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Steven W. Evans ^a, Theodore P. Beauchaine ^b, Andrea Chronis-Tuscano ^c, Stephen P. Becker ^d,
Anil Chacko ^e, Richard Gallagher ^f, Cynthia M. Hartung ^g, Michael J. Kofler ^h, Brandon K. Schultz ⁱ,
Leanne Tamm ^d, and Eric A. Youngstrom ^j

^aDepartment of Psychology, Ohio University, Athens, USA; ^bDepartment of Psychology, The Ohio State University, Columbus, USA; ^cDepartment of Psychology, University of Maryland, College Park, USA; ^dCincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Ohio, USA; ^eDepartment of Applied Psychology, New York University, USA; ^fDepartment of Child and Adolescent Psychiatry, Grossman School of Medicine, New York University, USA; ^gDepartment of Psychology, University of Wyoming, Laramie, USA; ^hDepartment of Psychology, Florida State University, Tallahassee, USA; ⁱDepartment of Psychology, East Carolina University, Greenville, North Carolina, USA; ^jDepartment of Psychology and Neuroscience, University of North Carolina, Chapel Hill, USA

ABSTRACT

News of a videogame that received FDA clearance to treat youth with attention-deficit hyperactivity disorder (ADHD) garnered a great deal of media attention and raised questions about the role of digital cognitive training programs for treatment. In order for clinicians and clients to understand this news for the purposes of making treatment decisions one must have an understanding of what it means for a treatment to be considered evidence-based and an understanding of what is required to obtain FDA clearance. Finally, in order to fully inform decisions about treatment, clinicians and parents must be able to consider the evidence supporting cognitive training programs in relation to other treatments available for children with ADHD. A review of these standards and the evidence supporting cognitive training in general, and the new videogame that received recent FDA clearance (EndeavorRXTM) specifically, revealed an overall lack of support for this approach to treatment. There are multiple psychosocial and pharmacological treatment options with much more evidence supporting their effectiveness than any commercially available cognitive training program. The contrast between receiving FDA clearance without evidence of any observable benefits to the child is explained within a description of the FDA process for clearance and approval. Finally, these conclusions are described in the context of clinicians' decisions regarding services offered and procedures for explaining this to families who may have seen the media attention related to FDA clearance.

Non-pharmacological treatments for attention-deficit/hyperactivity disorder (ADHD) rarely make national news. Yet on Monday June 15, 2020, almost all major news networks reported the Food and Drug Administration's (FDA) clearance of EndeavorRXTM – a videogame treatment for children ages 8–12 years with the inattentive and combined presentations of ADHD (see e.g., <https://www.cnn.com/2020/06/16/health/adhd-fda-game-intl-scli-wellness/index.html>). EndeavorRXTM is a videogame-delivered cognitive training (CT) treatment intended to improve some neurocognitive deficits associated with ADHD. Children play the game repeatedly (30 min or more per day for several weeks) to “train” their brains. In theory, if core cognitive

deficits are addressed, problems that result from or are associated with these deficits will remediate. Because evidence for CT for ADHD is quite limited (see Evans et al., 2018), endorsement of EndeavorRXTM by the FDA caught many by surprise. To date, CT is not recommended in treatment guidelines from professional organizations including the American Academy of Pediatrics (AAP; Wolraich et al., 2019).

We begin this review by examining relevant theory behind and evidence for potential benefits of CT for children with ADHD. We then review established criteria for evaluating effectiveness of *any* treatment, before considering evidence for EndeavorRXTM. Next, we juxtapose research on EndeavorRXTM,

CONTACT Steven W. Evans  evanss3@ohio.edu  Department of Psychology, Ohio University, Athens, OH 45701, USA.

The authors listed from Stephen Becker to the end are listed in alphabetical order and not meant to reflect relative level of contribution among those authors.

other CT, and psychosocial treatments for ADHD. In doing so, we summarize support for CT in relation to other available treatments for children and families with ADHD. Next, we examine how EndeavorRX™ achieved FDA clearance and implications of that decision for practitioners. We conclude with recommendations for how clinicians might talk with parents about CT when discussing treatment options for their children.

What is the rationale for CT?

