fentanyl is an important control because its mechanism of action does not involve the NMDA or GABA system).

Dr. Wang discussed the following:

- Hypoglutamatergic states lead to sparse neuronal circuits
- Glutamate receptors
- NDMA receptors
  - Normal, physiological NMDA receptor activation is responsible for neuronal survival, synapse formation and neural plasticity

- NMDA receptor blockade by NMDA antagonist such as ketamine or PCP can result in cell death; too little is bad
- Pathologically high levels, for example, in the situation like stroke, glutamate and other neurotransmitters leak out, and too much glutamate is also bad
- In general, both too much or too little can initiate cell death. Developmental periods are particularly vulnerable.
- Subunits of NMDA receptors
- Ketamine chemical structure and properties
- Time windows of vulnerability to the neurotoxic effects of NMDA receptor antagonists for rat (postulated for monkey and human).

Dr. Wang asked: Is there a direct link between altered NMDA receptor expression and ketamine-induced neurodegeneration? He presented a variety of data on the effects of ketamine on primary cell culture of PND-3 frontal cortex cells of nonhuman primates, and he summarized the in vivo studies in the developing monkey:

- Pregnant rhesus monkeys (gestational day 122), PND-5 and PND-35 monkey infants were infused intravenously with ketamine to maintain a steady anesthetic plane for 3 or 24 hours followed by a 6-hour withdrawal period.
- Ketamine monkey was given an initial IM dose (20 mg/kg) and then continuously infused with ketamine at a rate of 20–50 mg/kg/h to effect.
- The brains were examined by histochemical approaches that included silver-staining and caspase-3 immunostaining.

Dr. Wang summarized:

- Ketamine administration results in a dose-related increase in neurotoxicity in vitro, in the developing monkey.
- Ketamine-induced neuronal cell death in the monkey is probably both apoptotic and necrotic in nature.
- Ketamine-induced cell death may involve the up-regulation of NMDA receptor NR1 mRNA and protein during development; coadministration of NR1 antisense oligonucleotide prevents synthesis of NMDA receptor NR1 protein and subsequently blocks the ketamine-induced neuronal cell death.
- The early developmental stages (GD 122 and PND 5) appear to be more sensitive to anesthetic neurotoxicity.
- Shorter duration ketamine exposures (ketamine infusion of 3 hours versus 24 hours) do not produce neuronal cell death in this model.

### **Oncology—Actinomycin-D and Vincristine**

*Jeffrey Barrett, Ph.D., FCP, Associate Professor of Pediatrics and Pharmacology, Children's Hospital of Philadelphia and University of Pennsylvania*

The background and rationale for this project are as follows:

- Actinomycin-D (AMD) and vincristine (VCR) are commonly used anticancer agents in children and are known to cause several toxicities, including hepatopathy.

- Infants and young children may be particularly susceptible to these toxicities.
- Despite decades of use, there is limited PK information available for these agents.
- AMD and VCR are poorly characterized in pediatric populations with respect to dosing guidance and management of pharmacotherapy.
- Their development occurred during an era when the requirements for drug substance characterization and preclinical/clinical evaluation were not as stringent as today.

The objectives and goals for the AMD/VCR project are as follows:

- **Project 1.** To conduct a retrospective analysis of historical data from Wilms tumor (NWTS-IV and NWTS-V) and rhabdomyosarcoma (IRS-IV and IRS-V) studies in which AMD and VCR were administered to various pediatric subpopulations to define exposure/toxicity relationships
- **Project 2.** To develop a dosing and PK sampling procedure for AMD and VCR using a single lumen central venous catheter
- **Project 3.** To construct PK/PD models based on AMD and VCR exposure/response relationships that incorporate physiologic-based and mechanistic expression when possible, and simulation to extend such relationships into a clinical trial paradigm in which trial outcomes may be predicted
- **Project 4.** To conduct a prospective PK/PD/outcome trial of AMD and VCR in children, primarily <3 years of age, receiving these drugs as a component of their therapy.

Dr. Barrett characterized project 1 data:

- IRS studies
  - 1,150 patients with toxicity and dose–history data
  - Currently computing planned (protocol) doses
- NWTS-4
  - 656 patients with toxicity and dose-history data
  - Currently computing planned (protocol) doses
- NWTS-5
  - 2,668 patients with toxicity information, but no date of toxicity, no dose data
  - Currently processing subcontract for data abstraction.

Dr. Barrett listed project 1 milestones to date:

- Completed basic data checking and data corrections for IRSG and NWTS-4 studies
- AMD/VCR study-specific toxic event outcomes defined and implemented
- Statistical analysis planned; software prepared and piloted
- NWTS-5 data abstraction planned and piloted.

Project 1 plans include:

- Completion of protocol planned dose calculation for IRS and NWTS-4
- Identification of “unreported” toxic-event occurrences (based on planned versus received doses), data checking
- NWTS-5 data abstraction and entry
- Statistical analysis to estimate AMD/VCR toxicity probability by age and dose groups.

Dr. Barrett reviewed project 2 experiments to examine drug clearances from catheters:

- Explore variables (preclinical experiment)
  - Catheter length, diameter, style/brand
  - Presence of Luer lock, t-port
  - Flush solution, volume
- In vitro equivalence
  - Simulated plasma exposure
  - PK sampling with LC/MS/MS
- Validation (clinical experiment)
  - Comparison between central catheter samples and peripheral catheter samples in clinical setting
  - Equivalence within 25 percent difference
  - Usable procedure for contamination prevention.

Key variables of interest in project 2 include:

- Presence or absence of stopcock
- Change of Luer lock after dose
- Diameter of catheter
- Timed drug instillation
- pH effect of flush
- Instillation of albumin
- Volume of normal saline flush
- Volume of whole blood flush
- Number of blood flushes.

Project 2 analytical methods are validated liquid chromatography-tandem mass spectrometry method to detect AMD and VCR in human plasma to a limit of quantitation (LOQ) of 0.05 ng/mL. Previous LOQ was published at 0.5 ng/mL, which is now improved tenfold.

Catheter configuration includes:

- Five French 27-cm catheter fragment
- 200- $\mu$ L pipette tip
- Catheter syringe connector
- Three-way stopcock
- 5-mL syringe for waste collection
- 3-mL syringe for sample collection.

Dr. Barrett presented data for the initial results and most recent results for the catheter fragment. He concluded that there was:

- No difference in residual drug concentration after varying pH or content of flush or in drug contact/exposure time
- A moderate decrease in residual drug concentration following increased flush volume
- A decrease in residual drug concentration following at least four clearing cycles.

Dr. Barrett presented an overview of project 2 validation of single patient data.

- A single patient with rhabdomyosarcoma, age 16 years (60 kg), scheduled to receive AMD and VCR as part of routine chemotherapy, was evaluated following an AMD dose of 0.05 mg/kg and a VCR dose of 0.05 mg/kg.
- Two sets of 12 blood samples each were obtained; one set from an indwelling central venous catheter, and a second set from a newly placed peripheral venous catheter.
- Prior to drawing the first and second samples from the indwelling catheter, a three-way stopcock was fitted to the catheter hub, and 5 mL of blood was pulled and then returned to the patient. This was repeated four times, followed by the pulling of a 5-mL waste, then a 2.5-mL sample. A total of 24 blood samples were obtained over a 48-hour period.

Dr. Barrett presented data from the project 2 validation, and he offered an additional validation proposal: ongoing in vivo validation of the clearing procedure and validation with a subset of initial patients enrolled onto ADVL06B1.

Protocol language for the project 2 prospective study is as follows:

- Sterile conditions required. Drugs administered per protocol and followed by a 3-mL 0.9 percent normal saline flush. Sterile three-way stopcock is fitted with both a sterile 3-mL sample (proximal) and 5-mL waste (distal) syringe, primed with normal saline, and connected to the catheter via a needle-less access hub. A 5-mL 0.9-percent normal saline flush should be attached to the third and inline end lumen of the three-way stopcock.
- Distal valve opened and 4 mL blood drawn and returned four times. Close valve and open to saline flush. Two mL saline infused and valve closed. Reopen to distal syringe and obtain 4 mL of blood. Close valve and open to sample. Obtain 2.5-mL sample. Close valve and reopen waste and return to patient. Infuse remaining saline and remove apparatus and sample.

Dr. Barrett presented the following overview of the project 3 modeling and simulation strategies to examine dose/exposure of AMD and VCR:

- Construct population PK models to describe AMD and VCR disposition in children from limited prior data
- Incorporate uncertainty in the parameter estimates implemented as inter-trial variability
- Perform clinical trial simulations incorporating parameter uncertainty for the design and evaluation of a prospective large-scale AMD/VCR trial in pediatric cancer patients, and subsequent sensitivity analysis
- Power the study to be able to accurately and precisely estimate clearance for children <1 year old.

Dr. Barrett characterized project 3 model evolution:

- AMD: developed from PK data in 33 children, ages 1.5–20 years
  - Three compartment
  - Allometric scaling for all parameters
- VCR: developed from data reported in five VCR PK studies

- Two-compartment
- Weight-normalized parameters
- Exponential error model to describe intersubject variability for AMD and VCR (V1, CL)
- Parameters were log-transformed for both models to ensure values >0
- AMD individual predicted concentrations were in close agreement with observed values
- Simulated VCR profiles were comparable to those reported in the literature.

Dr. Barrett characterized the project 3 model evolution, which accounts for potential age effect on drug CL:

- Numerous drugs have demonstrated decreased clearance in children <1 year old
- Uncertain to the extent, if any, for changes in CL for AMD or VCR
- Hypothetical age effect on CL added to both models
- 500 values for  $\theta_{\text{AEFF}}$  drawn from a random uniform distribution between 0.15 and 1
- For children >1 year,  $\theta_{\text{AEFF}} = 0$
- Represents a 20 percent to 75 percent decrease in CL for a 3-month-old infant.

For project 3 simulation strategy, the final study design was chosen based on:

- Feasibility of study design
- Ability to accurately estimate V1, CL
- Bias +/- 20 percent, no trends over range of unbiased parameters
- Powered accurately to estimate clearance for children <1 year old.

Key simulations had several effects on study design. PK sampling schemes were adjusted to sufficiently obtain accurate characterization for both AMD and VCR disposition properties. A feasible and informative trial design was identified for an AMD and VCR clinical trial in pediatric patients. This design was modified to be robust across the uncertainty in PK parameters. The trial is appropriately powered to characterize potential clearance differences in children <1 year old ( $n = 35$ , age <1 year).

Project 3 simulations to examine historical exposure targets:

- Simulate AMD and VCR exposure profiles based on D9803 study protocols
- Examine the possible effects of an assumed reduced clearance in children <1 year old
- Compare AMD and VCR exposure metrics resulting from the three protocol dosing variations
- $N = 100$  for each age group and protocol version
- Metrics of exposure examined AUC0-24 and C24
- Subset of simulations performed where CL in <1 year reduced by 50 percent.

Dr. Barrett presented the study design for prospective trial in project 4:

- Cohorts of <1 year,  $\geq 1$  to <3 years,  $\geq 3$  to <12 years,  $\geq 12$  to <17 years; 50 patients per cohort
- Randomized to one of two PK schedules
- Patients will receive AMD and/or VCR as prescribed
- Five plasma PK samples and two urine samples will be obtained

- Population PK analysis performed
- Pharmacogenetic analysis will also be performed (CYP 3A4, 5).

### **National Toxicology Program Center for the Evaluation of Risks to Human Reproduction and Activities Supporting the BPCA Prioritization Efforts**

*Michael Shelby, Ph.D., Director, Center for the Evaluation of Risks to Human Reproduction, National Institute of Environmental Health Sciences, NIH*

The main activities of National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) are:

- Convene expert panels to evaluate selected chemicals for effects on human reproduction and development
- Maintain a Web site for information and communication
- Respond to individual inquiries on reproductive health issues.

Dr. Shelby described the following NTP-CERHR reports:

- 16 NTP-CERHR monographs released since the series started in 2003
  - DEHP monograph will soon be released
- NTP briefs on soy formula and genistein
  - Available for public comment through December 8
  - Undergoing external peer review
- Draft Expert Panel Report on Hydroxyurea available for public comment through December 15
- Draft Expert Panel Report on Bisphenol A will be released for public comment on December 15.

For the BPCA drug list prioritization efforts in 2003, CERHR prepared reviews on the efficacy, safety, and pharmacokinetics of 24 drugs. In addition, CERHR provided reviews to NICHD in hard copy and CD and provided copies of all publications cited as pdf files. Reviews went to an expert panel to aid them in prioritizing drugs to be reviewed for pediatric use. Dr. Shelby characterized the Hydroxyurea Expert Panel:

- Nominated for evaluation by NICHD in May 2005
- Expert Panel members approved in April 2006
- Draft Expert Panel Report released in November 1, 2006
- Expert Panel meeting held January 24–26, 2007, in Alexandria, VA.

The methylphenidate and Adderall<sup>®</sup> study is designed to determine whether there are cytogenetic effects in children treated for attention deficit/hyperactivity disorder (ADHD).

### **Measurement of Cytogenetic Endpoints in Lymphocytes of Children Diagnosed with ADHD and Treated with Methylphenidate or Adderall**

*Kristine Witt, M.S., Genetic Toxicologist, Environmental Toxicology Program, Division of Intramural Research, NIEHS, NIH*



Dr. Witt explained that NIEHS and the ADHD program at Duke University Health System are collaborating for this clinical research study. This presentation describes a study to measure cytogenetic endpoints in lymphocytes of children diagnosed with ADHD and treated with methylphenidate (MPH) or Adderall. MPH is the active agent in Ritalin<sup>®</sup>, which has been in use since the 1950s. Since 1990, use has been rapidly increasing, and there are a variety of new products. Annual prescriptions for MPH in the United States exceed 5 million. Adderall is a stimulant composed of mixed amphetamine salts; it was introduced in 1999. Today, almost 50 percent of all new prescriptions for stimulants for ADHD are for Adderall. The American Academy of Pediatrics and American Academy of Child and Adolescent Psychiatry recommend the use of stimulants such as Adderall and MPH as front-line treatment for ADHD.

Cytogenetic effects in children treated with MPH were published by El Zein et al. in 2005. The study showed that 3 months of MPH treatment resulted in significant increases in three endpoints of chromosomal damage in lymphocytes of all 12 study subjects. Endpoints evaluated included sister chromatid exchanges (SCE), chromosomal aberrations (CA), and micronuclei (MN). There was no clear, consistent evidence for MPH-induced genetic damage, including:

- Negative in bacterial and mammalian cell mutagenicity assays
- Mixed results in in vitro chromosome damage assays (negative in human lymphocytes)
- Negative results in four in vivo mouse micronucleus tests
- No potential for chromosome damage in well characterized in vivo mammalian test system.

In response to these study results, NICHD convened a group of scientists from federal agencies to review and evaluate the report. The participating agencies were NICHD, NIEHS, FDA, the Environmental Protection Agency, and the Centers for Disease Control and Prevention. Protocol deficiencies were identified, and the El Zein et al. publication raised a red flag. The consensus from the federal meeting was that there is a clear need for a well designed study to clarify potential risk for MPH-induced cytogenetic damage. Study design considerations included:

- Sufficient statistical power was needed to provide definitive data.
- Evaluation of SCE, CA, and MN endpoints was necessary.
- Adherence to stringent GLP, international guidelines in cytogenetic analyses at experienced analytical laboratory (Covance Laboratories, Vienna, VA).
- Comparable data on the two most frequently prescribed ADHD medications was desirable.
- Clinical work conducted at a highly respected ADHD research, diagnostic, and treatment center.

The Duke ADHD program ([www2.mc.duke.edu/adhdprogram/](http://www2.mc.duke.edu/adhdprogram/)) is a nationally recognized leader in ADHD research, diagnosis, and treatment. The program has been involved in numerous NIH- and industry-sponsored trials. It has an internationally respected staff, which is directed by Scott Kollins, Ph.D.

The basic study design includes two cohorts of 30 ADHD children each for whom pharmacological treatment with stimulant is indicated. Baseline blood samples will be drawn before 3 months of treatment with either an MPH-based product (cohort 1) or an Adderall-based product (cohort 2). A second blood draw will be taken after the 3-month treatment period.

Standard lymphocyte cultures will be prepared for each study subject prior to the initiation of drug therapy and again after 3 months of therapy. SCE, CA, and MN will be assessed in lymphocytes. In addition, MN will be measured in reticulocytes using flow cytometry. Study inclusion criteria are:

- Age 6–12 inclusive, either sex
- Any ethnicity/race
- Diagnosed at Duke with ADHD, any subtype, using rigorous comprehensive criteria
- Appropriate candidate for pharmacological therapy with MPH or Adderall
- Stimulant-drug naïve.

