The Preschool ADHD Treatment Study (PATS) as the Culmination of Twenty Years of Clinical Trials in Pediatric Psychopharmacology

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In this celebration of 50 years of the Journal of the American Academy of Child and Adolescent Psychiatry’s contributions to child and adolescent psychopharmacology, it is proper and heuristically valuable to use the Preschool ADHD (attention-deficit/hyperactivity disorder) Treatment Study (PATS) to illustrate how the Journal and the field have matured over the previous two decades. It is proper because the PATS is the flagship clinical trial in preschoolers funded by the National Institutes of Mental Health in the previous decade, and heuristically valuable in the sense that it illustrates the evolution of the field, the state-of-the-field at this point in time, and allows us to look into the future.

But first a little diversion through the Journal’s history, where a search using the terms clinical trial and placebo yields approximately 300 randomized, placebo-controlled trials that begin with Magda Campbell’s pioneering studies in the early 1990s and extend into the present decade and that include hundreds of primary and secondary articles from industry- and National Institutes of Mental Health-funded clinical trials. Of these, the great majority are explanatory trials that are by design intended to maximize signal detection; a very few claim pragmatic intent. Reflecting our history and the needs of children, the lion’s share of the cited trials focus on ADHD, although all therapeutic areas are represented. Initially, trials in ADHD explored the benefits and harms of immediate-release psychostimulants in children before moving on to examine their comparative efficacy, a broader age range, extension to comorbid populations, and effects across divergent settings. Not surprisingly, trials over time developed greater sophistication in design and to some extent in implementation (for a Journal review, see Greenhill et al.1). The culmination of these efforts for the field as a whole was a series of comparative treatment trials that began with the Multimodal Treatment of Children with ADHD (MTA) study,2 which contributed 25 empirical articles to the Journal, and included Journal articles focused on ADHD, depression, bipolar disorder, obsessive-compulsive disorder, autism, and schizophrenia (for Journal reviews, see Vitiello3). At the same time, a new generation of pediatric psychopharmacologists, who grew up as clinical trialists around these studies, came together in part under the auspices of the American Academy of Child and Adolescent Psychiatry to address key topics for a modern clinical trials agenda, including recruiting subjects,4 the role of placebo,5 safety in pediatric psychopharmacology,6 the commitment to evidence-based practices,6 and the use of medications in preschoolers.7

Taken together, this body of work set the stage for the PATS as the flagship clinical trial in ADHD, some might say, in pediatric psychopharmacology in the previous decade, after the MTA study in the preceding decade. Funded by the National Institutes of Mental Health (NIMH), the PATS is a multicenter, randomized, efficacy trial designed to evaluate the short-term (5 weeks) efficacy and long-term (40 weeks) safety of methylphenidate in preschoolers 3 to 5 years of age with severe ADHD that was unresponsive to a 10-week psychosocial intervention. Given multiple levels of review—scientific, the NIMH Data Safety Monitoring Board, the Food and Drug Administration, and local institutional review boards—designed to protect the science and the subjects, the final PATS design (as described by Kollins et al.8 in a Journal article on the rationale and design of the PATS) included a complex mix of eight phases: screening/enroll-
ment; a 10-week, uncontrolled parent training; baseline assessment; a 1-week, open-label, safety lead-in; a 5-week, random sequence double-blind, crossover titration trial; a 4-week, optimal dose, double-blind, placebo-controlled parallel trial; a 10-month, open-label maintenance phase; and a 6-week, placebo-substitution discontinuation phase. Highlighting the sensitivity around patient safety, informed consent was obtained at each phase of the study. Surely, the PATS is the prototypical trial designed not just by one committee but by many committees.