In the *DSM-5* (American Psychiatric Association, 2013), ADHD is classified into three presentations (formerly subtypes): hyperactive-impulsive (HI), inattentive (IN), and combined (C). Distinguishing among presentations is a prevailing approach in clinical research, as well as within prominent theoretical models and neuroimaging research examining various neural substrates for ADHD-HI/C and ADHD-IN (e.g., De la Peña et al., 2020; Fair et al., 2013). Much of this research assumes that understanding etiology will eventually improve treatment efficacy because neural and behavioral deficiencies might be targeted directly (e.g., Rubia et al., 2009).

Although presentation construals of ADHD vary in specific details, many attribute HI either in part or whole to *frontostriatal dysfunction*. This neural network projects from the striatum to the prefrontal cortex and is involved in all reward- and extinction-based learning (Schultz, 2016). Among those with ADHD-HI/C, the striatum is under-responsive to anticipated rewards (Plichta & Scheres, 2014). Compared with controls, larger, more immediate rewards are required to activate the striatum in those with ADHD-HI/C, suggesting a reward-seeking model of HI whereby affected children (a) require more immediate reinforcement to obtain the same hedonic value as their peers, and (b) habituate to rewards more quickly (Beauchaine et al., 2017). Put another way, those with ADHD-HI/C obtain limited “bang-for-their-buck” from ordinary reinforcers and therefore engage in high levels of reward-seeking behaviors. This provides a basis for understanding why behavioral interventions that emphasize consistent, immediate, and salient rewards are effective.

In some models, inattention among those with ADHD-HI/C is proposed to emerge *epiphenomenally*

(secondarily) to HI, and is expressed as distractibility (e.g., Lee et al., 2016). Although specific accounts vary, attention problems for those with ADHD-IN – which are primary and often expressed as low motivation or being easily bored – are attributed primarily to *frontoparietal and temporal lobe dysfunction* (Diamond, 2005). The frontoparietal system maintains attention, mediates declarative memory, and facilitates decision-making (Liu et al., 2020). Interventions focused on organization, planning, and problem solving may be beneficial for those with ADHD-IN.

In addition to these neural mechanisms, ADHD symptoms are associated with a range of underdeveloped neurocognitive abilities, which vary by individual. This leads to the well-documented heterogeneity in cognitive and performance deficits exhibited by children with ADHD (Kofler et al., 2019). Thus, children may exhibit impairment related to ADHD symptoms for a variety of reasons, and similar symptoms may arise from different neural sources across individuals. Nevertheless, some deficits are more likely to account for impairment than others. There is particularly strong evidence for working memory deficits (present in 62% to 85% of children with ADHD) as a core mechanism (see Kofler et al., 2020). Such evidence includes experimental studies in which working memory demands are manipulated and effects on objectively-measured behaviors are evaluated (Kofler et al., 2010; Kofler, Spiegel et al., 2018). Children with ADHD become disproportionately hyperactive and inattentive as working memory demands increase. In contrast, they are no more hyperactive or inattentive than their peers when working memory demands are low. In addition, longitudinal studies show that children whose working memory improves from ages 7–13 show symptom remission over the same period (Karalunas et al., 2017). Children with better working memory also show larger responses to behavioral parent training (BPT; Fosco et al., 2018). Although such findings point toward working memory as a target for CT, it is unlikely that any single treatment will help all children with ADHD given the etiological heterogeneity noted above.

An additional challenge concerns transfer. CT is only useful insofar as it improves both the neurocognitive deficiency targeted *and* impairment exhibited by children with ADHD (e.g., failure to complete

tasks, difficulties maintaining friendships). In other words, clinical success requires that proficiencies gained through CT *generalize* beyond outcomes closely related to the training condition (near transfer) to meaningful functioning (far transfer). Generalization is challenging because CT places far fewer demands on children than complex environments where effective daily function is required (e.g., school). Following CT, children may improve skills related specifically to the training; however, more complex skill deployment is required when interacting with other people and when organizing one's time and belongings. In other words, neurocognitive abilities are only one necessary skill for success in real-world contexts. To offer an analogy, strength and endurance are two elements needed to improve performance in sports such as basketball and baseball. One can have exceptional strength and endurance, yet be terrible at basketball (Chacko et al., 2014). Similarly, one may show improved neurocognitive abilities but continue to struggle with school, social, and family functioning. Put more simply, improving neurocognitive functioning may be necessary but insufficient for improvement in daily tasks.