Study exclusion criteria are not meeting any of the above, plus:

- Comorbid psychological conditions
- Diagnostic x-rays within the past 3 months
- Abnormal ECG.

Subjects will receive exceptional medical care, including:

- Thorough physical/psychological examination by Duke University Medical Center physicians/psychologists
  - Determination of ADHD status, appropriate treatment regimen
- Physical/psychological exams administered weekly for the first month, monthly thereafter
  - Monitor health
  - Effectiveness of medication
- At study completion, transition counseling is provided to family
  - Medical records sent to private physician or
  - Arrangements made within network of physicians assisting Duke ADHD program in providing continuity of care.

The study's current status is:

- 35 subjects enrolled; 10 additional subjects scheduled for screening through December 2006
- Pre- and posttreatment blood samples for 22 subjects
- Attrition: 3 early terminations, 1 lost to follow-up, 1 termination by study staff.

The projected study timeline is:

- Enrollment to be completed by end of April 2007
- Final blood samples obtained by early August 2007
- Data collection completed by November 2007
- Data analysis completed by December 2007.

### **Methylphenidate: Relevant Animal Models for Genetic Toxicity**

*Suzanne Morris, Ph.D., Research Geneticist, Division of Genetic and Reproductive Toxicology, National Center for Toxicological Research (NCTR), FDA, DHHS*

Dr. Morris described three studies of MPH genetic toxicity in humans, nonhuman primates (NHPs), and mice. The NHPs and mice studies were designed to develop relevant animal models

for studying MPH genetic toxicity. These studies were funded through an interagency agreement between NICHD and NCTR.

Dr. Morris described the design of the El-Zein et al. (2005) human study:

- Juvenile human patients with ADHD were exposed to MPH for 3 months
- Gene-toxicity endpoints measured in peripheral blood samples after 3 months of exposure
- Induced frequencies compared with pre-exposure frequencies for each patient
  - Increase in micronucleus frequency
  - Increase in SCE frequency
  - Increase in chromosome breakage.

The design for studying MPH in nonhuman primates (NHPs) was as follows:

- Test subjects
  - 2-year-old, male NHPs
  - Test subjects passed all health checks and were released from quarantine
  - Underwent preliminary training for dosing, blood withdrawal, and behavioral testing
  - Test subjects underwent chair training
- Exposure to MPH
  - Dispersed in Prang (dose certification)
  - Dosed 2x per day (dosing syringe)
  - Three dose groups
    - Control: 10 NHPs
    - Low: 0.15 mg/kg 2x/day, 10 NHPs
    - High: 1.50 mg/kg 2x/day, 10 NHPs
- Behavioral assessments
  - NCTR OTB: NHPs evaluated daily for acquisition of skills during treatment
- Exposure assessments and PK studies
  - Determine MPH and ritalinic acid levels in serum at monthly intervals
- Genetic toxicology evaluation
  - Micronucleus frequency
    - Baseline
    - 1-month intervals
  - Chromosome painting
    - Baseline
    - 3-month intervals
  - HPRT (hypoxanthine phosphoribosyltransferase) gene mutant frequency
    - Baseline
    - 3-month intervals
    - Mutants sequenced for confirmation.

Dr. Morris characterized chromosome painting methodology as follows:

- Accurate and rapid method for the detection of chromosome translocations
- Translocations are detected as “color junctions” that demarcate the position of the rearrangement of two chromosomes (red and green chromosomes)

- Translocations are considered to be a stable rearrangement
- Associated with an increased incidence of cancer.

A previous study (NTP, 1995. Toxicology and carcinogenesis studies of methylphenidate hydrochloride [CAS 298-59-9] in F344/N rats and B6C3F1 mice [feed studies]. *Technical Report Series*, number 439) reported:

- Increases in liver adenocarcinomas in B6C3F1 mice after administration of MPH
- No increases in mutant frequency in Salmonella with or without S-9 (metabolic activation)
- Tumors arose through cell proliferation rather than mutation
- Mutations were not measured in the target tissue (liver)
- Comparison to human difficult because PK studies had not been performed in the mouse.

Dr. Morris described the experimental design of the mouse studies:

- PK study
  - Ritalinic acid is major metabolite (same as primates)
  - NCTR B6C3F1
- Dose-range study
  - Doses ranged from 250 ppm to 4,000 ppm for 28 days
  - Expected toxicities from the 2,000-ppm to the 4,000-ppm doses were not observed
    - HPRT gene mutant frequency: no increase
    - Micronucleus frequency: no increase
    - Taconic Farms B6C3F1
- Mutation study
  - Ongoing at present time
  - Focus on liver, but all tissues to be frozen at sacrifice
  - Stratagene/Taconic BigBlue (B6C3F1) mice.

Dr. Morris described the cII gene mutation assay in the BigBlue mouse model. The cII gene is integrated into the genome of every cell of the animal. The gene can be retrieved as a reporter gene for mutational analysis in any tissue with sufficient DNA extracted from that tissue.

BigBlue mutation studies are as follows:

- BigBlue mice exposed to 0, 50, 150, 250, 500, 1,000, 1,500, 2,000, and 4,000 ppm for 24 weeks; intermediate sacrifice of high dose (three animals) at 4 and 12 weeks
- These doses include those used in the cancer bioassay and additional doses to inform the dose–response curve
- Livers will be used to determine the cII mutant frequency
- Peripheral blood will be used to determine the frequency of micronuclei
- Splens will be used to determine the mutant frequency in the HPRT gene
- Data will be used to determine mode of action for mouse liver tumor formation by MPH (cell proliferation versus mutation).

Future directions include: (1) sensitive populations, (2) evaluation of possible neurological changes in NHP by PET scan, and (3) evaluation of possible mutation (cII) in mouse brain (frozen BigBlue tissue).

## **Morphine Analgesia**

*John van den Anker, M.D., Ph.D., Executive Director, Research Pharmacology Unit, Children's National Medical Center*

The purpose of this presentation was to describe a proposed clinical trial to define the effective and safe dose of morphine in preterm infants. The final goal of the proposed research is to define the effective and safe dose of morphine for preterm infants. Dr. van den Anker began by briefly reviewing the historical drug “development” of morphine for children, such as tonics containing morphine and opium for colic, diarrhea, and teething. Dr. van den Anker also briefly reviewed the epidemiology-of-pain studies such as Anand et al. (1987, 1992), Porter and Anand (1998), and Simons et al. (2003). These studies revealed that few neonatal procedures were preceded by analgesia. Two subsequent studies examined appropriate morphine dosing in neonates:

- Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomized trial (Anand et al., 2003)
- Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial (Simons et al., 2003).

Dr. van den Anker listed the following reasons to study morphine analgesia in children:

- Recognition that pain is experienced by preterm neonates
- More common use of morphine
- Use of “customary” mg/kg therapeutic doses
- High incidence of serious adverse drug events.

The proposed clinical trial has four hypotheses and five specific aims. Hypotheses 1 and 3 are:

- Enzymatic activity of UGT2B7, which can be characterized by the formation clearances of morphine to M3G and morphine to M6G, is directly related to gestational and postnatal age.
- The elimination rate of morphine and its metabolites is dependent on GFR and therefore on the stage of development.

Specific aims 1 and 3 are to evaluate the relationship of:

- Developmental stage (defined by gestational and postnatal age) to UGT2B7 activity
- GFR to the elimination clearances of morphine, M3G, and M6G; and morphine concentrations in blood and urine.

The study design for specific aims 1 and 3 is:

- 60 preterm infants, stratified according to gestational age
- Clinical indication for morphine administration
- Measurement of GFR and morphine and its metabolites in blood and urine.

Other reasons to study morphine analgesia in children include:

- Interindividual variation in morphine PK/PD may arise from differences in enzyme expression and/or the presence of allelic variants (SNPs)

- Genotyping of known SNPs and the discovery of new SNPs might further improve the use of morphine in these infants.

Dr. van den Anker presented current evidence (Lötsch and Geisslenter, 2006) for a genetic modulation of the response to analgesics, describing frequencies of the following genes: OPRM, COMT, MC1R, CYP2D6, and ABCB1.

Hypotheses 2 and 4 are:

- Variations in the UGT2B7 gene (SNPs) are associated with variable activity of the UGT2B7 enzyme.
- Clinical response to morphine in preterm infants is related to variation in the COMT (catechol-O-methyl transferase) gene and the OPRM ( $\mu$ -opioid receptor) gene.

Specific aims 2 and 4 are to evaluate the relationship of:

- UGT2B7 genetic variability to the UGT2B7 activity
- OPRM and COMT genetic variability to clinical response after administration of morphine.

The study design for specific aims 2 and 4 is:

- Pain assessment using validated pain assessment tools (PIPP, NIPS)
- Videotaping of all preterm infants in the study (total body and face separately)
- SNP genotyping and SNP discovery.

Specific aim 5 is to develop a population PK/PD model of morphine dosing based on gestational age, postnatal age, GFR, and variability in UGT2B7, OPRM, and COMT genes.

The current status of the study is:

- 14 patients (10 males, 4 females, 9 African Americans, 2 Hispanics, 3 Whites)
- Gestational age 23–30 weeks
- Postnatal age 1–30 days
- 10 patients were studied during 96 hours
- One 24 hour, one 48 hour, one 72 hour, and one 4 hour
- 2 patients needed additional morphine.

Dr. van den Anker concluded:

- UGT2B7 activity and GFR determine metabolism and excretion of morphine in the neonate.
- Mutations in UGT2B7 and renal drug transporters may play a role.
- Mutations in OPRM and COMT genes significantly change the experience of pain.
- Disease, environment, and therapeutic interventions may play a role.

## Setting Priorities for Off-Patent Clinical Drug Trials for Children: A Decision Model for Consideration

Bryan R. Luce, Ph.D., M.B.A., Senior Vice President, Science Policy, United BioSource Corporation

The goal of this project was to develop recommendations for an objective priority-setting process for clinical trial priorities of off-patent drugs that still values subjective knowledge and input of stakeholders. Methods to achieve the goal included:

- Literature review
  - Identified key theoretical aspects of priority setting
  - Provided best practice and ethical considerations
- Identified institutions with strong priority setting processes already in place
  - Domestic and international
  - Evaluated each on basis of findings from literature review
- Compiled the most common criteria and approaches used and refined to fit NICHD's specific needs.

The following primary “practical” approaches were analyzed:

- National Institute of Mental Health (NIMH)
- Centers for Disease Control and Prevention
- National Institute of Health and Clinical Excellence
- Catalan Health Services (CatSalut)
- The Hospital for Sick Children (SickKids)
- Institute of Medicine (IOM)
  - Priority Areas for National Action (2003)
  - Priorities for Health Technologies Assessment (1992).

Criteria to consider in priority setting include:

- Relevance to organization's mission and goals
- Prevalence of disease
- Health burden/severity
- Cost burden
- Feasibility
- Likelihood of impact
- Urgency of need
- Potential for innovation
- Transparency
- Potential for growth and change
- Ethical considerations

The recommended priority setting process was based on *Setting Priorities for Health Technologies Assessment: A Model Process* (IOM, 1992). This process:

- Was developed to use subjective measures in priority setting using standardized rankings
- Uses three inputs
  - Criteria: facets on which decisions are to be made
  - Criterion weights: relative importance of each criterion selected
  - Criterion scores: performance of a potential priority option within each criterion selected.

Model output is a number meant exclusively for the purpose of comparing priority setting options; higher is better.

Dr. Luce characterized criteria and criterion weights:

- Criteria
  - Can include any number of criteria; potentially chosen from previous list of priority setting themes
- Criterion weights
  - Before any priority options are considered, each criterion is assigned a weight
  - All weights are relative to the criterion deemed least important
  - Method
    - Define scale (exact numbers used are irrelevant so long as scale kept constant and starts at 1)
    - Determine least important criteria and assign it a weight value of 1
    - Give all other weights a value  $1 \leq W_x \leq \text{Max}$ , based on relative comparison to least important.

Some sample criteria are:

- Prevalence
- Relevance to NIH/NICHD missions and goals
- Health burden/severity
- Cost burden
- Likelihood of impact
- Urgency
- Immediacy of benefit
- Feasibility
- Innovation

Dr. Luce listed sample weights and sample scores for the above sample criteria, and he characterized the criterion scores as follows:

- Each priority option gets a score for each criterion selected
- Objective scores should be used whenever possible
- Subjective scores should be set by consensus of experts; ideally separate from those who set the weights.

The weights and scores for various criteria can be used to calculate priority scores for drugs to treat different conditions. Dr. Luce characterized priority score comparisons as follows:

- Standardized scores allows comparison of all priority options even when the treatments, goals, etc. differ dramatically
- Subjective measures given equal impact across all options; minimizes “randomness” often associated with subjective, group-based decision-making.

The final process should remain dynamic, with criteria and weights reevaluated for every approval cycle, but not within a cycle. The process is as follows:

- Define criteria
  - Internal board/advisory process
  - Workgroups
  - Stakeholder consensus meetings



- Ideally not same people that will eventually score priority options
- Define weights given to each during given time period using same group options as above
- Score priority options
  - Best recommendation: Delphi consensus group (workgroup)
  - Clinician input vital for subjective measures
  - Ideally not same people that did criteria/weights
- Draft recommendations for acceptance
- Public feedback opportunity
  - Sharing some aspect of scoring methodology should add credibility
  - Can offer equation and final scores in support, if so inclined
- Decision finalization.

### **Approaches to Prioritization**

*Anne Zajicek, M.D., Pharm.D., Pediatric Medical Officer, OPPB, NICHD, NIH, DHHS*

The purpose of prioritizing is to focus on drugs with most pressing health need (health benefit) to study. For BPCA, prioritization began with a master list of all off-patent drugs that lacked adequate pediatric labeling ( $N = 200$ ). The next steps were to consider criteria: (1) availability of safety and efficacy data, (2) whether additional data are needed, (3) whether new studies will produce health benefits, and (4) reformulation. In addition, there was consultation with experts in pediatric practice and research as well as others. The goal of this prioritization was to develop, prioritize, and publish an annual list of pediatric drugs requiring further study ( $N = 5-15$ ). The biggest challenge to developing a prioritized list of pediatric drugs is objective measures. Additional criteria concerning feasibility are: (1) frequency of use/frequency of condition, (2) ability to study the patient population, and (3) ability of the study to be performed: consent.

There is an IOM report on NIH criteria for priority setting (Committee on NIH Research Priority Setting Process. *Scientific Needs: Improving priority setting and public input at the National Institutes of Health*. Washington, DC: National Academy Press, 1998). The report described NIH criteria as public health needs including (1) incidence, (2) severity, (3) cost of disorder, (4) need to act rapidly, and (5) selection of measures as an expression of values. Other criteria to be considered include:

- Frequency of conditions: upper respiratory infections, otitis media
- Mortality: no study of chronic disease
- Economic costs: questions of how costs are quantified; underfunded diseases that are short and/or lead to rapid death
- Public health emergencies: divert funds for research of broader long-term impact (asthma).

Additional criteria are:

- Scientific quality of research
- Potential for scientific progress
- Portfolio diversification
- Adequate support of infrastructure
  - Training

- Equipment
- Overhead
- Need for public input.

The following criteria should be considered in priority setting:

- Relevance to NIH’s mission and goals
- Prevalence of disease
- Health burden/severity (health benefit)
- Likelihood of impact (need for more data)
- Urgency of need
- Potential for innovation
- Transparency/public input
- Feasibility
- Ethical considerations
- Need for new formulation

## Update of Current Conditions Under Development

### Introduction

*Robert Ward, M.D., Chair, BPCA Drug List Prioritization Experts, Professor of Pediatrics, University of Utah Health Sciences Center*

BPCA was enacted in January 2002 with the overall purpose of improving the level of information about pharmaceuticals used to treat children with the following goals:

- Identification and prioritization of drugs for further study
- Conduct of clinical trials to learn more about the efficacy and safety of drugs in children
- Development of a process for prioritizing drugs used in children.

In developing and prioritizing the list of drugs for study in children, the following must be considered:

- Availability of information
- Whether additional information is needed
- Whether new pediatric studies will produce health benefits
- Whether reformulation of the drug is necessary.

In an effort to maximize the gathering of sufficient data and to target key areas of research interest in the medical community for the list in 2006, NICHD and FDA modified the previous individual drug/indication approach to a therapeutic class or condition-based approach. With this proposed condition-based approach, the goals have been to identify gaps in scientific knowledge and determine key research agendas in pediatric medicine and the treatments of these conditions that need further study. NICHD and FDA believe that this approach will:

- Allow a comparison of drugs within a therapeutic class (on- and off-patent)
- Give a broader description for the availability and use of these drugs in children
- Allow for focused expertise in therapeutic areas that will subsequently give more insight into feasibility and study designs.

