

Introduction

Developmental Neurobiology and Psychiatry: Challenges and Best Practices for Studies in Children and Adolescents

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The current era in psychiatry and neuroscience is an exciting time that has no precedent in terms of the amount of new information that will further our understanding of the biological underpinnings of mental illness. Advances in genetics, neurobiology, and clinical psychiatry have converged to begin a new epoch in psychopharmacology. These are fortunate developments, because nowhere in the field of mental health is the need for new discoveries and better research more urgent than in child and adolescent psychiatry. Until quite recently, psychiatrically ill youngsters were not included in treatment studies. Even with an increased research effort in the past decade, the number and quality of studies in this population continue to lag far behind studies conducted in adults. Alone, the small number of controlled clinical studies is notable. However, in the context of the greatly increased use of psychopharmacology in pediatric patients, the paucity of data is striking. Child and adolescent psychiatrists struggle

every day to treat their patients without an adequate evidence base that documents the efficacy and safety of available medications.

With the objective of addressing the tremendous unmet needs in the field of child and adolescent psychiatry, Otsuka Pharmaceutical, Inc., convened a 2-day meeting entitled "Developmental Neurobiology and Psychiatry: Challenges and Best Practices for Studies in Children and Adolescents." Experts in the fields of neuroscience, peptide biology, genomics, and child and adolescent psychiatry delivered state-of-the-art presentations of relevance to the topics of developmental psychiatry, new drug development, clinical trial design for pediatric populations, psychopharmacology of depression and bipolar disorder, and the use of antipsychotic agents in children and adolescents.

Keynote presentations provided a broad overview of neurobiology, genomics, and the integration of these fields to better understand the biology of depression. Because most psychiatric illnesses are complex and polygenetic in origin, the knowledge gained now and in the near future by the human genome inventory and related technology will greatly enhance scientists' ability to discover the etiology of mood and anxiety disorders. Thus, new drug development will only come from a deeper understanding of the biology that underlies depression and other diagnoses.

One of the most replicated biological findings in psychiatry is the abnormal stress response in patients with depression. Wylie W. Vale, Ph.D., provided a historical overview of the discovery of corticotropin-releasing factor (CRF) and its related endogenous ligands and receptors and described their function in regulating the stress response. Depression is widely believed to occur because of the interaction between genetic predisposition and environmental factors. Appreciation of the link between an exaggerated stress response and vulnerability to mood and anxiety disorders has spurred an intense research effort to identify causal events. Because the CRF system is such an important component of the maladaptive response to stress, the CRF receptors are logical targets for new drug

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The symposium "Developmental Neurobiology and Psychiatry: Challenges and Best Practices for Studies in Children and Adolescents" was held October 3-4, 2003, in Henderson, Nev., and was sponsored by Otsuka Pharmaceutical, Inc.

Dr. Nemeroff's financial associations include receipt of research grants, consultancies, participation in speakers bureaus, ownership of stock, and board of directors memberships from multiple companies that produce psychoactive pharmaceutical agents. He holds a patent for a method and devices for transdermal delivery of lithium (US 6,375,990 B1) and has a provisional filing (April 2001) for a method to estimate serotonin and norepinephrine transporter occupancy after drug treatment using patient or animal serum. He also has equity in Reevax, BMC-JR LLC, and CeNeRx. Dr. Wagner's financial associations with multiple pharmaceutical companies include receipt of research support and consultancies.

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development. Dr. Vale also reviewed progress in the development of CRF antagonists in the treatment of depression.

Charles B. Nemeroff, M.D., Ph.D., reviewed a large body of data offering compelling evidence that stressful or traumatic events during childhood, such as sexual or physical abuse, result in persistent changes in the neuro-circuitry of the CRF system that significantly increase the risk of depression and anxiety disorders in genetically predisposed adults. A reanalysis of a large comparative study of an antidepressant, psychotherapy, and combination treatment revealed that patients with a history of trauma exhibited distinct responses to treatment compared to patients without a trauma history. These findings suggest that there may be subpopulations of patients with distinct biological forms of depression that respond differently to treatment. Further study is clearly warranted.

In the section on depression in children and adolescents, Neal D. Ryan, M.D., addressed the developmental issues associated with depression in pediatric patients, with an emphasis on possible reasons why this population appears to respond differently than adults. The findings from randomized, controlled trials of the tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and other newer antidepressants in children and adolescents with major depression were reviewed by Karen Dineen Wagner, M.D., Ph.D. Of the antidepressants, only some SSRIs demonstrated a significant difference between drug and placebo in a priori primary efficacy outcome measures. Graham J. Emslie, M.D., reexamined findings from the antidepressant clinical trial database and considered possible reasons, including nonstandardized methodology and the influence of study site selection, patient characteristics, study design, and outcome measures, for the failure of controlled studies to demonstrate efficacy in pediatric depression. The use of antidepressants in children and adolescents and issues of safety and efficacy have come under close scrutiny recently from clinicians, researchers, the U.S. Food and Drug Administration (FDA), and the lay public. In 2004, the FDA reviewed the extant literature on the 9 short-term, placebo-controlled antidepressant trials in children and adolescents and found that, although there were no completed suicides in these studies, the risk of suicidal thinking and behavior (4%) was twice that of placebo (2%). Subsequently, the FDA required inclusion of a black box warning for antidepressants that applies to all antidepressants, whether or not they have been studied in children and adolescents.

The validity of bipolar disorder in children and adolescents has engendered heated debate in the psychiatric community, primarily because of high rates of comorbidity and overlapping symptoms with attention-deficit/hyperactivity disorder (ADHD) and other conduct disorders. This controversy has in many cases stifled clinical studies of prepubertal children with mania and hindered clinicians from diagnosing and treating these patients. Barbara Geller, M.D., and Rebecca Tillman, M.S., reflected on this issue and presented data from their group which demonstrate that bipolar disorder is a valid diagnosis in pediatric patients and that the use of specific assessment tools can reliably disentangle bipolar disorder from ADHD and other conduct disorders.

The use of the atypical antipsychotics for schizophrenia, bipolar disorder, maladaptive aggression, and other diagnoses is also increasing markedly in children and adolescents. As is the case with depression and bipolar disorder, data from adult studies have been extrapolated to pediatric patients because of a lack of data from controlled trials in children. Pediatric patients are not small adults, and the safety and efficacy of antipsychotic agents in prepubertal children and young adolescents require investigation. Issues of weight gain, hyperprolactinemia, and sedation are of great concern for school-age children, particularly those who may need to receive chronic treatment. These issues were addressed and the scarce clinical trial data were reviewed by 3 experts in child and adolescent psychiatry. The available data on the use of antipsychotics in pediatric schizophrenia were presented by Robert L. Findling, M.D. Elizabeth B. Weller, M.D., discussed antipsychotic treatment studies in children with bipolar disorder, and Hans Steiner, M.D., reviewed the published literature on the use of antipsychotics for aggression in pediatric patients. Despite their different topics, the conclusions reached by these presenters were remarkably similar: the body of data available to guide treatment of schizophrenia, bipolar disorder, and aggression in children and adolescents is minimal. Well-designed studies are urgently needed.

In conclusion, these presentations convincingly demonstrated the need to persist in the search for the biological underpinnings of depression and other mental illnesses, which will undoubtedly shed light on risk and resilience, treatment response, and the design of clinical trials. Randomized, double-blind, controlled trials that enroll a sufficiently large number of patients are needed to better guide treatment decisions in children and adolescents with psychiatric illness.