Despite such obstacles, considerable effort is being invested in developing CT to improve impairment by enhancing neurocognitive abilities for a variety of disorders. For example, targeted CT appears to improve useful-field-of-view (UFOV) – a speeded visual processing skill – among older adults who are at-risk for or already showing cognitive decline (Wolinsky et al., 2013). Randomized controlled trials (RCTs) suggest that UFOV training generalizes beyond the lab and improves real-world driving and activities of daily living for these elderly individuals (Edwards et al., 2018). Although far transfer has been achieved for some problems with some populations, far transfer is rare, and most attempts in the CT literature fail (Simons et al., 2016).

There is some indirect support for the potential to achieve far transfer, such as studies examining effects of commercial videogames, particularly in domains of perception, spatial cognition, and top-down attention (Bediou et al., 2018). This work, most of which is cross-sectional and nonexperimental, shows that self-identified gamers outperform non-gamers in specific cognitive domains – especially gamers who play fast-paced, highly interactive videogames (Bediou et al., 2018). Some

research suggests that game-naïve individuals can improve their performance in similar cognitive domains after playing videogames for brief periods (e.g., Green & Bavelier, 2003). Attempts to replicate such findings, however, have been mixed (Sala et al., 2018). Nevertheless, many researchers and developers speculate that customized computer programs designed to train specific cognitive skills may achieve far transfer and meaningful benefits. Such speculation has invigorated computer-based CT research and a multibillion dollar “brain training” industry (Cookson, 2014).

How is the evidence supporting treatments evaluated?

To provide context for understanding the state of the evidence for CT, it is important to consider how interventions of any kind are evaluated as effective for youth with ADHD. A great deal of research has addressed this question and is summarized in recent scholarly reviews and treatment guidelines (e.g., Evans et al., 2018; Fabiano & Pyle, 2019; Wolraich et al., 2019). Four aspects of such research are crucial for evaluating CT (or any treatment): (a) study design; (b) outcome measures; (c) measurement timing; and (d) magnitude of effects.

Study design concerns *how* a treatment is manipulated to test its efficacy. Including control participants or conditions is essential for treatment evaluation. Control participants or conditions must be present in everything from single-case designs to large RCTs. In RCTs, control groups (e.g., no treatment, alternative treatment) are necessary because some participants improve over time without intervention. Treated participants need to fare better than controls to confirm change over-and-above chance, placebo effects, regression to the mean, and/or maturation. Some studies compare new treatments with existing or ideally established treatments to determine which is better. In either case, participants are assigned randomly to treatment and control conditions, which reduces confounds and alternative explanations for results.

Outcome measures concern *what* should be assessed. Such measures should assess concerns that parents and youth describe as presenting problems (i.e., the problems that prompted them to seek treatment). Connections between outcome

measures and presenting problems form the basis for why clinical research is relevant to practice. Common outcome measures include symptoms, proximal intervention-specific measures, and impairment. Symptoms of ADHD are the most common outcomes in treatment studies because these data directly inform the question of whether the treatment alters characteristics of the disorder. As a result, symptoms of ADHD are often selected as primary outcomes in clinical trials, but they are not always the best match to presenting problems. For example, a parent may bring her son to treatment because a teacher complains he does not complete his work, is disruptive in class, and annoys other students. If the treatment for this child improves symptoms (e.g., fails to give close attention to details), but does not improve work completion, disruption, and behaviors that annoy peers, it fails to address family's primary concerns and needs (Kazdin, 1977).

Proximal outcomes (i.e., measures of direct treatment targets) provide valuable information about treatment, but may not directly address presenting problems. Keeping with our example from above, a clinician might hypothesize that the maintaining factors for the son's poor grades is forgetting his assignments, losing academic materials, and not remembering when tests or quizzes are scheduled. In this case, an organization measure might serve as a proximal outcome to determine if the maintaining factor changes during intervention. But these data would not address the broader presenting problems (e.g., poor grades) that remain distal, both temporally and conceptually. As in the case of symptoms, measures of organization might improve even though the son continues to fail his classes. So, although proximal measures (organization) reflect the maintaining factors, separate measures are typically required to assess the impact of treatment on presenting problems (poor grades).

Many outcomes assessed in CT studies fall into the category of proximal outcomes. Changes in computerized tests of attention, for example, are proximal to training in terms of timing and in terms of measurement method and underlying construct (Podsakoff et al., 2012). Proximal measures are helpful in establishing underlying mechanisms of treatment and their relations to presenting problems (Lambert et al.,

2005), but are rarely considered the most important outcomes. Thus, although changes in proximal outcomes may indicate movement in the right direction, they are not the finish line (Youngstrom et al., 2017).