The following conditions are under consideration for 2007:

- Infectious diseases: methicillin-resistant *Staphylococcus aureus* (MRSA)
- Cardiovascular diseases: pediatric HTN

- Oncology: neuroblastoma
- Respiratory diseases: asthma
- Analgesia: neonatal pain.

Dr. Ward posed the following questions regarding MSRA:

- Is this condition of sufficient frequency to warrant a clinical trial?
- Is this condition of sufficient severity to warrant a clinical trial?
- Are the diagnostic criteria clear; is the condition easily diagnosed or are there issues that make the diagnosis problematic?
- Drugs prescribed for this condition include: clindamycin, tetracycline, doxycycline, trimethoprim-sulfamethoxazole. Would participants propose adding or deleting other drugs on this list?
- What study designs would participants propose for this condition using these drugs?

Dr. Ward posed the following questions regarding HTN:

- Is this condition of sufficient frequency to warrant a clinical trial?
- Is this condition of sufficient severity to warrant a clinical trial?
- Are the diagnostic criteria clear; is the condition easily diagnosed or are there issues that make the diagnosis problematic?
- Most common treatments include: calcium channel blockers, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and diuretics. (Adolescent HTN is associated with obesity.)
- Would participants propose adding or deleting other drugs on this list?
- What study designs would participants propose for this condition using the aforementioned drugs considering obesity as a confounding factor?

After the initial induction therapy for high-risk pediatric neuroblastoma, 13-cis-retinoic acid treatment may be used to slow tumor growth. Dr. Ward asked the following questions about neuroblastoma:

- What is the PK of 13-cis-retinoic acid in children with neuroblastoma?
- Are there any problems regarding formulation?
- How would participants address these issues?

Dr. Ward posed the following questions regarding asthma:

- Is this condition of sufficient frequency to warrant a clinical trial?
- Is this condition of sufficient severity to warrant a clinical trial?
- Are the diagnostic criteria clear for all age groups; is the condition easily diagnosed or are there issues that make the diagnosis problematic?
- Drugs prescribed for this condition include: beta agonists, corticosteroids, leukotriene modifiers, anticholinergics, and xanthines.
- Would participants propose adding or deleting other drugs or classes on this list?
- What study designs would participants propose for this condition using the aforementioned drugs?

Dr. Ward posed the following questions regarding neonatal pain:

- Is this condition of sufficient frequency to warrant a clinical trial?
- Is this condition of sufficient severity to warrant a clinical trial?
- Are the diagnostic criteria clear; is the condition easily diagnosed or are there issues that make the diagnosis problematic?
- Besides chlorprocaine, which has been suggested as an off-label drug to consider for study under BPCA, would participants propose adding or deleting other drugs on this list?
- What study designs would participants propose for this condition using the aforementioned drug or are there other drugs they would consider?

## **Mortality, Hospitalizations, Physician Visits, and Chronic Conditions in Children in the United States**

*Norma Gavin, Ph.D., Senior Research Economist, RTI International*

The objectives of this project were to determine the relative medical burden of selected conditions as measured by rates of physician visits, hospital stays, and mortality; and investigate patterns in these rates over age groups, gender, and principal diagnoses.

Dr. Gavin defined two condition-specific measures:

- Rates of medical events = number of events among children with the condition ÷ population estimate
- Prevalence of medical events = number of children with the condition ÷ population estimate.

Dr. Gavin explained the relationship between the condition-specific measures:

- Rates of medical events = prevalence × average number of events per child with the condition
- For conditions where the average number of medical events per child >1 (e.g., physician visits), rates of medical events > prevalence.

Data requirements for computing condition-specific rates of medical events include:

- Be representative of the U.S. pediatric population
- Report medical events for a comprehensive range of pediatric medical conditions treatable by prescription medications
- Report age and gender of the children with the medical events
- Be of adequate size to stratify the medical events by condition and the selected demographic characteristics
- Code conditions or disease categories similarly enough to enable cross-file syntheses by condition.

Potential data sources from person-based files and their characteristics include:

- Medical Expenditure Survey
  - Provides a nationally representative sample that provides prevalence and average number of medical events per child

- Small sample size for BPCA purposes
- Conditions are from parent report and not specific enough for BPCA purposes
- Claims data
  - Provide estimates of the prevalence and average number of medical events per child for specific populations (e.g., Medicaid, health maintenance organization [HMO] enrollees)
  - Larger sample sizes
  - Data are not nationally representative.

Alternative data sources from medical-event-based files provide data sources for which the medical event is the unit of observation. Condition-specific rates of medical events rather than prevalence estimates can be computed from these data sources. They provide comparable measures of the relative medical burden across a variety of medical conditions.

Data sources used as numerators in the condition-specific rates of medical events include:

- Physician visits: National Ambulatory Medical Care Survey (NAMCS)/National Hospital Ambulatory Medical Care Survey (NHAMCS), 2000–2004
- Hospital discharges: Kids' Inpatient Database (KID), 2003
- Mortality: Multiple Cause of Death Public Use Files, 2000–2003, from the National Vital Statistics System (NVSS).

There are several limitations of medical event-based files:

- Cannot obtain prevalence estimates or estimates of the average number of events per child
- Cannot link events across children
- Need external source of population estimates for denominators to produce rates.

Data sources used as denominators in the rates of medical events include:

- Number of births in year for neonatal and postneonatal age groups from NVSS
- Mid-year Census estimates for the gender and other age categories
  - Noninstitutionalized civilian population for physician visit data
  - Resident population for the hospital discharge and mortality data.

NAMCS and NHAMCS are nationally representative sample surveys of physician visits conducted annually. NAMCS is a weighted national sample of physician visits to nonfederal office-based physicians. Its sample covers most physician specialties (anesthesiology, pathology, and radiology excluded). NHAMCS is a weighted national sample of patient visits to emergency departments (EDs) and outpatient departments (OPDs) of nonfederal short-stay hospitals.

Dr. Gavin characterized the physician visit data from the combined NAMCS/NHAMCS files for 2000–2004:

- 104,015 observations for children (<18 yrs)
- Sample size too small for estimates of rare conditions
- Diagnosis variables and coding
  - Three diagnostic variables coded in five-digit ICD-9-CM for each physician, ED, and OPD visit

- Only captures diagnosis if (1) provider is included in the sample—reproductive and mental health providers appear to be underrepresented and (2) provider records it in the medical record.

Dr. Gavin characterized the hospital discharges data from KID for 2003:

- Only all-payer inpatient care database specifically for children in the United States
- Sample of pediatric discharges from short-term general and specialty hospitals in 36 states
  - Systematic random sample includes 10 percent of uncomplicated in-hospital births and 80 percent of other pediatric discharges in the State Inpatient Databases (SID)
  - 2,410,920 discharges for children ages birth to 17 years
  - Not geographically representative so weighted to national totals based on data from the American Hospital Association Annual Survey of Hospitals
- Diagnosis variables and codes
  - Principal diagnosis and up to 14 secondary diagnosis codes for each hospital stay
  - Codes are presented in five-digit ICD-9-CM.

Dr. Gavin characterized the mortality data from Multiple Cause of Death Public Use Files for 2000–2003:

- Universe of all deaths in the 50 states plus Washington, DC
  - Combined files for 2000–2003
  - 185,916 observations for decedents (<18 years old)
  - Sample size is too small for estimates of rare conditions
- Diagnosis variables and codes
  - Underlying cause of death and 19 contributing causes of death reported for all decedents
  - Codes are presented in four-digit ICD-10 categories.

Dr. Gavin explained how condition coding from ICD-9-CM and ICD-10 can be combined to estimate condition-specific rates. Type of medical event can be distinguished by the variable used to define the relevant cases and tabulated as follows:

- First column: primary or principal diagnosis or underlying cause of death only
- Second column: any of the 3 physician visit diagnoses, 15 hospital discharge diagnoses, or 20 cause of death fields
- Rows for all children and for children broken out by age group, gender, and principal diagnosis.

Dr. Gavin provided the following example for asthma rates per 100,000 children:

	<u>Primary or Principal Diagnosis</u>	<u>Any Diagnosis Field</u>
• Physician visits	8,601.03	13,722.60
• Hospital discharges	226.91	452.90
• Deaths	0.28	0.36

Dr. Gavin compared estimated asthma physician visit rates derived from NAMCS/MHAMCS for 2000–2004 with estimated asthma prevalence rates derived from 2001–2002 Michigan Medicaid

claims data (Dombkowski et al., 2005). NAMCS/NHAMCS estimates are consistent with the prevalence estimates from Dombkowski et al. All physician visit rates are greater than the prevalence estimates. Similar patterns are found over age groups (physician visit rates and prevalence decline with age) and gender (males have higher physician visit rates and prevalence than females)

Dr. Gavin presented estimates of asthma hospital discharges derived from Dombkowski et al., 2005, and KID 2003, as well as hospital admissions among Medicaid versus employer-insured children. Taking into consideration the difference in the populations, the Dombkowski et al. estimates of the percentage of children with one or more hospital stays for asthma are consistent with our hospital discharge rates. Similar patterns are found over age groups (younger children are more likely to be hospitalized than older children) and gender (males are more likely to be hospitalized than females).

Data showing disease-specific average annual rates of physician visits, hospital discharges, and mortality provide information on the total medical burden of the disease. These data do not show the prevalence of the disease in the population because they are based on data where medical events are the unit of analysis. They are, however, consistent with estimates of disease prevalence in the literature.

## **Frequency of Medication Usage in the Pediatric Population**

*James Korelitz, Ph.D., Senior Epidemiologist, Westat*

The objective of this project is to provide estimates of the frequency of medication use in pediatric populations: (1) among all children and (2) among children with a specific medical condition. The following data sources were used to determine estimates:

- Secondary data sources (i.e., existing databases)
- Populations specified by type of insurance:
  - Medicaid >25 percent
  - Commercial >60 percent
  - Uninsured <15 percent
- Current analysis restricted to children covered by public or private insurance plans (i.e., Medicaid and commercial populations)
- Focus on outpatient prescription drugs—data available from administrative claims
- Medicaid
  - Centers for Medicare and Medicaid Services
  - Medicaid Analytic eXtract (MAX) files
- Commercial
  - Prescription claims
    - Pharmacy benefits manager
    - Medical and prescription claims
    - Managed care organization.

Dr. Korelitz characterized the Medicaid/MAX files:

- Demographic, outpatient pharmacy, and other paid medical service claims
- 18 states selected in year 1 (drug data only)
- 7 states in common with Kids' inpatient database included in year 2 (drug and medical data)
- 3.1 million children enrolled during 2000–2001 included in year 2 analyses.

Dr. Korelitz characterized the commercial data:

- Prescription claims
  - Caremark; pharmacy benefits manager
  - Participant level prescription data from 50 states
  - 11.5 million children enrolled during 2005
- Medical and prescription claims
  - Ingenix LabRx Database™ (UnitedHealth MCO)
  - Employed, commercially insured population
  - Participant level medical and prescription data from 50 states and Washington, DC
  - 4.3 million children enrolled during 2004–2005.

Another aspect of this project is to estimate the frequency of drug use for specific medical conditions. Dr. Korelitz provided an example of estimating asthma-related medications among children with asthma. Three files were examined:

- Personal: age, gender, eligibility
- Drug: national drug code (NDC), fill date
- Diagnosis: ICD-9-CM, visit/diagnosis date.

The following methods and definitions were used to estimate frequency of drug use:

- Asthma: claim filed with an ICD-9-CM code starting with “493” from an outpatient service (e.g., physician visit, ED visit)
- Asthma medications: classified by general, class, and subclass categories that incorporate route of administration (e.g., inhaled versus oral corticosteroids)
  - Claim filed for outpatient prescription asthma-related medication
  - Includes asthma-related drugs dispensed within 90 days following diagnosis of asthma
- Requires child to be enrolled for 90 days following diagnosis of asthma.

In this example, the estimated asthma prevalence was 241,614 children with a claim submitted for asthma. Data were derived from a 2004–2005 commercial population. “Treated prevalence” of asthma was 5.7 percent. This data source estimated that 178,561 children received an asthma-related outpatient drug prescription dispensed within 90 days of asthma diagnosis. The percentage of asthma-related drug use among children with asthma was 73.9 percent.

Dr. Korelitz listed the strengths and limitations in using the just-described approaches to estimate frequencies of medication usage in pediatric populations. Limitations include:

- Secondary data source
- Subset of all drugs used: prescription, drug claim submitted, outpatient use
- Some misclassification/data errors
- Features of insurance plan affect use/claims



- Medicaid reporting issues
- No clinical validation of medical diagnosis
- No direct data on indication for drug prescription.

Strengths include:

- Large, nationwide study population
- Separate estimates for Medicaid and commercial populations
- Separate estimates by gender, age, race/ethnicity
- Continuous and non-continuous enrollees included
- Drug coding algorithm used to define meaningful “drug entities”
- Drug description (NDC) and fill date accurate
- Medical diagnosis recorded by medical staff.

Dr. Korelitz compared the estimated percentage of children with an episode/claim of asthma in past 12 months from five data sources:

- National Health Interview Survey (2003): 5.5 percent
  - 0–17 years old; parent-reported
- Medical Expenditure Panel Survey (1996): 4.9 percent
  - 5–17 years old; medical provider report
- Michigan Medicaid (2002): 5.8 percent
  - 0–17 years old; inpatient, outpatient, or ED claim
- Commercial claims data (2004–2005): 5.7 percent
- Medicaid claims data (2000–2001): 5.6 percent.

The percentage of children taking asthma medication among all children was estimated from the following data sources:

- Among all children
  - Michigan Medicaid (2002): 13 percent
  - Commercial claims data (2004–2005): 15 percent
  - Medicaid claims data (2000–2001): 14 percent
- Among children with asthma
  - Medical Expenditure Panel Survey (1996): 94 percent
    - Drug prescribed within year of diagnosis
  - Commercial claims data (2004–2005): 74 percent
  - Medicaid claims data (2000–2001): 81 percent
    - Drug prescribed within 90 days of diagnosis.

Additional potential analyses include:

- Updated/timely prevalence estimates
- Broader geographic representation of Medicaid
- Inpatient prescription data, especially for neonates
- Changes over time (i.e., is prevalence increasing, decreasing, or stable)
- More analysis of co-morbidities

- Analysis of concomitant medications
- Analysis of diagnoses prior to prescription
- Respond to ad hoc requests for special analyses (e.g., medical condition, drug group).

In summary:

- Frequency/prevalence of medication use is an important component in the decision-making process.
- Medication claims data provide estimates of frequency of use (with appropriate caveats).
- These estimates can be examined by subgroups (e.g., gender, age, race/ethnicity).
- Individual drug entities can be grouped and presented by meaningful drug classes.
- Frequency of use estimates can be examined by indication for use.
- Changes over time can be monitored.

### **Pediatric Infectious Diseases Working Group**

*Victor Nizet, M.D., Associate Professor, Pediatrics and Pharmacy, University of California, San Diego*

In this presentation, Dr. Nizet described the goals, initial discussions, and solicitation of input for the Pediatric Infectious Diseases Working Group. The overarching goal of the working group is to develop strategies to improve the understanding and treatment of pediatric infectious diseases. Specific goals are:

- Help to inform the activities and approaches of BPCA to pediatric infectious diseases
- Encourage better use of existing treatment modalities
- Identify novel research and clinical approaches to the treatment of pediatric infectious diseases
- Consider new paradigms for understanding host–microbe relationships through development.

The scope of the Pediatric Infectious Diseases Working Group includes basic, translational, and clinical research. Working group activities are as follows:

- Monthly conference calls
- NIH workshops of 20–30 invited experts (first workshop planned for March 2007)
- Draft statement(s) for public comment
- Summary recommendations in the *Federal Register*
- Influence on BPCA listing and NIH request for applications.

The following is a tentative, evolving agenda for the March 2007 workshop:

- Introductory session
  - Review of BPCA and *Federal Register* anti-infectives
  - Keynote: study design, data standards, endpoints (the OM experience)
- Serious pediatric infectious disease problems without standard management
  - Necrotizing enterocolitis
  - Community-acquired pneumonia
  - MRSA infections
  - Encephalitis in childhood

- Neonatal sepsis in the developing world
- Novel approaches in clinical study design
  - Improved use of electronic data
  - Genetic signatures of infection (microarray of host immune response)
  - Tissue-specific PK analysis
- AEs and medication toxicities.

Dr. Nizet briefly reviewed topics discussed at two workshops on novel antimicrobial therapeutics:

- Mining the natural world: discover, diversify, and deliver
  - 65–85 percent of antibiotics have come from microbes
  - 99 percent of world's microbial flora yet to be discovered
- Alternatives to direct killing of microbes
  - Targeting specific bacterial virulence factors
- Immunomodulation as a novel therapy for infections
  - Pharmacologically boost innate defenses
- Marine antibiotic discovery
  - >12 new genera of actinomycetes, fungi
  - >3,500 strains obtained
  - About 35 percent of strains show antibiotic activity against drug-resistant pathogens.

