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Proceedings of the 2013 Annual Meeting of the Fetal Alcohol Spectrum Disorders Study Group

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A B S T R A C T

The 2013 Fetal Alcohol Spectrum Disorders Study Group (FASDSG) meeting was held in Orlando (Grand Cypress), FL with the theme "Developing Brain-Based Interventions for Individuals with Fetal Alcohol Spectrum Disorders." Children with fetal alcohol spectrum disorders have significant impairments in cognitive functioning and behavioral regulation skills, which lead to a lifetime of challenges for themselves and their families; thus, developing interventions that remediate or compensate for these deficits is of great importance. The conference included 2 keynote presentations, FASt data talks, award presentations, and updates by government agencies. In addition, a lively panel discussion addressed the challenges faced by FASDSG researchers in the translation of intervention strategies developed in preclinical studies to clinical trials and, ultimately, to clinical practice.

The Fetal Alcohol Spectrum Disorders Study Group (FASDSG) held its annual meeting on June 22nd, in Orlando (Grand Cypress), FL as a satellite of the Research Society on Alcoholism meeting. The 2012/2013 FASDSG officers (Julie A. Kable, Ph.D., President; James N. Reynolds, Ph.D., Vice-President; C. Fernando Valenzuela, M.D., Ph.D., Treasurer; and Alexandre E. Medina, Ph.D., Secretary) organized the meeting. Approximately 200 individuals attended the study group meeting, including 146 professionals and 57 students. Attendees were largely from the United States but included researchers from Canada, Australia, Brazil, France, South Africa, and the United Kingdom. The theme of the meeting was: Developing Brain-Based Interventions for Individuals with Fetal Alcohol Spectrum Disorders (FASDs).

Milestones in the clinical care of children with an FASD

FASDSG is composed of a tapestry of researchers who focus on various aspects of FASD research, including basic and clinical investigations. The unique combination of researchers who come from multiple disciplines has greatly facilitated the advancement of knowledge pertaining to the impact of prenatal alcohol exposure (PAE) and the basic mechanisms of action of alcohol on neural development. This combination of research skills is also needed as we attempt to advance our science in the area of intervention research. The study of the impact of PAE on development was initiated in the applied clinical setting following the identification of clusters of children with common dysmorphia and neurodevelopment problems after a history of PAE (Jones & Smith, 1973; Lemoine, Harousseau, Borteyru, & Menuet, 1968). For over 20 years, the FASDSG's primary focus was on education, prevention, and identification of the nature of the negative impact and the basic mechanisms involved in the teratogenic effects of alcohol. The overwhelming amount of information regarding the teratogenic effects of PAE and the negative ramifications on quality of life resulted in 3 major professional organizations in the United States recently recommending alterations in their practice to appropriately accommodate individuals with FASDs (American Academy of Pediatricians, 2012; American Bar Association, 2012; American Psychiatric Association, 2013). The massive amount of scientific evidence generated over many years by FASDSG researchers directly contributed to these dramatic societal changes in policy and practice toward alcohol-affected individuals.

The science of brain-based interventions for individuals with FASDs is relatively young when compared to other areas of FASD research. In the mid-1990s, targeted diagnostic clinics began to engage in the process of assisting with the identification of children impacted by PAE and to aid in treatment and habilitative care of the

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affected children and the families who care for them. Around the same time, the Institute of Medicine's report (Stratton, Howe, & Battaglia, 1996) was released, providing guidelines regarding diagnosis and a plan for advancing knowledge of how to care for children with FASD. At the turn of the century, the field began to focus on targeted habilitation and intervention efforts because of a prevailing belief that the existing interventions and systems of support were not adequately meeting the needs of these individuals.

Although we have made some definite gains in our understanding of how to habilitate children with a history of PAE, considerable effort is still needed to meet the needs of those with FASD. Key areas in need of development were identified at the onset of the meeting, providing a focus for discussions throughout the day. One of the biggest challenges to advancing the care of individuals with PAE is the limited number of treatment clinics that are available. Although more a public advocacy issue than a research issue, it is vital that there be improvements in access to care for individuals affected by PAE. Improving recognition and availability of services will also aid in advancing treatment science by the creation of databases of affected individuals from which participants may be recruited for clinical trials. The development of new behavioral interventions that address differences in family characteristics is needed, to facilitate use among the various individuals and families impacted by PAE. Additional work is also needed to develop innovative pharmaceutical interventions, since traditional psychiatric medications have had limited success. It is also necessary to expand our methods for assessing treatment effects using emerging technologies that will aid in objectively determining whether interventions are targeting specific alcohol-related brain damage. In order to expedite evaluation of treatment programs and facilitate transmission of our interventions across clinics, multi-site clinical trials need to be pursued. Finally, there is a need to develop standardized methodologies and protocols for evaluating treatments, such that valid comparisons of treatment effects across different interventions can be made.