Effective interventions produce meaningful changes in the specific impairments that bring families to treatment. Functional impairments in daily life (e.g., problematic parent-child relationships, academic difficulties, peer relationship problems, risky driving behaviors in adolescents) are typically what motivates families to seek treatment, so improvement in these outcomes must be prioritized. Impairment measures assess whether and how these most salient problems change over time. Some measures of impairment are global (e.g., Impairment Rating Scale; Fabiano et al., 2006), whereas others are precise (e.g., grades in classes, disciplinary referrals, inclusion in social activities, peer sociometrics). Still others are derived directly from presenting problems and individualized to clients (e.g., Daily Report Cards). Treatments that produce changes in these domains have the greatest impact on clinical practice because they speak directly to the youth or family's presenting problems.

It is also important to know *when* to measure outcomes. Typically, intervention effects are evaluated prior to and immediately following treatment. Although these are key measurement occasions, many studies also assess outcomes months (and sometimes years) after treatment to evaluate long-term effects. Short- and long-term outcomes may differ. The largest ADHD treatment trial ever conducted with children found clear pre- to post-treatment benefits of intense doses of behavioral and medication treatments (The MTA Cooperative Group, 1999); however, most treatment benefits faded one year later, and were not sustained at longer-term follow-ups (Molina et al., 2009). In contrast, the magnitude of effects for some treatments increase over time even after treatment ends, changing the interpretation of the value of treatment from that which was based only on post-treatment effects (Margherio et al., 2020).

Both short- and long-term outcomes are important to measure, but sustained, long-term benefits are most critical, particularly for a chronic disorder such as ADHD. Although parents may be happy to observe important gains immediately post-treatment, if those

gains evaporate 6 months later, satisfaction with treatment will diminish. Furthermore, parents may consider time and money spent as wasted and no longer pursue care. Thus, clinicians are wise to prioritize treatments with demonstrated long-term gains.

Finally, *magnitude* of change must be considered. Statistical significance pertains to group-level differences, which may not translate into a meaningful magnitude of change for the individual. Several metrics for assessing clinical significance are available, all of which index meaningful change (e.g., Atkins et al., 2005). Minimally important difference (MID) is an approach often used in medicine. Sometimes MID is defined using focus groups of patients who are asked how much change on an outcome is required to feel improvement (Thissen et al., 2016). More commonly, MID is approximated using simple statistical rules of thumb, such as Cohen's $d \geq 0.5$ (one-half standard deviation), or by more elaborate statistical procedures (Thissen et al., 2016). Taken together, treatments are most effective

when they result in meaningful individual change on an ecologically valid outcome (i.e., one that is of real-world importance) that is prioritized by the client and that persists over time.

Clinical child psychologists and pediatricians are two groups of professionals who often provide services to children with ADHD. Both of their professional organizations have used the methods described above to evaluate effectiveness of treatments. The Society of Clinical Child and Adolescent Psychology (SCCAP; Division 53 of the American Psychological Association) has adopted standards for defining well-established treatments (see Figure 1; <https://effectivechildtherapy.org>, Southam-Gerow & Prinstein, 2014). Their approach prioritizes multiple, rigorous RCTs, ideally from independent research teams (as summarized by strong effect sizes in meta-analyses, when available). These studies must demonstrate treatment-related improvement in ADHD symptoms and functional impairment for a treatment to be identified as "well-established." Treatments not