Dr. Nizet reviewed some recent research findings about identifying and targeting specific bacterial virulence factors and boosting host innate immune defenses. Dr. Nizet concluded by listing some considerations for bacteriophage therapy:

- Used rather extensively in countries of the former Soviet Union
- Research institute in Tbilisi, Georgia
- Renewed research interest in the United States due to problems of drug resistance
- Very safe (specific to bacterial cells)
- Targeted to individual pathogen
- Self-propagating therapy
- Resistance emerges, but phage can mutate to keep up.

### **Pediatric Hypertension: The 2006 Perspective**

*Rae-Ellen Kavey, M.D., M.P.H., Coordinator, Pediatric Cardiovascular Risk Reduction Program, Office of Prevention, Education, and Control, NHLBI, NIH, DHHS*

Dr. Kavey briefly reviewed some epidemiological aspects of HTN:

- More than half of adults >65 years have HTN
- Lifetime risk of HTN at age 55 = 90 percent
- HTN is the number one cause of cardiovascular disease (CVD), accounting for 62 percent of strokes and 49 percent of coronary events
- Globally, HTN is the leading cause of death in the world
- Children with HTN have a significantly increased risk for HTN as adults
- Even in children, HTN is associated with evidence of end organ damage

- Childhood HTN leads target organ damage such as left ventricular (LV) hypertrophy
- Carotid intima media thickness is increased in childhood primary HTN independent of the effects of obesity.

**Pediatric HTN Epidemic.** *The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents* defines pediatric HTN (blood pressure standards based on gender, age and height) as follows:

- Stage 1 HTN: systolic blood pressure (SBP) + diastolic blood pressure (DBP) >95th percentile but <99th percentile + 5mmHg
- Stage 2 HTN: SBP + DBP >99th percentile + 5mmHg.

Dr. Kavey reviewed the results of several studies that focused on:

- Prevalence of HTN in childhood (Rosner et al., 2000)
- Prevalence of HTN in obese children (Reinher et al., 2004)
- Cardiovascular risk factors in overweight children: relationship to gender, age, and degree of overweight (Reinher et al., 2004)
- Overweight, ethnicity, and prevalence of HTN in school-aged children (Sorof et al., 2004)
- HTN prevalence by body mass index (BMI) percentile (Sorof et al., 2004)
- BMI percentile by ethnic group (Sorof et al., 2004)
- Obesity prevalence and socioeconomic status (SES), gender, and race (Miech et al., 2006)
- Screening and counseling associated with obesity diagnosis in a national survey of ambulatory pediatric visits (Cook et al., 2005)
- Frequency of blood pressure measurement in children in four EDs (Silverman et al., 2000).

Regarding the question of whether there is a pediatric HTN epidemic, Dr. Kavey concluded:

- Overall, at least 5 percent of all children should have HTN.
- Obesity is strongly associated with HTN.
- The obesity epidemic should significantly increase frequency of HTN diagnosis.
- In specific ethnic groups and those with low SES, prevalence of HTN is much higher—as high as 25 percent.
- Ambulatory care surveys suggest that blood pressure measurement/interpretation is significantly underused.
  - Recognition of HTN is suboptimal.
  - Training of pediatric care providers in the importance and technique of blood pressure measurement/ interpretation is essential.

**Dietary Salt and HTN.** In adults, a consistent linear relationship between blood pressure and salt intake has been established. Dr. Kavey reviewed the results of several studies that focused on:

- Effects on blood pressure of reduced dietary sodium and the DASH diet (Sacks et al., 2001)
- Importance of salt in determining blood pressure in children (He and MacGregor, 2006)
- Sodium intake and blood pressure in newborn infants (Hofman et al., 1983)
- Long-term effects of neonatal sodium restriction on blood pressure (Geleijnse et al., 1997)

- Increased sodium concentrations in drinking water increase blood pressure in neonates (Pomeranz et al., 2002)
- Effects on blood pressure of a decrease in sodium use in institutional food preparation (Ellison et al., 1989).

Regarding dietary salt and HTN, Dr. Kavey concluded:

- Consistent linear relationship between dietary salt intake and blood pressure in children
- Salt intake early in life may have a programming effect on subsequent blood pressure
- Consider
  - A long-term trial of lower salt intake beginning in early infancy
  - A trial of reduced salt intake in children with pre-HTN or Stage 1 HTN.

**Drug Treatment of HTN in Children.** Dr. Kavey listed findings from *The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents*:

- “Pharmacologic therapy should be initiated with a single drug. Acceptable drug classes for use in children include ACE inhibitors, angiotensin-receptor blockers, beta blockers, calcium channel blockers and diuretics.”
- Dosing recommendations provided
- No information on appropriate sequence for selection of blood pressure medications in children.

The Food and Drug Administration Modernization Act of 1997 (FDAMA) led to a significant increase in pediatric trials of relatively new antihypertensive medications. Twelve medications are now approved by FDA for use in pediatric HTN. There are three ongoing pediatric HTN trials. To date, there is no information on the appropriate sequence for selection of blood pressure medications in children.

NICHD convened a Pediatric Hypertension Workshop in June, 2005, to develop a list of research gaps/priorities in drug treatment of pediatric HTN and discuss limitations of current trials. The workshop participants concluded:

- There are no trials of older medications with expired patent protection
- All current reports are of short-term therapy
- There are no trials to any endpoint except blood pressure itself
- There are different mechanisms for HTN in the pediatric age group
- There is very limited information on drug selection relative to pathophysiology
- There is a need for a pediatric version of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

ALLHAT examined major outcomes in high-risk hypertensive patients randomized to ACE inhibitor or calcium channel blocker versus diuretic. The results of ALLHAT showed that there was no difference between:

- Chlorthalidone and amlodipine for primary outcomes; amlodipine group had a 38 percent higher risk of hospitalized/fatal heart failure

- Chlorthalidone and lisinopril for primary outcomes; lisinopril group had a 15 percent higher risk of stroke, 10 percent higher risk of combined CVD, and a 19 percent higher risk of hospitalized/ fatal heart failure
- Chlorthalidone was superior to both ACE inhibitor and calcium channel blocker therapy in preventing major coronary events and increasing survival
- Chlorthalidone achieved better blood pressure control with better drug tolerance.

**Other Drug Trial Opportunities in Pediatric HTN.** Dr. Kavey suggested the following:

- RCT of early intervention using surrogate endpoints with long-term cohort follow-up to hard cardiovascular endpoints
- DASH diet versus beta blocker in HTN secondary to obesity with severely increased left ventricular mass index, with a minimum 1-year trial with blood pressure and left ventricular mass index as endpoints
- RCT of selected drugs for different settings with rational staged approach to treatment; for example, in HTN secondary to obesity: diuretic versus beta blocker versus combination
- RCT with graded blood pressure goal in pediatric populations at established high risk for very early CVD; for example, adolescents with end-stage renal disease: blood pressure target <75th percentile versus current goal (<90th percentile); minimum 5-year trial with surrogate and hard endpoints.

Dr. Kavey concluded that multicenter randomized long-term trials of drug and behavior change therapy for HTN in children, including surrogate endpoints, are an appropriate and achievable goal.

### **PK-Guided Dosing of Drugs in Pediatric Oncology**

*Victor Santana, M.D., Director, Division of Solid Malignancies, Department of Oncology, St. Jude Children's Research Hospital*

Therapeutic drug monitoring entails the measurement and interpretation of drug concentrations in biological fluids and the individualization of drug dosages or schedules with the goal of maximizing the therapeutic effect, minimizing the toxicities, or both. Although this concept has been widely applied to a variety of medications in different therapeutic classes including antibiotics, cardiovascular agents, and antiepileptics, the application has seen limited use with antineoplastic agents. For example, methotrexate is the only drug routinely monitored in most pediatric cancer institutions. One of the reasons for lack of acceptance is the poorly defined concentration–effect relationship for most anticancer drugs. Ultimately, the aim of this process is to deliver the optimum dose of each drug to each patient to maximize the probability of tumor response while minimizing toxicity.

Theoretically a drug should meet several criteria for PK-guided dosing to be useful, including:

- Narrow range between therapeutic and toxic systemic exposure (i.e., therapeutic index)
- Difficult to monitor drug effect (i.e., delayed or unpredictable)
- Large interpatient variability in drug disposition relative to inpatient variability.

Variability in drug disposition is clinically important. Drug disposition depends on four basic PK processes: absorption, distribution, metabolism, and elimination. These processes vary among patients and produce considerable differences in plasma concentrations for the same dosage given to all patients receiving treatment. Variability in the systemic clearance between patients causes them to have different systemic drug exposures. The extent of the systemic exposure further determines the position of the response in the concentration–effect relationship.

Despite the challenges of therapeutic drug monitoring for anticancer drugs in children, there is great potential in applying this concept in particular for maximizing information in phase I studies. In traditional phase I studies, fixed doses and escalations are predefined, which result in large PK variability, even when the magnitude of dose escalations is relatively small. Hence there is great clinical utility for establishing the therapeutic range that defines the concentrations producing efficacy as well as those producing undesirable AEs—also known as the concept of maximal tolerated systemic exposure. Dr. Santana summarized:

- Traditional phase I studies (maximum tolerated dose)
  - PK variability in anticancer drugs large (e.g., threefold to tenfold range CI)
  - Magnitude of dose escalations relatively small (e.g., 20–50 percent between dose levels)
- Maximal tolerated systemic exposure
  - Escalate “systemic exposure” rather than dose
  - Patients receive different doses within each level of treatment intensity.

Dr. Santana discussed an example of PK variability versus topotecan dose escalation. There was a large interpatient variability in clearance (about 500 percent); the increments between dose levels were about 20 percent; and there was an overlap in drug exposure across dose levels. Thus in this example, PK guided dosing could have minimized the PK variability among patients and improved efficacy and avoided toxicity.

Potential limitations of PK-guided dosing are:

- Characterize relation between drug exposure and drug effect
- Assess inter- and inpatient variability in drug exposure
- Practical considerations
  - Availability of accurate and precise analytical methods
  - Application of modeling and adaptive control strategies for dosage adjustments
  - Financial and patient considerations
- Export dosing approach to multiple institutions.

Design considerations that need to be taken into account for PK-guided dosing to be successful include the essential role of the pharmacokineticist to construct, evaluate, and select mathematically correct and physiologically appropriate models to determine the PK parameters. This analysis is essential because it determines the accuracy of the calculated PK parameters and subsequent dosage adjustments to achieve the target drug concentration. By establishing optimal sampling strategies, investigators can avoid excessive blood sampling of patients and facilitate studies in larger populations. Design considerations for PK-guided dosing of anticancer drugs include:

- PK metric to express drug exposure
- Selection of initial systemic exposure and dose
- PK structural model
- Plasma sampling strategy
- Logistics of dose adjustment.

In planning future studies that incorporate this approach, investigators must:

- Be aware of criteria for selection of a drug for PK-guided dosing
  - Narrow therapeutic index
  - Large inter-individual variability
  - Delayed and unpredictable pharmacologic effects
  - Relationship between drug exposure and effect
- Identify potential clinical application
- Gather resources and make necessary design considerations
- Begin with small studies, then export to larger cooperative group studies.

Dr. Santana summarized:

- PK-guided dosing improved use of some anticancer drugs (methotrexate, carboplatin).
- PK-guided dosing of topotecan is currently under study.
- There are many perceived advantages to this approach
  - Potential efficiencies in dose escalation process (few patients for Phase I)
  - Greater likelihood patient treated with pharmacologically active dose of new drug
  - Increased potential to identify active new agents in early drug development for Phase II studies.

### **13-cis-Retinoic Acid for Neuroblastoma in Children**

*C. Patrick Reynolds, M.D., Ph.D., Director, Developmental Therapeutics Program, Childrens Hospital Los Angeles, University of Southern California*

Dr. Reynolds explained that high-dose, pulse retinoic acid induces neuroblastoma differentiation. He described how retinoids regulate transcription and briefly discussed the relationships among naturally occurring retinoids (retinol [vitamin A], retinal, 9-cis-retinoic acid, all trans-retinoic acid, and 13-cis-retinoic acid). Studies have shown that 13-cis-retinoic acid causes sustained growth arrest of neuroblastoma:

- Neuroblastoma cell line given two pulses (2 weeks each) of 5  $\mu$ M 13-cis-retinoic acid
- MYCN protein expression by immunoblotting was down-regulated
- Phase I study achieved levels of  $7.2 \pm 5.3$   $\mu$ M peak and  $4.1 \pm 2.7$   $\mu$ M trough.

Dr. Reynolds discussed a Phase III trial in high-risk neuroblastoma (CCG-3891). Patient characteristics were as follows:

- 539 patients
- Study open from January 1991 to April 1996
- Average age at diagnosis = 2.5 years (range = 3 months to 17 years)
- 85 percent Stage IV



- 40 percent with MYCN genomic amplification.

Eight weeks after induction chemotherapy, patients received marrow harvest and purging, surgery, or local radiation. Patients were then randomized into (1) consolidation chemotherapy or (2) myeloablative chemotherapy/total body irradiation/autologous bone marrow transplant (ABMT). At 34 weeks after induction, these two groups were randomized into subgroups: (1) 13-cis-retinoic acid or (2) no 13-cis-retinoic acid. The second randomization produced a four-arm study.

Dr. Reynolds presented CCG-3891 study results for the following:

- Event-free survival for first randomization
- Event-free survival for second randomization
- Event-free survival from time of second randomization
- Overall survival from time of second randomization
- Overall survival stage 4 >1-year-old patients not in CR or VGPR after two cycles of induction chemotherapy

The CCG-3891 data showed at 6 years:

- An apparent 15 percent increase in survival for adding 13-cis-retinoic acid to ABMT
- An apparent 30 percent increase in survival for 13-cis-retinoic acid + ABMT versus chemotherapy.

Study results showed that, after adjustment for multiple comparisons, 700 patients (175 in each arm) may be required to establish a statistically significant effect on overall survival of ABMT + 13-cis-retinoic acid.

The following conclusions were made:

- Both myeloablative therapy and postmyeloablative therapy with high-dose, pulse 13-cis-retinoic acid improved event-free survival for high-risk neuroblastoma.
- There was an apparent increase in overall survival for both ABMT and 13-cis-retinoic acid, which was highest for patients randomized to receive myeloablative therapy followed by 13-cis-retinoic acid.
- Based on phase I PK data, plasma levels of 13-cis-retinoic acid are highly variable and likely subtherapeutic in many patients due to either differences in metabolism, bioavailability, or both.

The use of 13-cis-retinoic acid to treat neuroblastoma can be improved as follows:

- A registered indication for neuroblastoma would enable labeling of recommended dosing and approaches to use for the existing formulation in pediatric oncology.
- Labeling for neuroblastoma may help diminish burdens of the iPLEDGE system, will ensure drug reimbursement, and will facilitate availability to neuroblastoma patients in Japan.
- Pharmacokinetic and possibly pharmacogenomic studies could allow for PK and/or pharmacogenomic-guided dosing and would provide formal study of the various methods used to administer 13-cis-retinoic acid capsules to small children

Other opportunities include:

- Obtain data required for labeled indication for 13-cis-retinoic acid from the Children's Cancer Group (now the Children's Oncology Group [COG]) legacy data
- Continue ongoing United Kingdom/COG collaboration on PK and pharmacogenomic studies of 13-cis-retinoic acid in children
- Speed completion of PK and pharmacogenomic studies by considering international collaborations with countries such as Japan, Germany, and Brazil.

### **Information Gaps in the Management of Pediatric Asthma: Outpatient Setting**

*Stanley Szeffler, M.D., Head, Pediatric Clinical Pharmacology, National Jewish Medical and Research Center*

From the 1960s through the 2000s, the goals of asthma management and the medications used for treatment changed. Some of these changes evolved from a systematic review of the evidence, which resulted in updated treatment guidelines in 2002. For example, controller therapies for persistent asthma in children and adults were refined for mild, moderate, and severe conditions. However, there are still areas of need for treating and managing pediatric asthma in the new era of "asthma control." These areas include (1) early diagnosis and intervention, (2) prevention of progression, (3) management of severe asthma, and (4) improved management of significant exacerbations. Dr. Szeffler commented on labeling of pediatric medications:

- Overall industry has been very responsive; several companies have been outstanding
- Limited to safety and PK, especially in young children
- Efficacy difficult, but not impossible, to measure in young children
- New tools are being identified for application to studies, such as symptom measures, pulmonary function, biomarkers, and genetics.
- Need for standardization of these new tools.