Reflecting an increasingly prominent role for the Journal in publishing high impact articles in pediatric psychopharmacology, the PATS team chose to publish the five “primary” articles in a Journal special section in 2006, beginning with the rationale and design article by Kollins et al.\(^8\) In the primary outcome article by Greenhill et al.,\(^9\) methylphenidate proved efficacious in decreasing ADHD symptoms. However, for the preschoolers randomized into the parallel group trial, only 21% on best-dose methylphenidate and 13% on placebo achieved remission. Notably, end doses were lower and the effect sizes (0.4 to 0.8) proved considerably smaller than those cited for school-age children.\(^9\) In part, as described by Wigal et al.,\(^10\) this was due to lower tolerability for methylphenidate in this population compared with older children. One in 10 children discontinued medication and 30% experienced moderate to severe adverse events, including emotional outbursts, difficulty falling asleep, repetitive behaviors/thoughts, appetite decrease, and irritability. After similar findings in the MTA study, the PATS also identified a clinically significant decrease of growth rates.\(^11\) Reflecting the trend toward using -omics (genomics and proteomics) strategies to personalize treatment, McGough et al.\(^12\) employed candidate gene approaches to explore genetic moderators of symptom decrease and side effects in the PATS. Analyses revealed associations between symptom response and adverse events and variants at the dopamine receptor (DRD4) promoter and synaptosomal-associated protein 25 (SNAP-25). Allowing for careful attention to adverse events, including slowing in growth, the PATS findings show that with slower titration and lower doses in acute and maintenance treatments, at the least a substantial minority of preschool age children with ADHD benefit from treatment with psychostimulants much like their older counterparts, but a larger number do not, perhaps because of genetic variation and, hence, much greater attention to personalization of treatment in this patient population is warranted.

The PATS, which was conceived in 1999, was out of date out of the box, as shown by the use of immediate-release rather than sustained-release methylphenidate, which by the way was a gift from the MTA study. Even so, the PATS contributed important new information to a growing literature on preschool psychopharmacology. In so doing it anticipated the need for interventions based in translational developmental neuroscience is already beginning to drive rapid and dramatic shifts in drug, biological, device, and psychosocial intervention developments.\(^13,14\) As highlighted in a recent article by the NIMH director, Tom Insel, on transforming psychiatry as a clinical discipline,\(^15\) the age of symptomatic diagnosis and current-generation treatments is passing; the age of interventions that emerge from the revolution in translational developmental neuroscience has begun.\(^16,17\) Because these newer interventions will emerge from an improved understanding of the fundamental biology of the illnesses, these will be more effective in patients who are ill and, excitingly, will eventually become preventive if not preemptive, e.g., they will be delivered to very young children who are at risk but not yet showing early signs of mental illness. Accordingly, pediatric psychiatry will become the front end (the most important end) of a life-span developmental model for mental illnesses based not on serendipity or clinical observation but in -omics approaches to systems biology and its information processing counterparts. Science drives innovation and innovation drives application in the form of interventions. For a while then, studies in adults will lead studies in youth, but new interventions for mentally ill youth will emerge once the fundamental biology catches up. Paralleling the resizing (downward) and realigning (to phase I and proof-of-concept trials) exercise taking place in industry,\(^18\) the NIMH also will shift to T1 “early-phase” research as an inevitable part of capitalizing on the enormous investment the NIMH is currently making in discovery and translational neuroscience. In the meantime, T2 “late-phase” intervention development will focus not so much on clinical trials but on developing an optimized infrastructure for conducting data-mining exercises, registries, cohort studies, and randomized
Maximally effective interventions for mental illness across the life span will emerge by accelerating the translation of fundamental biological insights into clinical application by supporting a smooth continuum of intervention development—from preclinical studies to first-in-man and proof-of-concept research in humans and eventually into pragmatic clinical trials. For our field to thrive it will be important to embrace and actively participate in this process so that mentally ill youth are viewed as a key target population and, consequently, truly preemptive, preventive, and curative interventions will be developed for children by first intent. Likewise, by fully embracing the molecular revolution, including progress in neuroimaging, and developing expertise in early phase clinical pharmacology, the journal will be prepared to embrace the next generation of psychopharmacologic interventions in pediatric psychiatry.

In celebration of its 50th anniversary, the journal presents a yearlong series of editorials that discuss and reflect on pivotal research published in these pages over the previous five decades. The editorials show how the foundations of the science in child and adolescent psychiatry have been laid, describe how they influence us today, and suggest how they will continue to guide us over the next 50 years and on.

REFERENCES