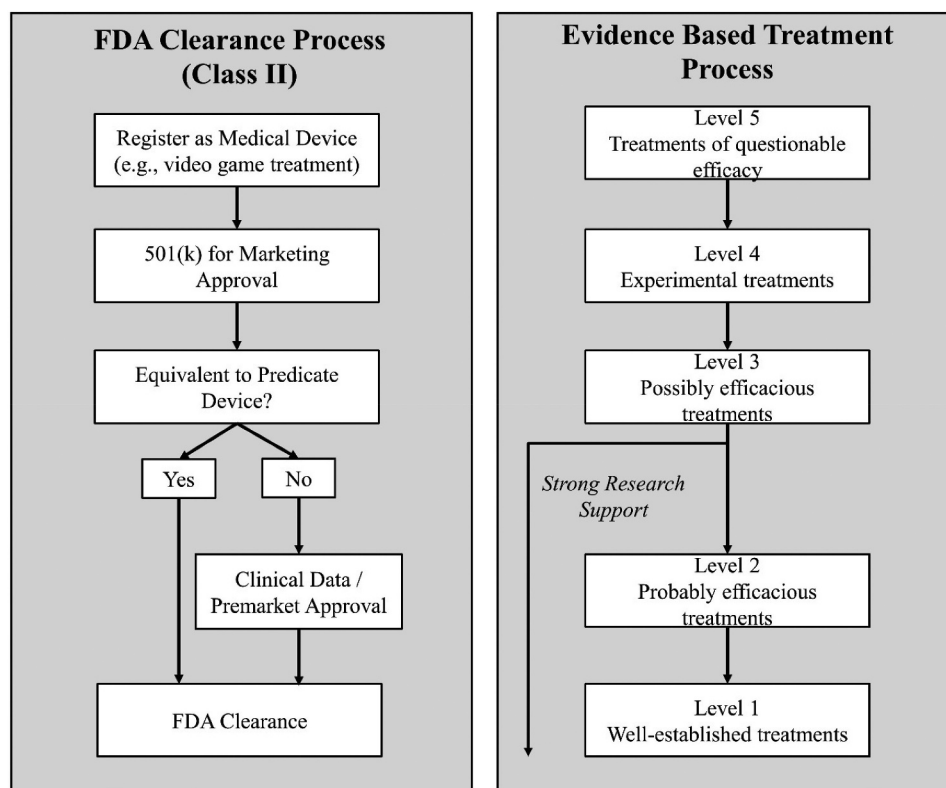


Figure 1. Different processes and end-point goals for obtaining FDA clearance and determining evidence based treatment. FDA clearance process summarized from the FDA website (www.fda.gov; accessed in August 2020). Evidence based treatment from levels from Southam-Gerow and Prinstein (2014) outlining review criteria used for evidence-based updates in the *Journal of Clinical Child and Adolescent Psychology*; see that article and/or effectivechildtherapy.org for further details regarding criteria for each level in addition to methods criteria. Figure CC BY 4.0 Becker & Tamm, DOI 10.17605/OSF.IO/GZBJN.

meeting this standard may be classified as either “Probably Efficacious,” “Possibly Efficacious,” “Experimental,” or of “Questionable Efficacy.” The AAP publishes treatment guidelines for children and adolescents with ADHD. These guidelines classify treatments based on the quality of the evidence and result in either “Strong Recommendation,” “Moderate Recommendation,” or “Weak Recommendation.” As reviewed in the following sections, both organizations publish their reviews and recommendations and both recently considered the evidence for CT (Evans et al., 2018; Wolraich et al., 2019).

What is the evidence for CT as a treatment for youth with ADHD?

The most recent SCCAP review classified CT as “Experimental” because CT was evaluated in RCTs, but the majority of studies reported no significant benefits on ratings of symptoms or functioning (Evans et al., 2018). The AAP summarized evidence for CT by stating, “Some nonmedication treatments for ADHD-related problems have either too little evidence to recommend them or have been found to have little or no benefit.” (Wolraich et al., 2019, p. 13). Similar conclusions were offered in the treatment guidelines provided by the Society for Developmental and Behavioral Pediatrics (Barbaresi et al., 2020; p. S45) as they stated that CT has, “shown some improvement in laboratory-based, task-specific outcomes, none have demonstrated sufficient evidence of effectiveness in real-world domains of functioning . . . to recommend them for use in practice with children and adolescents with ADHD.” These characterizations indicate that, on the whole, the CT literature is beset by methodologic and analytic problems, including small samples, poorly-matched control groups, failure to account for expectation effects, and lack of statistical corrections for multiple comparisons (Simons et al., 2016). There are, however, exceptions.