There have been medication labeling changes for long-term asthma controllers, including age of treatment initiation. Treatment approaches have shifted from monotherapy to combination therapy. The following are examples of long-term controllers, with age of treatment initiation:

- Inhaled steroids: preferred long-term controller
  - Budesonide nebulizing suspension—1 year
  - Metered-dose inhalers (MDIs) and dry powder inhalers (DPIs)—most about 4–5 years, but mometasone 12 years
- Inhaled corticosteroid (ICS)/long-acting beta agonist (LABA): preferred supplementary therapy
  - Advair DPI—4 years
  - Symbicort MDI—12 years
- Leukotriene antagonists (LTRA): alternative initial and supplementary therapy
  - Montelukast—6 months (allergic rhinitis label)
  - Zafirlukast—5 years
- Leukotriene synthesis inhibitors: alternative to LTRA
  - Zileuton—12 years

- Anti-IgE (Omalizumab, Genentech)—12 years; studies in progress to 6 years
  - Theophylline: age limit unclear, monitoring required for adjusting dose, limited interest, diminishing use
  - Cromolyn—2 years with nebulizer, very safe, limited interest, and diminishing use.

Labeling changes for acute asthma management medications include:

- $\beta$ -adrenergic agonists (inhaled)
  - Albuterol—4 years
  - Levalbuterol—4 years
  - Terbutaline—12 years
- Special issues regarding inhaled medications
  - Lung delivery
  - Delivery device, that is, propellant, spacer, suspension
  - Systemic effect
- Corticosteroids
  - Prednisone, methylprednisolone
  - Parenteral forms: Solu-Medrol, Solu-Cortef
  - Labeling of steroids based primarily on past experience, not specific for children.

Labeling changes are needed for asthma medications used frequently but used “off label.” These medications include:

- Anticholinergics not specifically approved for asthma
  - Ipratropium bromide (Atrovent)
  - Ipratropium bromide/albuterol (Combivent)
  - Tiotropium (Spiriva)
- Macrolide antibiotics, both chronic and acute use
  - Clarithromycin
  - Azithromycin.

Labeling changes are needed for asthma medications that are used occasionally but that are not specifically labeled for asthma. These medications include:

- Specific allergen immunotherapy: injectable
- Sublingual allergen immunotherapy
- Magnesium sulfate
- Combination therapy: budesonide/formoterol as needed application

The goals for long-term control therapy are to (1) prevent symptoms, (2) improve pulmonary function, (3), reduce inflammation, and (4) resolve and prevent progression. Potential approaches to improving asthma control include:

- Early intervention
- Combination therapy
- Biomarkers
- Genetics
- Immunomodulators

- Maintenance therapy with escalation of combination therapy based on asthma control
- Maintenance combination therapy with as needed combination therapy
- Individualized approach based on asthma characteristics, biomarkers, and genetics.

In concluding, Dr. Szeffler reviewed the following aspects of asthma management:

- Current status of asthma medication
  - Inhaled corticosteroids are the preferred long-term control therapy for persistent asthma.
  - LTRA is considered an alternative initial long-term controller.
  - LABA is the preferred supplementary therapy.
  - Anti-IgE is viewed as blocking IgE effect.
  - None is considered an immunomodulator.
- “Individualized” approach”
  - Use asthma characteristics, biomarkers, and genetics to “profile” asthma severity
  - Select medications based on driving factors of disease presentation and predictors of response
  - Monitor response and assess reasons for treatment failure
  - Develop proactive approach and adjust therapy accordingly
- Filling the gaps—general comments
  - Asthma in children differs from adults
  - Response has multiple components
  - Preventing exacerbations and asthma progression are important targets in children
  - Attention should be directed to young children
  - Efficacy can now be measured in young children
- Filling the gaps—general recommendations
  - Focus attention on demonstrating efficacy in young children
  - Explore and standardize measures of efficacy
  - Consider use of biomarkers as a measure of efficacy
- Filling the gaps—recommendations on specific medications
  - Inhaled steroids: efficacy and safety of MDI in young children
  - LABA: efficacy and safety of MDI in young children
  - Combination ICS/LABA: efficacy and safety in young children
  - LTRA: efficacy in young children
  - Anticholinergics: indication for asthma in children and adults
  - Omalizumab: efficacy and safety in children <12 years
  - Macrolide antibiotics: efficacy in asthma and safety of long-term use.

### **Critical Asthma Therapy**

*Jerry Zimmerman, M.D., Director, Pediatric Critical Care Medicine, Professor, Pediatrics and Anesthesiology, University of Washington*

According to the Centers for Disease Control and Prevention, the prevalence of asthma among U.S. children increased from 3.6 percent in 1980 to 5.8 percent in 2003. Asthma is the third leading cause of hospitalization among persons under 18 years of age in the United States,

exceeded only by pneumonia and injuries. Dr. Zimmerman reviewed the results of several studies that focused on:

- Increased prevalence of asthma from 1965 to 2005 (Waltraud et al., 2006)
- Percentage of children <18 years old with current asthma, by race/ethnicity and sex—United States, 2001–2004 (*Morbidity and Mortality Weekly Report*, 2006;55:185)
- Variation in therapy by center for ventilated and nonventilated children with asthma (Roberts et al., 2002)
- Regional variation in intensive care unit (ICU) care for pediatric patients with asthma (Bratton et al., 2005)
- Admissions to 15 U.S. PICUs for status asthmatics, 2002–2003 (Randolph, unpublished data).

Although corticosteroids, beta agonists,  $\beta_2$ -agonists, and anticholinergics are generally considered efficacious for treating pediatric asthma, concerns about the safety of these medications in children remain. There are also questions and concerns about nonestablished therapies such as aminophylline/theophylline, magnesium sulfate, heliox, volatile agents (halogenated anesthetic gases), and extracorporeal life support (ECLS). There are several topics open for debate in the management of severe asthma. Dr. Zimmerman reviewed study results for the following medications:

- **Theophylline.** When combined with systemic steroids and inhaled  $\beta_2$ -agonists in children older than 2 years, IV aminophylline improves lung function (FEV1, PEF) within 6 hours but has not been shown to effect mortality, ventilation rate, length of stay, or frequency of albuterol. Rate of vomiting increased threefold without more seizures or tremors. Proposed actions of theophylline include nonselective inhibition of phosphodiesterases, antagonism of adenosine receptors, enhancement of IL-10 release, stimulation of catecholamine release, inhibition of pro-inflammatory mediators (e.g. prostaglandins, TNF- $\alpha$ ), modulation of intracellular calcium release, reduction of NF- $\kappa$ B nuclear translocation, promotion of apoptosis, and induction of histone deacetylase activity leading to augmentation of corticosteroid action. However, theophylline is still recommended as a second line agent for severe asthma.
- **Magnesium sulfate.** Studies have shown nonsignificant benefit in PEF and admission rate overall (two of seven studies were pediatric) but severe asthma attacks had a significant benefit in PEF, FEV1, and admission rate. However, no definitive studies have established effectiveness. In a comparison of treatment with magnesium sulfate versus albuterol, 31 patients, 6–18 years old, with an acute asthma exacerbation (moderate-severe), the magnesium sulfate–treated group demonstrated superior FEV1, PEF, and FVC and was more likely to be discharged home.
- **Heliox.** No clear benefit overall has been shown. There may be in some benefit for severe asthmatics. Heliox is not useful if patient requires >40 percent O<sub>2</sub>. Case series of severe asthmatics showed decreased PaCO<sub>2</sub> and increased pH. Paired patient analyses have demonstrated decreased pulsus paradoxus and increased FEV1.
- **Terbutaline.** No subgroup was shown to benefit from IV  $\beta_2$ -agonists, and no studies to support advantage of IV over inhaled therapy. IV therapy ensures delivery if the patient's upper airway is obstructed or intubated. Effects of terbutaline toxicity include dysrhythmias,

increased myocardial O<sub>2</sub> consumption, myocardial ischemia, and hypokalemia. Terbutalline is of questionable value in the ED.

Additional topics open for debate in the management of severe asthma include:

- Inhalational anesthetics
- Optimal delivery device for aerosolized drugs
- Ketamine
- Mechanical ventilation strategy (noninvasive)
- Indications for intubation
- ECLS.

Dr. Zimmerman concluded by presenting some suggested future research directions for intervention, prevention, and therapeutics for pediatric asthma:

- **Pharmacogenetics to define drug treatment responses.** These are currently radically new approaches to the field and practitioners, and studies will need to be adequately powered to make meaningful comparisons.
- **Linkage of basic studies with clinical trials.** Progress would be expedited if basic studies and human studies were linked in some fashion. This would allow for cross-fertilization between investigators. This could allow for the development of:
  - Tissue banks, DNA banks, and proteomics banks from well-characterized patient populations
  - Ancillary studies as part of or distinct from the networks
  - Application of microarrays and methodologies of genomics and proteomics to look for expression patterns that correlate with clinical manifestations and/or treatment response
  - Development of standardized, NIH-accepted protocols that would facilitate the acquisition of human research samples and human investigation (e.g., bronchoscopy, sputum induction, DNA and protein acquisition and storage).

### **Incidence of Albuterol Toxicity in Critical Asthma**

*Joseph Carcillo, M.D., Associate Professor, Critical Care Medicine and Pediatrics, University of Pittsburgh*

Dr. Carcillo described aspects of albuterol's mechanism of action and toxicity:

- A  $\beta_2$ -agonist that is given as a continuous aerosol for critical status asthmaticus
- Dilates bronchial smooth muscle, reduces inflammation
- Toxicity: effects on hypotension not reported in literature
- Diastolic and systemic hypotension, chest pain, and elevated troponin common in practice.

One study (Sarnaik et al., 2007) found that the percentage of patients with critical status asthmaticus and diastolic hypotension increases as albuterol dose increases and the odds ratio of developing diastolic hypotension increases with increasing albuterol dosing. A hypothesis on  $\beta_2$ -agonist toxicity includes the following:

- Sudden death associated with  $\beta_2$ -agonist use
- At high dosage  $\beta_2$  agonism causes diastolic hypotension

- At higher dosage it is no longer selective and causes tachycardia
- When  $\beta_2$  toxicity occurs the heart becomes under perfused as evidenced by chest pain and increasing troponin levels
- If cardiac perfusion is too severe then sudden death may occur.

Dr. Carcillo described a proposed study design for investigating albuterol toxicity:

- Prospective cohort design
- Inclusion criteria: critical status asthmaticus treated with continuous albuterol
- Examine cohorts  $\leq 5$  mg/h,  $\leq 10$  mg/h,  $\leq 15$  mg/h,  $> 15$  mg/h
- Record hourly SBP, DBP, and heart rate
- Record sinus tachycardia changes noted on bedside monitor
- Test troponin levels in real time in patients with chest pain
- Document dose-related incidence of hypotension, tachycardia, chest pain, elevated troponin.

### **Update From the Neonatal Pain Group**

*Sunny Anand, M.D., Professor of Pediatrics, Anesthesiology, Pharmacology, and Neurobiology, University of Arkansas for Medical Sciences*

Although some drugs have been successfully developed for the neonate, drug development for the youngest, least mature, and most vulnerable pediatric patients is generally lacking. Most drugs are empirically administered to newborns once efficacy has been demonstrated in adults and usefulness is suspected or demonstrated in the older pediatric population. Unfortunately, this process undermines the ability to perform the appropriate studies necessary to demonstrate a drug's short- and long-term safety and efficacy, and to establish appropriate dosing in neonates. Regarding the study of neonatal pain under BPCA, several questions should be addressed:

- Are there additional scientific data needed for the treatment of neonatal pain?
- Are there some study designs or models that should be considered?
- How can NICHD/BPCA help to close any perceived gaps in knowledge of pain treatment?
- Which drugs should be considered for priority listing?

As part of the activities implementing BPCA provisions, NICHD and FDA are collaborating with neonatal experts and colleagues representing industry and academia, as well as practitioners, on the Newborn Drug Development Initiative (NDDI). NDDI will explore innovative approaches to improving clinical trial design for preterm and full-term neonatal populations with the goal of facilitating the study and ultimately labeling more drug therapies in these heterogeneous and complex populations. NDDI convened a planning meeting on February 10, 2003; recruited participants; established regular conference calls and discussions; and held an NDDI workshop on March 29–30, 2004. The Neonatal Pain Control Group was created at this workshop. During the NDDI workshop, the Neonatal Pain Control Group reviewed:

- Study design issues
- Ethical and regulatory concerns
- Management of procedural pain
- Intraoperative anesthesia and analgesia
- Management of postoperative pain

- Analgesia/sedation during mechanical ventilation
- Potential neurotoxicity of anesthetic agents.

Dr. Anand listed Neonatal Pain Control Group publications to date, and he reviewed the results of several studies that focused on the epidemiology of procedural pain and clinicians' opinions about pain intensity in neonates undergoing procedures. Dr. Anand characterized the epidemiology of prolonged pain:

- Postoperative pain—operative procedures on about 1.4 million infants in the United States every year
- Inflammatory pain—meningitis, necrotizing enterocolitis, phlebitis, other types
- Mechanical ventilation
  - About 35,000 preterm and 20,000 term neonates are ventilated in the United States every year.
  - 56 percent of infants with body weight <1,500 gm are intubated in labor and delivery.
  - 94 percent infants <28 weeks gestational age ventilated on average for 25 days.
- Visceral pain—hydronephrosis, meconium ileus, others?
- Neuropathic pain not well characterized or documented in infancy.

Salient gaps in the knowledge of neonatal pain include:

- Pain assessment for neonates 23–26 weeks gestational age or with neurologic impairment
- Pain assessments for prolonged, established, or chronic pain
- A gold standard for pain assessment
- Defining short-term and long-term goals of analgesia and/or sedation
- Relationship of pain scores to clinical benefit
- Developmental regulation of pain responses, including regulatory mechanisms, alteration by early pain, and alteration by analgesic exposure
- Whether elements of neonatal pain responses or pain treatments affect pain processing in later life or susceptibility to chronic pain
- Noninvasive measures of pain (e.g., neuroimaging)
- PK/PD data for analgesic drugs in term or preterm neonates, including single or repeated doses and different formulations
- Optimal methods for designing PK studies in neonates
- Issues of drug combinations or analgesics combined with nonpharmacological therapies
- Developmental domains altered by analgesic drugs
- Biological variations in efficacy or metabolism of analgesics—systemic, neuraxial, or local effects
- Pharmacogenetics and pharmacogenomics of analgesic drugs in infancy
- Economic analyses of neonatal pain and pain management.

The Neonatal Pain Control Group discussed several study design considerations such as sample size issues, effect size issues, and alternative trial designs, including:

- Crossover studies
- Factorial trial design
- Dose-ranging study
- Single-patient trials



- Equivalence trials
- Randomized treatment withdrawal
- Flexible randomization
- Adaptive study designs

Additional design issues include duration of study, PK/PD considerations, drug–drug interactions, and ethical and practical concerns. Outcome measures include pain assessment scales, use of biomarkers, patterns of response, intermediate- and long-term outcomes, and process and safety outcomes.

Ongoing Neonatal Pain Control Group activities since the NDDI workshop include:

- Follow-up conference calls
- Collaborative projects across institutions
- Potential for collaboration with NICHD-funded clinical networks
- Plenary session at the 7th International Symposium on Pediatric Pain, Vancouver, BC (June 25–28, 2006).

Dr. Anand offered the following suggestion on how NICHD/BPCA can help close current knowledge gaps regarding neonatal pain control:

- Provide a regular forum for critical evaluation of advances and clinical practices in anesthesia/analgesia
- Develop transdisciplinary training programs; support new investigators; collaboration in clinical networks
- Characterize the developmental neurochemistry of pain transmission and endogenous analgesic systems
- Promote regulations for the preclinical testing of all new drugs in immature animals
- Develop a “funding home” for studies on
  - Pain assessment/measurement/neuroimaging
  - PK/PD models for different age groups
  - Novel measures of clinical efficacy and safety
  - Long-term effects of neonatal pain/analgesic exposure
  - Developmental regulation of analgesic efficacy, safety
  - Biological variations in analgesic efficacy, safety, drug responses, drug metabolism
  - Genetics, genomics, proteomics, metabolomics of pain
- Encourage emerging areas of research
  - Knowledge transfer: translating what is known from research into clinical practice
  - Long-term use of opioids in complex surgical babies
  - Safety/efficacy of combined opioids and benzodiazepines over prolonged periods of time
  - Focus on drug pharmaceuticals for infants and children
  - Neurotoxicity of NMDA antagonists, GABA agonists
  - Develop methods for fetal anesthesia.

The Neonatal Pain Control Group recommended that the following drugs be further studied: ketamine, ibuprofen, clonidine, methadone, and 2-chloro-procaine. Other drugs to be considered for study include tramadol, dexmedetomidine, propofol, ketorolac, morphine, and fentanyl.

