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Review article

Challenges in developing drugs for pediatric CNS disorders: A focus on psychopharmacology

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ABSTRACT

Many psychiatric and behavioral disorders manifest in childhood (attention deficit hyperactivity disorder, obsessive compulsive disorder, anxiety, depression, schizophrenia, autism spectrum disorder, etc.) and the opportunity for intervening early may attenuate full development of the disorder and lessen long term disability. Yet, pediatric drug approvals for CNS indications are limited, and pediatric testing generally occurs only after establishing adult efficacy, more as an afterthought rather than with the initial goal of developing the medication for a pediatric CNS indication. With pharmaceutical companies decreasing funding of their neuroscience research divisions overall, the prospects for moving promising investigational drugs forward into pediatrics will only decline. The goal of this review is to highlight important challenges around pediatric drug development for psychiatric disorders, specifically during clinical development, and to present opportunities for filling these gaps, using new strategies for de-risking investigational drugs in new clinical trial designs/models. We will first present the current trends in pediatric drug efficacy testing in academic research and in industry trials, we will then discuss the regulatory landscape of pediatric drug testing, including policies intended to support and encourage more testing. Obstacles that remain will then be presented, followed by new designs, funding opportunities and considerations for testing investigational drugs safely.

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Abbreviation: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; OCD, obsessive compulsive disorder; NAC, *N*-acetylcysteine; CNS, central nervous system; FXS, Fragile X Syndrome; O3FA, omega-3 fatty acids; MDD, major depressive disorder; mGluR5, glutamatergic metabotropic receptor; PREA, Pediatric Research Equity Act; BPCA, Best Pharmaceuticals for Children Act; FDASIA, The Food and Drug Administration Safety and Innovation Act; HbA1c, glycosylated hemoglobin; PD, pharmacodynamics; 1H-MRS, proton magnetic resonance spectroscopy; Glx, combined glutamate and glutamine content; PEACE, Pediatric Epilepsy Academic Consortium on Extrapolation; POS, partial onset seizures; GCP, Good Clinical Practice; Fast-AS, Fast-autism spectrum disorder program; RDOC, NIMH Research Domain Criteria; BARDA, Biomedical Advanced Research and Development Authority; NF1, Neurofibromatosis 1; human iPScells, human induced pluripotent stem cells; CF, cystic fibrosis; CFFT, Cystic Fibrosis Foundation Therapeutics, Inc.

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1. Public health need

There is a critical need for new treatments for psychiatric disorders, and especially those targeting pediatric populations. In the US alone, approximately one in five children is experiencing or has previously faced a seriously debilitating mental disorder. It is estimated that $247 billion is spent each year on childhood mental disorders (Perou et al., 2013). Attention Deficit hyperactivity disorder (ADHD) is the most common disorder, affecting up to 8% of the population, followed by mood disorders at 3.7%. While many psychiatric medications are approved to treat behavioral symptoms in adults with psychiatric illness, relatively few are approved for use in the pediatric population and even then, there are significant numbers of children and adolescents that do not respond effectively to current treatments. Case in point, treatments are effective in 40–60% of pediatric patients with obsessive compulsive disorder (Stewart et al., 2004), and the rate of remission in pediatric major depressive disorder is 30–40%. (Cheung et al., 2005). Even when children with ADHD are given intensive, state of the art behavior or medication management for a year, they still exhibit significant impairment in adolescence, as measured by school performance, arrests, psychiatric hospitalizations, etc. (Molina et al., 2009). Meanwhile, for autism spectrum disorder (ASD), there are no drug treatments available that treat the core symptoms.

Another concern that should not be overlooked is the serious side effects that can occur with some commonly prescribed medications. These side effects, arising early in development, could have more profound impacts on health and life expectancy compared to medication exposure starting later in adulthood. Antipsychotics, used both on and off label to treat various pediatric CNS disorders, are associated with three times the risk of diabetes in children and adolescents 6–17 years old and these effects were observed within the first year of follow-up (Bobo et al., 2013). Pediatric patients gain a significant amount of weight; as much as a 7% increase in weight in as little as 12 weeks of antipsychotic treatment (Correll et al., 2009). Both the amount of weight gain and the speed at which it occurs after treatment begins, highlights how sensitive pediatric patients are to antipsychotics, even though these drugs are prescribed off label routinely. Stimulants, used as the first line of treatment for ADHD, increase heart rate and blood pressure in patients with ADHD. In rare cases, chronic administration of these drugs can produce serious cardiovascular events in adolescents and children. While these events are rare, they are twice as likely to occur in stimulant users with or without an ADHD diagnosis versus non stimulant users (Dalsgaard et al., 2014). Given the clinical implications of these side effects, continued monitoring of children and adolescents on these treatments over extended periods of time is important. And the need for safer medications with fewer side effects in pediatric populations remains great.

2. Issues in pediatric drug development

2.1. Limited "new" investigational drugs tested in pediatric trials

Murphy et al., performed an analysis of drug trials registered in the publicly available database *clinicaltrials.gov* between 2006 and 2011 that centered on pediatric neuropsychiatric conditions, specifically focusing on depression, schizophrenia, migraine, bipolar disorder and epilepsy. In that analysis, only 10% of clinical drug efficacy and safety trials were pediatric trials, and of those pediatric trials, only a small portion of currently available drugs were being tested (Murthy et al., 2013). We performed our own search of pediatric psychopharmacology trials in *clinicaltrials.gov* to look more in depth at both industry and academic research trials to better delineate the types of drugs being tested and the indications studied.

2.1.1. Academic clinical trials

In searching *clinicaltrials.gov*, we observed that a common strategy for academic clinical trials is to use marketed/generic compounds that already have FDA-approved indications for use in adult or pediatric patients, testing them for efficacy in new pediatric indications. Serotonin reuptake inhibitors have been