Keynote addresses

The 2 keynote speakers addressed specific areas in need of further development in our treatment science. The first speaker was **Craig Garner, Ph.D.,** of the Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA, who spoke on his work attempting to understand synaptic mechanisms that underlie neurodevelopmental disorders and his efforts to develop pharmacotherapies. Dr. Garner first discussed his efforts in understanding the neural basis of the cognitive deficits seen in children with Down syndrome, and in developing a pharmaceutical intervention to improve their cognitive functioning. The presence of excessive inhibitory tone in the neural circuitry of children with Down syndrome was discussed. His initial work was done in the context of an animal model and focused on improving cognitive outcomes by using different drugs that reduce inhibitory tone (i.e., NOR 2) (Garner & Wetmore, 2012). In an animal model, this approach resulted in improved cognitive performance on a discrimination-learning task and normalization of synaptic plasticity. Dr. Garner discussed his involvement in a Phase II placebo-controlled study to evaluate the safety and tolerability of Bilobalide (BTD 001) in adolescents and young adults with Down syndrome (13–35 years), where they also will be assessing neurodevelopmental outcomes, including memory, reaction time, language skill, daily activities, and behavioral functioning. Dr. Garner provided insightful commentary on his experiences moving an intervention from the bench to a clinical trial phase in order to develop novel treatments for children with Down syndrome.

Dr. Garner then presented his work investigating potential molecular mechanisms underlying Autism Spectrum Disorder (ASD) and the contribution of genetic and environmental insults to specific ASDs. ASDs have been associated with loss or mutations of individual synaptic proteins (i.e., ProSAP2 and Shank3) that can alter synaptic transmission, neural circuits, behavior, and cognitive functioning (Arons et al., 2012). As deletions or mutations of ProSAP2/Shank3 have been associated with ASD, and other synaptic molecules that are associated with ProSAP2/Shank3 have been found to be mutated in patients with ASD, Dr. Garner explored whether ProSAP2/Shank3 was a key regulator of synaptic function, coordinating pre- and post-synaptic maturation via the neuroligin-neurexin (Nlg/Nrx) trans-synaptic signaling complex. He found that ProSAP2/Shank3 functions to couple pre/postsynaptic signaling and that this trans-synaptic signaling requires the activation of ProSAP2/Shank3 by zinc and a functional Nlg/Nrx signaling complex. He also found that ASD mutations in ProSAP2/Shank3 disrupt trans-synaptic signaling by reducing zinc sensitivity. He concluded that several forms of ASD appear to result from disruption of a common synaptic signaling pathway and that the second messenger signaling molecule zinc appears to be a key component of this signaling pathway. Data suggest that low dietary zinc may similarly adversely affect this pathway, neuronal circuit function, and behavior, suggesting that nutritional variability in the diets of children with ASD may differentially affect the expression of the protein mutations involved in the ProSAP2/Shank3 trans-synaptic signaling.

The second keynote speaker was **Brian Christie, Ph.D.,** of the Division of Medical Sciences, Island Medical Program University of Victoria, Victoria, BC, Canada, who spoke on his experiences in studying the recovery of function after a history of PAE and his recent, innovative work assessing the impact of traumatic brain injury and recovery of function (Boehme et al., 2011). Dr. Christie's research has included using an animal model to explore recovery of function after a history of PAE. Providing physical exercise activity resulted in improvements in neurogenesis, synaptic plasticity, increased levels of brain-derived neurotrophic factor, and improved behavioral performance on learning tasks. The positive results in animal models led him to initiate a clinical study with children impacted by PAE. He designed a study to use cardiovascular exercise to elevate levels of brain-derived neurotrophic factor to enhance cognitive functioning. Unfortunately, he experienced difficulties with obtaining enough subjects for these studies, which points to the need for multi-site studies to aid in recruiting sufficient participants to complete clinical trial studies in a timely manner.

Dr. Christie then turned his attention to exploring recovery of function after mild traumatic brain injury (mTBI), which has become a timely area of investigation because of the media focus on the impact of mTBI among professional athletes. Statistics on the prevalence of mTBI or concussions dramatically underestimate the number of individuals impacted, as many athletes are reluctant to report their symptoms. When asked to report anonymously about symptoms of mTBI, Dr. Christie reported that the prevalence of symptoms is dramatically higher. He then discussed innovative methodologies being used to assess the mild cognitive impairment seen after mTBI, including application software and computer programs (i.e., Sport Concussion Assessment Tool 2, Immediate Post-Concussion Assessment Cognitive Test, and CogniSens) that appear to be sensitive to both the impact of the injury and the recovery of function. These tasks have not yet been used among children with FASD but may provide a mechanism for evaluating recovery of function associated with a given treatment protocol.