## DAY 2

### Updates on BPCA-Related Activities

#### Introduction

*Dr. Mattison*

Dr. Mattison welcomed the participants to the meeting's second day, and he explained that the presentations would continue with updates on BPCA-related activities and describe future directions for 2007 and beyond.

#### Use of Exception from Informed Consent in a Pediatric Clinical Trial

*Jill Baren, M.D., M.B.E., Associate Professor of Emergency Medicine and Pediatrics, University of Pennsylvania School of Medicine*

Dr. Baren characterized this pediatric clinical trial as follows:

- Randomized double-blind comparison of lorazepam and diazepam for the treatment of pediatric status epilepticus
- Simple study design
  - Drug administered after 5 minutes
  - Data collected over 48 hours
  - Adverse event tracking for 30 days
- Status epilepticus defined as generalized seizure >5 minutes
- Very narrow therapeutic window.

Recognition of possible need to conduct trial without consent includes:

- Significant logistical barriers identified during Study 1 (PK study of lorazepam)
  - Patient recruitment outside the ED
  - Slow enrollment (multiple study extensions)
  - Protocol violations
- Federal regulations for research without consent exist and could be applicable to Study 2
- Pediatric seizure study group investigators collective expertise that Study 2 could not be done with prospective informed consent.

The plan for this pediatric clinical trial was to seek exception from informed consent (EFIC) under 21 CFR 50.24

- FDA-regulated trial
- All criteria must be satisfied and accepted by FDA as part of investigational new drug (IND) application and local IRBs of participating sites.
- Sponsor must inform other investigators at all sites and the FDA if protocol not approved by any single site.

The conditions for an FDA-regulated trial under 21 CFR 50.24 are:

- Subjects are in a life threatening condition, available treatments unproven or unsatisfactory, collection of valid scientific evidence is necessary to determine safety and effectiveness of intervention
- Informed consent not feasible within the therapeutic window
- Participation holds prospect of direct benefit
- Study cannot be practicably carried out without the waiver
- Appropriate attempts to contact legally authorized representative (LAR) or family member are made within the therapeutic window
- IRB has reviewed and approved the consent procedures.

Additional protections were sought through:

- Community consultation
- Public disclosure before the trial
- Established opportunity to object to procedures (opt-out or refusal)
- Public disclosure after the trial
- Independent data monitoring committee
- Process to contact and obtain informed consent of LAR as appropriate.

The process for initiating the trial involved several steps. The project team:

- Held discussions with ethicists and experts in pediatric research
- Initiated IRB dialogue early in planning stage
- Prepared IRB resource binder
- Operationalized the additional human subjects protections required
  - Developed materials and tested content of messages
  - Developed standardized community consultation methods
  - Developed standardized public disclosure methods
  - Developed plan for contact of LARs during study enrollment.

Additional protections through community consultation were to:

- “Ensure that the relevant communities have opportunity for input into the IRB’s decision-making process before initiation of the study”
- Provide an opportunity for the community to:
  - Understand the proposed investigation and its risks and benefits
  - Discuss the investigation
  - Help define the community.

Defining a community involved (1) describing the catchment area surrounding hospitals where the study will be conducted; (2) considering factors such as social influences, regional health services, and health profile; and (3) seeking assistance from public affairs or community relations departments in hospitals and universities. Challenges to defining a community include:

- Academic centers and regional hospitals typically serve a large geographic area due to the specialty nature of their services
- May not be feasible to define the community geographically for such centers

- Instead, could focus on disease-based community definitions and/or other features of a community such as cultural characteristics.

A disease-specific community can be identified from (1) a search of patients from ED administrative data, (2) repeat visits to the ED for seizures, and (3) a list of neurology patients diagnosed with epilepsy and regularly followed at the hospital.

There are four broad methodological categories for community consultation:

- In-depth qualitative methods (focus groups)
- Open public forums (meetings)
- Surveys/interviews (individual)
- IRB-enhanced/IRB-initiated activities (appointed members, liaisons).

Regarding community consultation, Dr. Baren cautioned not to expect sites to engage in all of these community consultation activities. Together, the sponsor (NICHD), principal investigator, local IRB, and site investigators will choose the activities that are most feasible, that are most cost-effective, and that in their best estimation will provide the most adequate information about the community. Public disclosure is defined as “dissemination of information about the emergency research sufficient to allow a reasonable assumption that communities are aware of the plans for the investigation, its risks and expected benefits and the fact that the study will be conducted.” This definition includes “dissemination of information after the investigation is completed so that communities and scientific researchers are aware of the study’s results.” Dr. Baren characterized appropriate public disclosure:

- Clear statement that informed consent will not be obtained for most subjects
- Information about the test articles include a balanced description of the risks and benefits
- Synopsis of the research protocol and study design
- How potential study subjects will be identified
- Participating sites/institutions
- Description of the attempts to contact LAR/family members
- Suggestions for “opting out” of participation.

Methods of public disclosure include:

- Public media: newspaper, television, radio (including foreign language)
- In-hospital resources: posters, flyers, newsletters, brochures, letters to providers and patients
- Electronic media/postal service/telephone hotlines.

Public disclosure must continue throughout the study period. The study team will provide monthly updates regarding enrollment and study updates. Sites may use any of the ideas described in the section above to disseminate those updates. Study results may be submitted to peer-reviewed journals and presented at national meetings.

Regarding the contact of LAR/family members, an investigator must attempt to seek written informed consent if feasible from LAR or contact family member if no LAR is available. The IRB must find and document that such procedures are in place. Upon contact of LAR, he or she

must be given the opportunity to object. The IRB must find and document procedures for families to refuse or to object to subject's participation. The investigator is required to summarize efforts to contact LAR or family member if no LAR is available.

In an effort to gather prospective informed consent, parents/patients with a known seizure disorder can be approached for consent/assent in neurology clinics and other clinical areas before a status epilepticus event. Prior experience has shown that this approach will only reach a few eligible patients. Potential study subjects are given the opportunity to object to preenrollment as follows:

- Toll-free phone number or Web site link provided during community consultation and public disclosure activities
- Continuous availability: identification of subjects who object (e.g., one type of wrist band for those who object and another type for those who have provided informed consent)
- List of objecting patients in the ED: linked to electronic tracking or registration procedures.

Within therapeutic window, potential subjects are given the opportunity to object as follows:

- Brief script read to parent/guardian/family member if present during ED arrival
- Content specifies that research study is taking place
  - No study details given
  - Not to be misconstrued as informed consent
  - Allows objection to participation in research in general.

After enrollment, subject may opt out as follows:

- Informed consent sought from the LAR when feasible
  - After medical and emotional stability achieved
  - After clinician has effective dialogue with LAR
- Can refuse further study procedures
- Attempts to contact LAR or family member will continue throughout hospitalization
- Age appropriate assent per local IRB.

Dr. Baren described the study's progress with IRB communications to date:

- 9 of 11 sites have begun dialogue with IRB
- All IRBs have shown willingness to work with investigators
- 2 sites have scheduled educational sessions for IRB members
  - Requirements of 21 CFR 0.24
  - Examples of community consultation and public disclosure from other trials
  - FDA 2006 Draft Guidance on Exception from Informed Consent Regulations
  - IRB resource binder.

Three sites have conducted prior trials using the EFIC. IRBs for two sites had recommendations for the principal investigator. One site had a premeeting with its IRB to review the plan in place for requesting review of EFIC studies. One site recently had two studies approved using EFIC. Other sites have preestablished IRB policies and instructions for a potential protocol that falls under 21 CFR 50.24. The IRB plan for review of EFIC includes:

- IRB liaison assigned to investigator: at two sites, the liaison will attend community consultation activities
- Special IRB subcommittee/section: one site that had previously refused to review studies that fell under 21 CFR 50.24
- Incorporate with existing community advisory boards: three sites.

Dr. Baren summarized the challenges for a pediatric clinical trial using EFIC:

- One IRB views community consultation results as indicative of community consent for study to take place (“threshold level” of agreement)
- Several IRBs have concerns about identification procedures for patients who “opt out”
- Investigators have differing opinions on methods of obtaining informed consent
- Various definitions of community
  - Seizures relatively rare in general population
  - Messages may not be well received
- Public disclosure
  - Potential for enormous expense with little effectiveness
    - TV and radio ads could cost thousands of dollars
    - Not sure how to get message to interested public.

The next steps for sites are to develop a site-specific plan for meeting requirements of EFIC, customizing community consultation and public disclosure, and considering stepwise IRB submission and roll-out of community consultation (i.e., more experienced sites going first). Potential to share information can have positive or negative implications.

Dr. Baren concluded by describing the clinical trial paradigm:

- If successful, this will be the first exclusive pediatric trial conducted under 21 CFR 50.24
- Other drugs will need to be tested in the emergency setting
- Will be similar in design and presence of a narrow therapeutic window
- Plan for multiple secondary studies: assess all aspects of human subjects protections and logistics of trial including costs of implementing special protections.

### **NICHD Pediatric Formulation Initiative Update**

*George Giacoia, M.D., Program Scientist, Pediatric Pharmacology Research Unit Network, CRMC, NICHD, NIH, DHHS*

Elements of the pediatric formulations “quagmire” include the use of adult formulations, extemporaneous formulations, age-appropriate formulations, and home preparations. Parental dispensing of pediatric formulations adds to the quagmire. The goals of the NICHD Pediatric Formulations Initiative (PFI) are to identify (1) scientific issues that prevent the development of appropriate pediatric formulations, (2) regulatory issues (both national and international) that affect the development and availability of pediatric formulations, and (3) solutions to facilitate the development and approval of pediatric formulations. PFI will provide a forum for interactive discussions and data sharing and feedback among industry, academia, regulatory agencies, and funding agencies.

The PFI approach is an on-going process. Working groups were established in June 2005. The four PFIs working groups are:

- Scientific, Technical, and Regulatory Challenges for the Development of Pediatric Formulation
- Use and Application in Pediatrics of New Technology Systems
- Taste, Smell, and Flavor Research in Infants and Children
- Economic Issues and Partnerships.

The Scientific, Technical, and Regulatory Challenges for the Development of Pediatric Formulation Working Group is addressing issues such as:

- Scope of the problem of lack of appropriate formulations
- Appropriate formulations for developmental age
- Regulatory issues (extension of Biopharmaceutical Classification System [BCS] classification to pediatrics)
- Poor documentation of formulations used in clinical trials
- Problems associated with the used of extemporaneous formulations.

At the first planning meeting, held in December 2005, recommendations and actions were reviewed and implemented by seven PFI task specific groups. The Pediatrician's Survey Task Specific Group is conducting a survey of practitioners on their use of compounded preparations for pediatric use. The survey will be completed in early 2007. This working group proposed a survey of American Academy of Pediatrics (AAP) fellows, which is pending review by the Board of AAP. The purpose of the proposed survey is to (1) assess acceptability and compliance issues associated with available pediatric drug formulations; and (2) provide information to the pharmaceutical industry, NIH, and FDA to better satisfy the needs of children according to stage of development and help determine areas where further research on taste perception, bitter masking, and dose delivery systems is needed.

Dr. Giacoia reviewed the BCS, which provides a scientific framework for classifying drugs based on their aqueous solubility and intestinal permeability, and supports request of biowaiver for subsequent in vivo bioavailability/bioequivalence studies of formulations after initial establishment of bioavailability of immediate release oral dosage forms. The BCS Task Specific Group has recommended the application of this system in developing pediatric formulations. Use of this method would help companies correctly predict permeability and bioavailability in children. The group is developing a proposal to develop a common research protocol in three laboratories (FDA and two pharmaceutical companies).

The Pediatric Formulations in Published Trials Task Specific Group is addressing poor documentation of oral formulations used in published clinical trials. For example, a review of 10 journals from 2002 to 2004 (5 pediatric, 5 general medicine) by Standing et al. (*Pediatrics* 2005;116:559) showed that:

- 63 percent provided inadequate information.
- 26 percent did not state what formulation was used.

- Only 37 percent contained adequate information for the study to be reproduced.
- When formulation reported, only 49 percent use pediatric formulations.

A survey under development by this task specific group will examine:

- Drug source/drug class
- Type of formulation
- Age of study subjects
- Expansion to all journals publishing pediatric trials over a 10-year period
- Administration procedure documentation
- Stability information for extemporaneous formulations
- Palatability/tolerability information.

Regarding pediatric extemporaneous formulations, Dr. Giacoia briefly reviewed risk management issues, placing extemporaneous formulation recipe in the label (e.g., lisinopril, benazepril, losartan, enalapril, sotalol). The Survey of Children's Hospital Pharmacies Task Specific Group is addressing issues that include:

- Limited compounding and stability information
- Stability data of syrups not done for many drugs
- Other stability considerations
  - Compatibility with excipients
  - Expiration dating/beyond-use dating
- Drug product as source of API (changes to drug by manufacturers; different excipients; change in pH)
- Improper use of water
- Taste/palatability
- Contamination/sterility problems
- Companies producing syrups may change formulation
- Lack of quality control mechanism.

The Survey of Children's Hospital Pharmacies Task Specific Group has developed a U.S. and Canadian children's hospitals survey on the use of extemporaneous liquid formulations. The survey will be administered and analyzed by the Pediatric Pharmacy Advocacy Group. A pilot study is currently being conducted. Thirty children's hospitals in the United States and Canada will be invited to participate. The survey will (1) include inpatient and outpatient and financial information, (2) determine extent of use and extent of deviations from published formulations, and (3) seek list of drugs for which stability data is needed. The purpose of the survey is to:

- Identify liquid formulations that are extemporaneously prepared for inpatient and outpatient use in children's hospitals
- Determine the extent of use of extemporaneously prepared liquid formulations in children's hospitals—both inpatient and outpatient—and identify the specific inpatient areas in which they are used
- Determine whether the preparation of extemporaneous liquid formulations is evidence-based and whether routine deviations from published formulations occur in children's hospital pharmacies



- Identify a list of drugs whose stability in a liquid formulation is unknown and information thereof may improve patient care.

Regarding taste testing in children, Dr. Giacoia explained that the sensory world of children is different than that of adults. Children have a heightened preference for sweets and salt, and reject some bitter tastes during development. Children differ from adults in perceptual sensitivity, and cognitive, emotional, and physical maturity. Distinguishing sensitivity from hedonic responses is difficult to do in infants and children. Use of electronic tongues and noses for initial screening of drugs is still in its infancy. Most of the applications of these technologies represent limited feasibility studies with poor reproducibility and predictive value. Current activities of the Prioritization of Research Needs in Taste Task Specific Group include:

- Acceptability and palatability survey
- Taste and flavor testing in infants and children (Identification of industry issues)
- Prioritization of research needs and possible NIH initiatives
- White paper of taste and flavor testing of children
- Series of related articles on basic research needed to make oral medicines more palatable for children.

Dr. Giacoia reviewed characteristics of the pediatric drug market and described some of the economic barriers to developing pediatric drugs. He listed some of the rewards and incentives used by the European Union to regulate medicinal products for pediatric use. The Economic Issues and Partnerships Working Group is addressing issues regarding possible solutions to economic barriers. Possible solutions include:

- Increase the market size
  - Combine incentives for pediatric and geriatric markets
  - Development of global standards
- Reduction of cost/risk/time to market
- Use of “existing” formulations
- Importation of approved pediatric drugs
- Legal, regulatory, legislative issues need to be addressed
- Incentives (limited exclusivity)/funding/tax breaks
- Incentives for priority extemporaneously formulated drugs
- Incentives for pediatric formulation of generic drugs (similar to European Union drugs—12 years of data exclusivity)
- Private-public partnerships for orphan drugs
- Creation of center of excellence pediatric formulations.

The Use and Application in Pediatrics of New Technology Systems Working Group is addressing issues regarding development and application of new methods of drug delivery, including:

- Novel alternative methods for the delivery of drugs
- Inhalation drug therapy
- Dermal delivery/gel technology
- Dendrimers/biopolymers

- Nanocrystal technology
- Fast melt technology
- Other methods (e.g., oral, rectal, needles drug delivery).

Dr. Giacoia explained that a commitment from all involved parties is needed to solve the problem of the lack of appropriate pediatric formulations. This commitment requires collaboration among industry, academia, government, funding sources, and science/research. Global advocacy issues include:

- Need for World Health Organization (WHO) pediatric-specific essential medicines list
- Need for appropriate dosage forms in resource limited countries
- Adoption by the executive committee of WHO of the Better Medicines for Children Finish proposal.

In concluding, Dr. Giacoia asked:

- Are oral liquid preparations the gold standard for young infants and children?
- Can other fast dissolving oral formulations partially replace them?
- What is the role of alternative drug delivery systems?

