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Workshop on evaluation of pediatric long-term neurocognitive development and medical products

Ann W. McMahon¹, Leonard P. Kapcala², and Philip H. Sheridan²

¹Office of Pediatric Therapeutics, Food and Drug Administration, Silver Spring, MD, USA

²Division of Neurology Products, Food and Drug Administration, Silver Spring, MD, USA

1 | INTRODUCTION

Information on adverse neurocognitive effects due to medical products derived only from adults does not address the potential effects on the developing brains of pediatric patients. This information must be obtained from clinical studies in children.¹ Two recent laws guide the conduct of pediatric clinical trials in the United States: The Best Pharmaceuticals for Children Act (BPCA), enacted in 2002, and the Pediatric Research Equity Act (PREA), enacted in 2003.

To focus on product development and medical product safety specific to pediatric patients, the FDA implemented a series of workshops in 2014 called *Advancing the Development of Pediatric Therapeutics* (ADEPT). These workshops have brought together stakeholders, including academia, industry, patient and professional groups, and government. On April 16 to 17, 2015, experts in the field of neurocognition were assembled to address pediatric neurocognitive outcomes following drug therapy.

Workshop topics and subtopics are outlined below.

1.1 | What are the major challenges in the evaluation of long-term neurocognitive and behavioral outcomes?

There are many questions at the forefront of evaluating long-term neurocognitive and behavioral outcomes in children exposed to medical products. Do effects of a medication given to children occur soon after treatment initiation or in the long-term? Will the medication require testing to evaluate such functions as motor speed or attention span? Will

Correspondence: A. W. McMahon, Food and Drug Administration, 10903 New Hampshire Avenue, Building 32, Room 5158, Silver Spring, MD 20993 USA. ann.mcmahon@fda.hhs.gov.

The participants at the ADEPT3 workshop (in order of appearance) were Lynne Yao, MD, Peter Como, MD, Marilee Allen, MD, Gahan Pandina, PhD, Richard Gershon, PhD, Natacha Akshoomoff, PhD, Philip H. Sheridan, MD, Deborah Waber, PhD, R. Daniel Mellon, PhD, Heather Adams, PhD, Elsa Shapiro, PhD, LP, Ann W. McMahon, MD, MS, and Marilyn Bull, MD, FAAP.

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ORCID

Ann W. McMahon <http://orcid.org/0000-0003-2617-6357>

the medication have a late effect on enduring traits? Should we be looking at the rate of development of cognition in young children? Should we use growth parameters, (eg, raw scores or mental ages) rather than standardized scores (eg, mental development index on the Bayley-III), or another score which might be determined by normative data? In older children, how do we decide which neurocognitive abilities to measure and can we rely on previous research or a current hypothesized mechanism? Should we use adult data to help determine what we should measure in children?

One of the greatest challenges in performing multicenter studies is the insufficient number of pediatric neuropsychologists or developmental psychologists trained to work in clinical trials and longitudinal research. The field of pediatric neuropsychology should focus on developing relatively brief but rigorous and focused neurocognitive evaluations for clinical trials.

1.2 | What are some examples in animals or humans of safety signals related to drug therapy that alert us to possible neurocognitive behavioral outcomes?

1.2.1 | Juvenile animals—Nonclinical support of safe use of drugs in children include studies of pharmacology, distribution in brain, neurobehavioral observations, and histopathology of the central nervous system. Neurobehavioral function including basic learning and memory assessments via complex maze performance evaluation is assessed in offspring of animals treated in utero with a drug. Studies in newborn rodents showing anesthetic-induced neuroapoptosis and long-term neurobehavioral deficits have been reproduced in nonhuman primate models. Retrospective clinical studies suggest that anesthetic exposure to neonates and young children may also correlate with reduced cognitive performance. An ongoing collaborative effort between the FDA and the Anesthetic community aims to further understand the potential risks of anesthetic agents on the developing brain.²

1.2.2 | The PING study: pediatric imaging, neurocognition, and genetics—The Pediatric Neuroimaging, Neurocognition, and Genetics (PING) study³ focuses on how development of neurocognitive skills relates to neuroimaging and genetics. Children who participated in the study were developing normally.⁴ Neuroimaging, Single Nucleotide Polymorphisms, and NIH Toolbox cognition measures were collected. An example of the power of the PING study approach emerged from various Toolbox tests on a sample of 440 participating children. There were two genes associated with reading disability and language impairment.⁵ This approach may help to delineate neurocognitive outcomes attributable to drug therapy.

1.2.3 | Long-term neurocognitive effects of patients surviving leukemia—A review of studies of long-term neurocognitive effects of acute lymphatic leukemia (ALL) included those in the 1970s to 1980s on late effects of treatment.⁶ Recent studies have identified variables affecting neurocognitive outcomes following various treatments and their relationship to genetic factors. One such study focused on two successive protocols. A Genome Wide Association Study (GWAS) was performed selecting genes related to the agents used in therapy: antifolate metabolism, glucocorticoids, oxidative stress, and

neurotransmission. Effects of genotype on neurocognitive outcomes were assessed using multivariate regression. This approach identified the NOS3 gene, showing a fivefold greater probability in a subset of children with the TT polymorphism having an IQ below 85.⁷ Susceptibility to toxicity may be influenced by common genetic variance.