### **Clonidine and ADHD**

*Jeff Mulchahey, Ph.D., Senior Director, Regulatory Affairs, Branded Products, IMPAX Laboratories, Inc.*

Dr. Mulchahey described the magnitude of the clonidine treatment for ADHD situation:

- Five percent of ADHD prescriptions are written for clonidine.
- The sales of clonidine for ADHD exceed \$100 millions.
- Psychiatrists write 10 percent of all prescriptions for clonidine.
- This use is impressive for a nonlabeled, generic drug lacking a champion.
- Clonidine is so popular because it is viewed by the prescribers as safe and effective.
- Safe and effective for what?

There are four classes of pharmacologic treatment options for ADHD:

- Stimulants
  - MPH
  - Dextroamphetamine
  - Mixed amphetamine salts
- Selective noradrenergic reuptake inhibitors (SNRIs)
  - Atomoxetine
- $\alpha$ -Adrenergic agonists (not FDA-approved for treatment of ADHD)
  - Clonidine
  - Guanfacine
- Other (not FDA-approved for treatment of ADHD)
  - Modafinil
  - Antidepressants
  - Selegiline (monoamine oxidase inhibitor).

These agents are not interchangeable. Latency to effect is 1 hour for stimulants and  $\alpha$ -adrenergic agonists; days or more for SNRI and others. Stimulants are the first-line intervention in most cases. They are regarded as being highly effective at improving measures of attention. Clonidine is regarded as being highly effective at improving behavioral measures such as hyperactivity. Clonidine is often used to treat ADHD behavioral comorbidities such as impulse control (e.g., oppositional defiance disorder).

Dr. Mulchahey reviewed the “Clonidine in ADHD Treatment (CAT)” Study (Randy Sallee, M.D., Ph.D., principal investigator)—a randomized, double-blind, placebo-controlled, flexible-dose study with a 2 x 2 factorial design (placebo, clonidine, MPH or clonidine + MPH). This investigation is the largest multicenter prospective controlled study of clonidine, alone and in combination with MPH, for pediatric ADHD (ages 7–12 years). The study enrolled 122 subjects into the four treatment groups. It was powered to detect clonidine effect, not compare groups. Unique trial features included:

- Primary outcome measure was ASQ-T (a teacher rating instrument)
- Titration profile based on teacher feedback
- Direct classroom observation to measure treatment response
- Secondary outcomes included ASQ-P (a parent rating instrument), clinical global impression (CGI), and safety.

Efficacy results were as follows:

- Primary outcome ASQ-T: MPH (clonidine + MPH or MPH alone) was superior to non-MPH treatment (clonidine alone or placebo); clonidine alone did not improve the ASQ-T.
- No significant interaction effect between clonidine and MPH was evident.
- Secondary measures (ASQ-P and CGI) favor combination treatment compared with placebo.
- ASQ-P and CGI: clonidine (clonidine + MPH or clonidine alone) was superior to MPH alone or placebo.
- Treatment outcome of ASQ-P and CGI for clonidine was not mediated by sedation, thus, improvement is not mediated by sedation.

Safety results were as follows:

- No severe AEs reported for any treatment group
- Numbers of AEs reported by treatment group
  - 30 in 10 subjects on clonidine
  - 10 in 3 subjects on MPH
  - 39 in 9 subjects on combination
  - 9 in 4 subjects on placebo
- Two early withdrawals
  - Tachycardia and chest pain on MPH (ECG and physical exam normal)
  - Mild asymptomatic elevations in QTc (about 440 msec) on combination; ECG suggested left ventricular hypertrophy; withdrawn as precautionary measure.

- Sedation was reported more frequently among subjects receiving clonidine (38 percent) compared with those not on clonidine (7 percent); otherwise the medications were well-tolerated
- No significant changes in ECG parameters (QRS, QTc, and PR intervals) or vital signs (sitting and standing blood pressure and pulse) across groups were observed.
- Increased effectiveness with clonidine came at the expense of a higher side-effect profile.
- Study demonstrated the relative safety of clonidine alone or in combination with MPH.

Dr. Mulchahey reviewed a study of clonidine in ADHD and Tourette's syndrome. This study was essentially identical to the CAT study in terms of treatments and timing. Subjects were diagnosed with ADHD and a chronic tic disorder. Subjects ( $N = 136$ ) were enrolled and assigned to treatment at follows:

- 37 to MPH
- 34 to clonidine
- 33 to combination (clonidine + MPH)
- 32 to placebo.

Study results were as follows:

- ASQ-T improvements (compared with placebo):
  - MPH  $p < 0.003$
  - Clonidine  $p < 0.002$
  - Clonidine + MPH  $p < 0.0001$
- Clonidine appeared to be most helpful for impulsivity and hyperactivity.
- MPH appeared to be most helpful for inattention.
- The proportion of individual subjects reporting a worsening of tics as an adverse effect was no higher in those treated with MPH (20 percent) than those being administered clonidine alone (26 percent) or placebo (22 percent).
- Compared with placebo, measured tic severity lessened in all active treatment groups in the following order: clonidine + MPH, clonidine alone, MPH alone.
- Sedation was the most common AE and occurred with most frequently with clonidine.

Dr. Mulchahey concluded by summarizing ADHD treatment with clonidine as follows:

- Clonidine has been studied in RCTs with enrollments  $>250$  subjects.
- Clonidine, alone or in combination with MPH, has been demonstrated to be to be safe and effective as pharmacotherapy for ADHD.
- The efficacy of clonidine in combination with MPH is robust.
- The efficacy of clonidine as monotherapy depends on the power of the trial and the outcome measure selected.
- The major side effect of clonidine is transient sedation.

## Future Directions—2007 and Beyond

### Introduction

*Perdita Taylor-Zapata, M.D.*

Dr. Taylor-Zapata said that presentations up to this point in the meeting had addressed BPCA-related issues that NICHD has been investigating or is considering for investigation. Several presentations focused on the process of prioritizing drugs and conditions and how to determine frequency of use and frequency of conditions. The next steps in BPCA activities involve studies across a diverse range of diseases, including rare diseases, diseases that have global impact, and diseases that have public health implications.

### Opportunities in Rare Diseases: Fragile X

*Linmarie Sikich, M.D., Associate Professor, University of North Carolina, Chapel Hill*

Fragile X is the most common inherited cause of developmental disability. About 1 in 4,000 males and 1 in 8,000 females are affected. Fragile X is a triplet repeat disorder, in which methylation of the promoter region silences the gene. Carriers with premutation have more subtle developmental and neuropsychiatric issues. Fragile X is a true “developmental” disorder. Its ontogeny is as follows:

- Birth: subtle dysmorphologies and joint laxity
- Toddler: language and cognitive delays, sensory issues, arousal issues
- Early childhood: seizures, ADHD, self-injurious behaviors, anxiety
- Mid-childhood: progressive declines in intelligence
- Adolescence: macro-orchidism
- 30–40: premature ovarian failure
- 50+: Fragile X tremor/ataxia syndrome, cognitive worsening.

Autism is common in Fragile X. About 25–30 percent of children with Fragile X have autism, and about 4 percent of children with autism have Fragile X. Cognitive and behavioral functioning of children with Fragile X and autism are more impaired than those of children with just Fragile X or just autism. Observed developmental trajectories for adaptive behavior of children with Fragile X and low autistic behaviors are greater than those of children with Fragile X and high autistic behaviors (Hatton et al., 2003). Early intervention services such as special education, speech therapy, and occupational therapy generally improve outcomes through age 5. Physical therapy provides improvement up to 4–5 years of age but then declines.

Medications that are commonly used to treat Fragile X include selective serotonin reuptake inhibitors (SSRIs), other antidepressants,  $\alpha_2$ -agonists, and antipsychotics. Medication use is currently symptom driven.

Knowledge about molecular actions of FMRP—a neuronal protein—suggests new treatments for Fragile X. FMRP is concentrated in dendritic spines, and its expression increases with synaptic activation and environmental stimulation. However, dendritic spines in Fragile X are immature

and inefficient. Studies in both humans and mice have shown that the loss of FMRP results in immature dendritic spines. Neuronal stimulation normally leads to mature spines, through long-term potentiation and microfilament rearrangement.

Investigators have proposed the mGluR model to explain the effects of FMRP loss. Possible interventions target steps in mGlu pathway. Methylphenylethynylpyridine (MPEP) is a potential therapeutic agent for Fragile X. MPEP is a noncompetitive mGluR5 antagonist. It has no cross reactivity to other glutamate receptors at up to 100  $\mu$ M. Other characteristics include:

- Anticonvulsant activity against audiogenic seizures
- Tolerance develops
- Anxiolytic-like effects in PLUS maze
- Can reverse behavioral changes in Fragile X fly when given to immature or adult
- Can block brain abnormality in Fragile X fly if given early in development.

Dr. Sikich characterized Bauchwitz lithium studies:

- Hypothesize acts by effecting GSK-3 $\beta$  to inhibit phosphorylation of Map1B and causing downstream MPEP effect
- Stops audiogenic seizures in FRX mouse.

There have been few clinical trials for treatment of Fragile X:

- 1 double-blind trial of ampakine in adults
- 4 small <20 crossover studies of stimulants in children
- 1 double-blind trial of carnitine over 1 year.

Problems/issues with treatment include:

- Outcomes not well established and validated, especially in younger children
- No culture of clinical trials
- Issue of when to intervene
- When in the course of development treatments should be provided
  - Prevention versus intervention
  - Critical or sensitive periods
  - Danger/benefits of early treatment.

There are opportunities in Fragile X:

- Clear molecular diagnosis
  - Move to newborn screening
- Fairly clear mechanisms
- Supportive animal studies
- Potential biologic outcomes
- Mentally retarded developmentally disabled center infrastructure
- Opportunity for developmental interventions
- Potential generalization to other disorders such as autism and mental retardation without clear etiology.

## Countermeasures Against Chemical Threats

David Jett, Ph.D., Program Director for Counterterrorism Research, National Institute of Neurological Disorders and Stroke (NINDS), NIH, DHHS

The goal of the NIH Countermeasures Against Chemical Threats (CounterACT) program is to develop new and improved medical countermeasures against chemical threat agents. BPCA and CounterACT may be overlapping programs, and there may be an opportunity for collaboration.

There are differences in military and civilian challenges in preparedness to chemical threats:

### Military Focus

- War fighter: 18–45 years old and healthy
- Open air environment
- High number of casualties is the goal
- Prophylactic measures are the focus

### Civilian Focus

- Broad age range: pediatric–elderly
- May have preexisting medical conditions
- Could happen in closed environment
- No need for high casualties
- Postexposure therapies are the primary focus
- First responders and decontamination personnel

There are three categories in the civilian threat spectrum:

### Biological

- Category A, B, C
- Bacterial (e.g., anthrax)
- Viral (e.g., small pox)
- Toxins (e.g., botulinum)

### Chemical

- Schedule 1, 2, 3
- Weapons of mass destruction (e.g., sarin)
- Toxic industrial chemicals (e.g., cyanide)
- Toxins (e.g., saxitoxin)
- Pulmonary (e.g., chlorine)
- Vesicating (e.g., sulfur mustard)

### Radiation/Nuclear

- Bomb detonation
- Radiation dispersal device
- Attack on nuclear reactor
- Attack on spent fuels

Higher priority chemical threat agents, for which there are few existing therapeutics, can be categorized by medical syndrome:

- Neurotoxic agents: anticholinesterase nerve agents (gases)
- Pulmonary agents: phosgene, chlorine
- Vesicating agents: sulfur mustard
- Metabolic poisons: cyanide.

To identify therapeutic targets, CounterACT is conducting research in the following areas:

- Basic/mechanistic research
- Development and use of in vitro and animal models for efficacy screening
- Medicinal chemistry optimization

- Preclinical IND development (e.g., absorption, distribution, metabolism, excretion, toxicology, and developmental chemistry)
- Phase I clinical trials.

Examples of research needs are:

- New and improved anticonvulsants, neuroprotectants, pulmonary edema therapies, skin and eye protectants
- Alternate routes of administration
- Improved rapid diagnostic techniques and technologies
- Basic research on short- and long-term pathophysiology from acute exposures.

The CounterACT Network is composed of government laboratories, program centers, contracts, and projects. Dr. Jett described the relationships among the various entities of the NIH CounterACT network. CounterACT Research Centers of Excellence, principal investigators, and research projects include:

- Lovelace Biomedical and Environmental Research Institute; Gary R. Grotendorst, Ph.D.; Identification of therapeutics for the treatment of sulfur mustard injury
- University of Medicine and Dentistry of New Jersey (UMDNJ), Robert Wood Johnson Medical School; Jeffrey D. Laskin, Ph.D.; UMDNJ/Rutgers University CounterACT Research Center of Excellence
- U.S. Army Medical Research Institute of Chemical Defense; David E. Lenz, Ph.D.; Center for Catalytic Bioscavenger Medical Defense Research
- National Jewish Medical and Research Center; Carl W. White, M.D.; Novel antioxidant therapeutics for sulfur mustard toxicity.

CounterACT Network Small Business Innovative Research grantees (6 of 29), principal investigators, and research projects include:

- University of Maryland School of Medicine; Edson X. Albuquerque, M.D., Ph.D.; Age and sex effects on nerve agent damage to the brain and antidotal therapies
- University of California, San Diego; Gerry R. Boss, M.D.; Preclinical and clinical studies of cobinamide, a new cyanide detoxifying agent
- Uniformed Services University of the Health Sciences; Maria F. M. Braga, D.D.S., Ph.D.; Efficacy of GluR5 antagonists against soman-induced seizures and neuropathology
- Human BioMolecular Research Institute; John R. Cashman, Ph.D.; Biosensor for real-time chemical monitoring
- University of Washington; William A. Catterall, Ph.D.; Receptor sites and antagonists for paralytic neurotoxins
- ArmaGen Technologies, Inc.; Yufeng Zhang, Ph.D.; Targeted paraoxonase fusion protein as a neurotherapeutic for nerve gas agents.

CounterACT Network contracts, clinical trials, and interagency agreements include:

- SRI International; Carol Green, Ph.D., D.A.B.T.; CounterACT Preclinical Development Facility



- University of Michigan, Clinical Trial Through Institute of Neurological Diseases and Stroke (NINDS) Network; Robert Silbergleit, M.D.; Intramuscular midazolam versus intravenous lorazepam in the prehospital treatment of status epilepticus (the RAMPArT trial)
- U.S. Army Medical Research Institute of Chemical Defense; David H. Moore, D.V.M., Ph.D.; Interagency Agreement between NIH and the Department of Defense—all aspects
- University of Utah; H. Steve White, Ph.D.; Anticonvulsant drug development program.

Children are more vulnerable to chemical threats. Survivors reported that children were disproportionately affected by the chemical attacks: “virtually all the dead who were seen by journalists were women, children, and old men” (Rotenberg and Nemark, 2003). To date, no epidemiologic or toxicologic studies have been published. Children are more vulnerable because of the following characteristics:

- Smaller body mass = lower dose needed
- Higher respiratory rate = greater systemic exposure
- Limited endurance of respiratory muscles
- Lower reserve of fluids = fluid loss bigger problem
- “Leaky” blood–brain barrier
- More vulnerable to seizures
- Other intrinsic difference in neurotransmitters, receptors, metabolism, etc.

Dr. Jett described the acute effects of nerve agents such as sarin and VX:

- Vapor/aerosol/dermal exposure
  - Sweating, fasciculation, miosis
  - Systemic effects: gastrointestinal
- Increasing dose/exposure
  - Loss of consciousness, seizures (a major component and part of long-term neurologic sequelae), apnea, flaccid paralysis, death.

There are three primary nerve agent therapies:

- Atropine (2 mg/0.7 mL)
  - A cholinergic blocking drug
  - Blocks excess acetylcholine
  - Clinical effects at muscarinic sites
    - Dries secretions
    - Reduces smooth muscle constriction
- Pralidoxime (2-PAM, 600 mg/2 mL)
  - Removes agent from enzyme
  - Reactivates acetylcholine
- Anticonvulsants
  - Diazepam, lorazepam, midazolam.

Pediatric management of therapies for nerve agent exposure include:

- Mark 1 kit for children of any age using dosage based on previous literature (e.g., Rotenberg and Newmark, 2003)

- Mark 1 kit only used for children <3 years old if it is the only source of atropine and 2-PAM
- AtroPen plus 2-PAM should be stocked and used if Mark 1 use is prohibited or not available.
- Anticonvulsants should be administered by IV or IM routes.

Dr. Jett characterized midazolam anticonvulsant as follows:

- Need rapid-acting drug in a prehospital setting that can be administered quickly in the field
- Midazolam is the only water soluble benzodiazepine.
- IM absorption of diazepam or lorazepam is irregular, and lorazepam has to be refrigerated.
- Rectal diazepam is messy and unreliable in treating overweight adults with seizures.
- Intranasal midazolam effective dose is difficult to determine plus it would be exhaled and less reliable in a person with seizures.

Dr. Jett concluded by noting the following about the IM Midazolam Clinical Trial:

- NIH/NINDS Neurological Emergencies Treatment Trials (NETT) Network
- Rapid Anti-epileptic Medication Prior to Arrival Trial (RAMPArT), a Phase II/III trial with IM midazolam in seizure patients
- Coordinated and in collaboration with Department of Defense Phase I trials and definitive animal studies with nerve agent.

## Emerging Health Issues

### Origins of the Metabolic Syndrome in Children

*Gilman Grave, M.D., Chief, Endocrinology, Nutrition, and Growth Branch, CRMC, NICHD, NIH, DHHS*

The roots of the obesity epidemic are familial but not necessarily genetic (i.e., obesity is not a heritable condition). It develops from the interaction of individual biology and the environment. Excessive body weight has been shown to predispose patients to various diseases, particularly CVD, type 2 diabetes, sleep apnea, and osteoarthritis. Obesity is an individual clinical condition and is increasingly viewed as a serious public health problem.

Dr. Grave presented 20 maps of the United States depicting the spread of the obesity epidemic from 1985 to 2004. Prevalence figures are based on self-reported data on height and weight in adults collected by the CDC's Behavioral Risk Factor Surveillance System (BRFSS). The maps show that in 1991 the states with the highest prevalence of obesity were Louisiana, Mississippi, West Virginia, and Michigan. Ten years later, nearly all other states caught up with these four sentinel states. Mississippi jumped out in front with >25 percent obesity. Over the past 3 years, eight other states have joined Mississippi in obesity prevalence, forming the American "stroke belt" up the Mississippi Valley and into Appalachia. These states are the most impoverished in the United States, have the largest African-American populations, or both. According to the 2004 BRFSS, about 60 million adults, or 30 percent of the adult population, are now obese, which represents a doubling of the rate since 1980.

The obesity epidemic has hit minority children the hardest. The prevalence of obesity has quadrupled from 5 percent to 22 percent over the past 30 years in African-American girls. This increase represents a straight line function with a slope of 1 percent every 2 years. The increase in prevalence shows no sign of reaching a plateau. Comparable figures for non-Hispanic White girls range from 5 percent to 12 percent.

Several investigators have predicted dire consequences of America's obesity epidemic, and research results provide increasing evidence of the accuracy of their predictions. Clinical data show that the obesity epidemic is plunging the United States into an epidemic of type 2 diabetes, which used to be a rare disease of this generation's grandparents but is increasingly a disease of its children. The number of cases of type 2 diabetes in critical care medical centers has increased tenfold in just 10 years, underscoring the fact that obesity is not a cosmetic issue but a disease of deranged metabolism with dire consequences. One researcher predicts a sextupling of cases of renal failure needing dialysis or transplant in the next 25 years, from about 350,000 to more than 2 million. In addition, there will be an increase in cirrhosis; 16 percent of obese children have nonalcoholic steatohepatitis. Obesity now costs about \$130 billion annually, with \$30 billion more spent on useless remedies. These consequences will eventually bankrupt America's medical care system.

From 1982 to 1994, the incidence of type 2 diabetes in adolescents increased tenfold from 0.7 to 7 per 100,000 per year. A study in Princeton County, Ohio, showed that the prevalence of type 2 diabetes among African-American adolescents is 10 times that of non-Hispanic Whites. This huge discrepancy reflects a genetic disposition to insulin resistance and glucose intolerance among African-American children.

In 2001, the Adult Treatment Panel (ATP) of the National Cholesterol Education Program (NCEP) defined the metabolic syndrome as having three, four, or five of the five positive risk factors. This means there are 16 different ways to have the metabolic syndrome (10 triads, 5 tetrads, 1 pentad). Dr. Grave listed the NCEP ATP III criteria for metabolic syndrome:

<u>Risk Factor</u>	<u>Defining Level</u>
• Waist circumference	
– Men	>102 cm (>40 in)
– Women	>88 cm (>35 in)
• Triglycerides	≥150 mg/dL
• High density lipoprotein (HDL) cholesterol	
– Men	<40 mg/dL
– Women	<50 mg/dL
• Blood pressure	≥130/≥85 mmHg
• Fasting plasma glucose	≥110 mg/dL

CVD is the primary cause of death in the United States, claiming 400,000 lives per year—one-fifth of them <55 years of age. Incredibly, 150,000 sudden deaths per year are the first indication

of CVD in asymptomatic individuals. CVD risk factors include SBP, triglyceride level, low density lipoprotein (LDL) cholesterol, BMI, and DBP. Other CVD risk factors are:

- High homocysteine levels
- High C-reactive protein levels
- High interleukin-6 levels
- Low adiponectin levels
- Low leptin levels
- High ghrelin levels
- High proinsulin:insulin ratio

Dr. Grave presented recent data from the Fels Longitudinal Study, which began enrolling babies at birth in the 1930s and followed them for a lifetime with frequent measurement of body composition, blood lipids, glucose, and insulin. This study is the largest and longest running longitudinal study in the world. NICHD has been funding the study since 1976. So far, 1,500 subjects have been born into the Fels Longitudinal Study. The presented data were:

- Phenotypes of the subjects with metabolic syndrome
- Waist circumference
- SBP
- HDL cholesterol
- Triglycerides
- Homeostasis model assessment (HOMA) insulin resistance
- Age at divergence (years).

Clinical implications of the Fels data are as follows:

- The metabolic syndrome begins in childhood.
- Prevention should start in childhood.
- If an elevated level of one risk factor is found in a child, then screen for the presence of the other four.
- Pay special attention to blood pressure in boys because one-third of adult males with the metabolic syndrome have high blood pressure but not abdominal obesity.
- Rule out nonalcoholic steatohepatitis, a silent member of the cluster.

Dr. Graves offered the following conclusions:

- The pathology of metabolic syndrome begins in childhood with central obesity and elevated blood pressure, followed by dyslipidemia and insulin resistance in adolescence.
- Age- and sex-specific values for risk factors that were measured during childhood in adults who are currently disease-free can be used as healthy target values by children and their pediatricians.
- One-third of the Fels adults (32 percent men, 28 percent women) had the metabolic syndrome.
- The most common diagnostic triads in women were waist circumference, HDL cholesterol, and triglycerides (54 percent) followed by waist circumference, blood pressure, and triglycerides (32 percent). Most common triads in men were blood pressure, HDL cholesterol, and triglycerides (28 percent) followed by waist circumference, blood pressure, and triglycerides (24 percent) and waist circumference, HDL cholesterol, triglycerides (24 percent).

- Few adults with the metabolic syndrome had fasting plasma glucose concentration >110 mg/dL.
- Values for waist circumference and blood pressure diverged in the second half of the first decade of life between adults with and without the metabolic syndrome.
- Values for lipid risk factors and insulin resistance diverged early in adolescence.

## **Pediatric Obesity and Its Treatment**

*Mary Horlick, M.D., Director, Pediatric Clinical Obesity Program, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, DHHS*

Dr. Horlick reviewed the classification of pediatric weight status using BMI-for-age categories, described current recommendations for clinical management of pediatric obesity, and summarized recent reports of medication trials in pediatric obesity, including the one FDA-approved agent. It is important to have effective long-term treatment for overweight (OW) pediatric patients because OW in childhood and adolescence is associated with (1) increased risk for OW in adulthood; (2) increased risk for adult diseases if OW in adolescence; (3) increased health risk factors in OW children, especially with BMI  $\geq$  99 percent; and (4) increased presence of obesity-related comorbidity in OW children and adolescents.

Obesity has traditionally been a measure of body weight. Not until 2000 did the use of BMI growth curves come into common practice. The CDC 2000 growth charts for boys show that BMI declines from about age 2 to about age 5, after which BMI increases steadily with growth. BMIs below the 85th percentile are generally considered acceptable. Children with BMIs >85th percentile but <95th percentile are considered at risk for OW. Children whose BMI is  $\geq$ 95th percentile are considered OW. For boys at age 20, the BMI cutoff for the 85th percentile is about 27, and the BMI cutoff for the 95th percentile is about 30.5. The cutoff for adult male obesity is a BMI of about 30, which intersects the 95th percentile for boys at about 19½ years of age. For girls at age 20, the BMI cutoff for the 85th percentile is about 26.5, and the BMI cutoff for the 95th percentile is about 30.5. The cutoff for adult female obesity is a BMI of about 30, which intersects the 95th percentile for girls at about 17½ years of age. Once girls are 17½ years old and boys are 19½ years old, practitioners should use adult BMI values.

Current recommendations for the clinical management of pediatric obesity include:

- <7 years of age
  - BMI 85 percent to <95 percent with or without comorbidities: prevent weight gain
  - BMI  $\geq$  95 percent without comorbidities: prevent weight gain
  - BMI  $\geq$  95 percent with comorbidities: weight reduction
- $\geq$ 7 years of age:
  - BMI  $\geq$  85 percent with comorbidities: weight reduction
  - BMI  $\geq$  95 percent: weight reduction.

The components of conventional treatment with goal of behavioral change should be family-based—with committed parents as role models—and should include three foci: (1) moderate dietary restriction, (2) increased physical activity and decreased inactivity, and (3) behavior

modification. Aggressive therapies are indicated for pediatric patients with obesity-related comorbidities that might not respond to conventional therapy. These therapies include: (1) severe caloric restriction: protein-sparing modified fast, (2) pharmacotherapeutic agents, and (3) bariatric surgery. Medications reported for treatment of pediatric obesity include:

- Leptin
  - This and gastric bypass surgery are the only current effective long-term treatment options.
- Octreotide
  - Somatostatin analogue that suppresses pancreatic secretion of insulin
  - Evaluated in patients with intractable obesity from hyperinsulinism secondary to hypothalamic insults
- Metformin
  - FDA-approved for treatment of type 2 diabetes in patients  $\geq 10$  years old
  - Suppression of hepatic glucose production through activation of insulin receptor
  - May have anti-inflammatory and lipolytic effects mediated through adipocytokines
- Sibutramine
  - Mechanism of action: reduction of energy intake
  - Sibutramine and its active metabolites block serotonin and norepinephrine reuptake.
- Orlistat
  - Only FDA-approved agent for pediatric obesity, for children  $\geq 12$  years old
  - Reduction in nutrient absorption
  - Gastrointestinal tract lipase inhibitor
  - Decreases intestinal fat absorption.

Dr. Horlick listed the following conclusions:

- Responses to weight loss interventions (as reflected in measure of weight status) are generally good through the first 6 months of intervention. However, after this period, measures of weight status tend to increase.
- In adults, loss of 10 percent of body weight improves many obesity-related conditions.
- In pediatric OW, very little is known about the effect of weight loss on comorbidities.
- Short-term intervention studies suggest benefit from weight loss, but long-term risks and benefits are not known.
- Long-term maintenance of weight loss and its beneficial effects are critical in this chronic condition.
- History of medications for weight loss in adults is one of unexpected AEs with longer and more generalized use.
- In addition, not all OW pediatric patients have comorbidities; although most very severe OW adolescents do.
- Difference in comorbidities imply that clinical management of pediatric OW should be individualized and stratified, based on severity and associated health consequences.
- More studies, using the same methods to phenotype the heterogeneous pediatric OW population and quantify the response to single and combined interventions (such as behavioral therapy plus medications) are needed.

## Psychoactive Drugs Safety Issues

*Benedetto Vitiello, M.D., Chief, Child and Adolescent Treatment and Preventive Intervention Research Branch, Division of Services and Intervention Research, National Institute of Mental Health (NIMH), NIH, DHHS*

Prominent safety issues in pediatric psychopharmacology include the risk of:

- “Suicidality” associated with use of antidepressants
- Sudden death during treatment of ADHD with stimulants
- Metabolic syndrome during treatment with atypical antipsychotics.

**Suicidality Associated with Use of Antidepressants.** Suicidality includes (1) a suicidal attempt that is actually carried out, aborted, or interrupted; (2) preparatory acts toward an attempt; or (3) suicidal ideation. A relationship between the use of antidepressants in children and an increase in the risk of suicide has been suggested. However, the relationship has not been substantiated. Dr. Vitiello characterized two meta-analyses of placebo-controlled clinical trials (Hammad et al., 2006; Mosholder et al., 2006):

- 24 trials (16 in major depression)
- 9 different antidepressants
- $N = 4,582$  children (age 6–18 years)
- Duration of trials: 8–12 weeks
- No suicides occurred
- Relative risk for suicidality: 1.95 (95 percent CI: 1.28–2.98).

Approaches other than RCTs included:

- Epidemiological studies: greater SSRI use was associated with lower suicide rate (Gibbons et al., 2006)
- Case-control studies of Medicaid data in 6–18 year olds: antidepressant treatment was associated with suicide attempts (OR = 1.52) and suicide (OR = 15.62) (Olfson et al., 2006).

In addressing issues on the risk of suicidality associated with the use of antidepressants, several questions need to be answered:

- Is suicidality a valid proxy for suicide?
- What is the mechanism of action of antidepressant-induced suicidality?
  - Behavioral activation?
  - Anxiety?
- Are there individual patient characteristics that predict antidepressant-induced suicidality?

Dr. Vitiello summarized the relationship between suicide and suicide attempt:

- Suicide is a rare event.
- For every death, there are many more attempts.
- Most of those who attempt suicide (“attempters”) are females; most of those who actually commit suicide (“completers”) are males.
- Attempt increases the risk of suicide.
- Most attempters will not die of suicide.

- About half of completers had not previously attempted suicide.

In November 2006, NIMH funded four grants addressing suicidal behavior and use of antidepressants:

- Veterans Administration registry data analyses
- Pediatric primary care databases
- Developing computerized screening instruments for SSRI adverse effects
- Validation of SSRI-induced “behavioral activation” in children.

**Sudden Death During Treatment of ADHD with Stimulants.** Sudden death during the treatment of ADHD with stimulants has been reported at usual doses (Adverse Event Reporting System):

- Estimated reporting rate: 0.2–0.7/100,000 patient-years (lower than background, but under reporting is likely)
- Structural cardiac abnormalities often found at autopsy
- Stimulants increase pulse (2–6 beats per minute) and both SBP and DBP (1–4 mmHg).

The labeling of stimulants should be revised to read:

**Warning:** Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Amphetamine generally should not be used in children or adults with structural cardiac abnormalities.

In addressing issues on the risk of sudden death during treatment of ADHD with stimulants, the following question needs to be answered:

- What is the rate of serious cardiovascular AEs among children treated with stimulants for ADHD?
- What analyses of large medical claim databases can inform on this issue?

**Metabolic Syndrome During Treatment with Atypical Antipsychotics.** Atypical (second generation) antipsychotics such as risperidone and olanzapine can cause:

- Dramatic weight gain
- Insulin resistance and diabetes
- Increased LDL cholesterol and triglyceride levels
- Decreased HDL cholesterol levels.

Dr. Vitello characterized the pediatric use of antipsychotics:

- Sharp increase from 1993 to 2002
- Atypical antipsychotics are widely used in children to treat aggression, mood disturbances, and psychosis.
- Obesity is a concern in childhood.
- Placebo-controlled trials have documented antipsychotic-induced metabolic abnormalities.
- Children appear to be more sensitive than adults.



In addressing issues on the risk of metabolic syndrome during treatment with atypical antipsychotics, several questions need to be answered:

- What is the exact mechanism of action?
- Are there individual predictors to identify patients are higher risk?
- Are there alternative treatments?
- Are there other types of antipsychotics?
- Are there add-on treatments to prevent metabolic syndrome?

## **Plans for the Coming Year**

*Donald R. Mattison, M.D.*

Dr. Mattison explained that BPCA plans for 2007 depend on reauthorization of the legislation, or at least on reauthorization of NIH's continuing role. Although BPCA laid out expectations for NIH in terms of pediatric drug development, it provided no direct funding from the Institute for these activities. Under the guidance of the director of NIH and the secretary of DHHS, BPCA funding has been provided by other institutes. If the NIH component of BPCA is not reauthorized, funding will most likely stop. The effect that cessation of funding will have on in-progress clinical trials is unknown. Over the past year, those involved in BPCA have emphasized that the program focus on a needs-based approach. BPCA has shifted from a drug-based approach to a condition-based approach, with the goal of gaining a better understanding of why children interact with the health care system and how they are treated. This new approach has enhanced the discussion of asthma, obesity, HTN, and infectious disease conditions. These discussions will continue in working groups, which will convene between the annual prioritization meetings. In the long run, the informal working group discussions will provide valuable input to the BPCA process. The plans for the coming year will be to continue building the needs-based approach and working closely with pediatric experts, FDA, and other institutes. Dr. Mattison thanked all of those people who have been involved in BPCA for their hard work and expertise that they have provided to the discussions. Although BPCA has made progress, there is still much to be accomplished. He thanked the meeting participants for their attendance and encouraged continuing support of BPCA.

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