1.2.4 | Strategies for studying cognitive and behavioral effects of antiepileptic drugs—The detection of neurocognitive adverse effects from an antiepileptic drug (AED) under study is particularly challenging because epileptic patients may have many nondrug factors that could adversely affect their cognition, including the underlying cause of their seizures (genetic or acquired cerebral dysfunction/damage), acute or chronic cerebral dysfunction due to repetitive or prolonged seizures, psychosocial disadvantages, and the effect of other concomitant AEDs. The most readily interpretable data comes from placebo-controlled randomized clinical trials, which are typically double-blinded, but these data reflect only effects observed during short-term treatment. Uncontrolled, open-label extension trials provide more long-term data. However, it may be difficult to attribute adverse effects observed during such long-term, open-label treatment specifically to the study drug. Nevertheless, the use of neurocognitive testing in these trials has helped differentiate adverse effects of different AED therapies⁸ and adverse cognitive or behavioral effects that may not be readily apparent nor easily recognized. It is also important to recognize that when neurocognitive assessments are conducted in controlled trials of AEDs, frequently such testing may be specific to the population and/or drug under investigation. Considering some of these shortcomings, in the future, these trial-specific assessments could be supplemented with several “standard” neurocognitive assessments chosen to be used in most controlled trials of AEDs to facilitate more informative cross-study comparisons.

1.3 | What are the tools to measure long-term neurocognitive outcomes in children?

1.3.1 | Normal neonatal and infant neurocognitive development and long-term outcomes—In neonates, the potential for cognitive development is examined clinically. Although formal neurocognitive assessment is not possible in the neonatal period, many methods have been used to help select neonates who are at higher risk for developmental problems.^{9,10} Most of these are based on the early work of Gesell,⁹ which has been refined to the Bayley Scale of Infant and Toddler Intelligence, most recently restandardized in 2005 as the Bayley-III and used to assess neurodevelopment in infants.^{11,12} Other tests, such as the Mullen Scales of Early Learning¹³ and the Griffiths III Mental Development Scales,¹⁴ are used for similar clinical situations. The Fagan Test of Infant Intelligence¹⁵ uses observation of visual processing and preference for novelty. Yet, we cannot diagnose cerebral palsy or cognitive abilities in a newborn infant. Observation of visual fixation as a reflection of visual attention may be a promising tool as a prognostic feature.¹⁶ Kutzberg et al¹⁷ found that approximately two-thirds of low-birthweight infants fell below the range of performance of the full-term group in auditory and visual orienting showing the discriminatory potential of this type of testing.

1.3.2 | Normal toddler, school age, and adolescent neurocognitive development—In general, child cognitive or psychiatric deficits become apparent at school age. Children may not develop at the same rate across all domains and may learn a

skill in one domain earlier than in another. In general, a child's individual pattern of variable performances over different domains reveals more than the child's average performance score. One should target testing based on known information about a specific patient relative to their parents' socioeconomic status (SES) and educational level. These factors are at least as important as comparison to same-aged peers. As they may learn a skill earlier in one domain than in another, children may not develop at the same rate across domains. Howard Gardner's theory of multiple intelligences¹⁸ proposes that intelligence is not dominated by a single general ability but is reflected by a unique blend of abilities. IQ tests, which assess a broad range of cognitive abilities, have a strong basis in cognitive theory. The Wechsler Intelligence Scale,¹⁹ the Stanford Binet Intelligence Scales,²⁰ the Woodcock-Johnson Tests of Cognitive Abilities,²¹ and the Kaufman Assessment Battery²² for children are all well-normed IQ measurements.

1.3.3 | NIH Toolbox for the assessment of neurological and behavioral function

—The goal of the NIH Toolbox project²³ is to develop a unified set of measures for a wide range of neuro-outcomes. It is based on clinical observations in four domains: cognitive, emotional, motor, and sensory function from ages 3 to 85 years, with only four or five instruments in each of these domains.²⁴

2 | CONCLUSIONS

1. Pediatric neurocognitive outcomes have been successfully utilized in a wide range of studies assessing the effects of medications and the environment.
2. Closer collaboration between clinical trialists and neuropsychologists may help investigators utilize available neurocognitive assessment tools to study neurocognitive drug effects in children.
3. The choice of neurocognitive testing measures for a specific study may be guided by the characteristics of the pediatric population at risk, the disorder under treatment, and/or the specific drug under study. In addition, encouraging the use of some standardized neurocognitive assessments in most studies could make cross-study comparisons among different drug therapies more informative.

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