In order to interpret the research, it is important to first note that neurocognitive abilities targeted in CT studies vary considerably, but typically include laboratory tasks tapping vigilance and sustained attention because these processes are thought to be associated with ADHD. Continuous performance tasks (CPTs) are frequently used to measure these

constructs. CPTs require an individual to either respond to or ignore stimuli that are presented briefly onscreen using a simple rule (e.g., location of stimulus in visual field), over a protracted period (e.g., 15 minutes). A meta-analysis examining near transfer of CT on such measures found no effect ($d = 0.05$; Rapport et al., 2013). The authors interpreted this finding as evidence that CT programs target many attentional processes (e.g., selective attention, divided attention) that are weakly associated with ADHD symptoms in the real world, thereby diluting effectiveness. Some CT programs target other deficits such as response inhibition, which are common to ADHD (21–46%; Kofler et al., 2019). However, response inhibition may not be a viable treatment target for CT because it (a) is resistant to training; (b) is unassociated with ADHD symptom severity; and (c) shows no correspondence with developmental changes in ADHD symptoms (Karalunas et al., 2017; Kofler et al., 2020). Similar limitations may apply to delay discounting or measures of impulsivity (e.g., Scheres et al., 2010). Furthermore, many cognitive attentional processes are largely intact in many children with ADHD, making these interventions less relevant to a sizable subset of youth with ADHD (Huang-Pollock et al., 2005).

In contrast, given the role of working memory deficits in ADHD and their responsiveness to training (Melby-Lervåg et al., 2016), other CT programs focus on improving working memory, with the ultimate goal of improving day-to-day functioning. Most working memory tasks require examinees to remember and manipulate information while either ignoring distractors or engaging in competing tasks. A classic example of a visual-spatial working memory test requires participants to view a series of different-colored dots that appear one at a time on a grid, and then mentally reorder them and recall them based on color (e.g., indicate the position of black dots in the order they appeared, then red dots in the order they appeared). CT elements designed to improve working memory often overlap with working memory measures. In some cases, CT elements are gamified versions of outcome measures and might capture variants of the same ability (e.g., recalling visual patterns). Although improvements in laboratory test performance may provide evidence of near transfer to the trained neurocognitive abilities, there is much less evidence that these gains

achieve far transfer to new domains (Simons et al., 2016). Thus, the challenge in this literature is to demonstrate meaningful outcomes beyond near transfer training effects (i.e., working memory abilities).

For children with ADHD, CT yields small to moderate improvements in laboratory test performance (near transfer), with little or no effects on academic achievement or behavior (far transfer) (Rappport et al., 2013). Thus, there is little evidence that attempts to improve working memory translate into objective, real-world benefits (e.g., task completion, mathematics, reading comprehension), even temporarily (Melby-Lervåg et al., 2016). In fact, although early attempts to train working memory in ADHD (most notably CogMed Working Memory Training) suggested promise (Chacko et al., 2013), several subsequent studies revealed that CogMed affects only short-term memory and not working memory as intended (Rappport et al., 2013; Roberts et al., 2016). After training, children with ADHD hold more information in short-term memory but cannot *do* more with that information. CogMed's minimal impact on ADHD symptoms and related impairment is therefore unsurprising because short-term memory, in contrast to working memory, is generally unrelated to ADHD.

Recently, progress in developing working memory using CT was reported in two preregistered clinical trials of Central Executive Training (CET). Both showed large improvements in “working” components of working memory relative to two active control conditions: gold-standard BPT and inhibitory control training (ICT). These improvements yielded significant reductions in ADHD symptoms, measured both objectively via actigraphy and subjectively via parent- and teacher-reports. In the first trial, reductions in ADHD symptoms were similar to those found for BPT (Kofler, Sarver et al., 2018). In the second, CET produced greater reductions in parent- and masked teacher-ratings of ADHD symptoms (Kofler et al., 2020). In both cases, improvements in working memory were associated with symptom reductions, and may therefore be the active ingredient. Although these results are encouraging, there is still no evidence that improved working memory yields far transfer to outcomes such as peer, family, and academic functioning. As a result, evidence for working memory training and other CT

is not adequate to warrant recommending for youth with ADHD at this time (Cortese et al., 2015; Evans et al., 2018; Wolraich et al., 2019).

News that EndeavorRXTM CT received FDA clearance warrants close examination of scientific evidence supporting the intervention. Although Akili (the company that owns Endeavor) claims “rigorous” evaluation across various clinical trials, as of November 2020 none of these involved a randomized clinical trial that demonstrated treatment gains in ratings or other indices of symptoms or impairment (see <https://www.akiliinteractive.com/news> for research updates). The most comprehensive evaluation of EndeavorRXTM was a carefully designed RCT of youth (ages 8–12 years) with ADHD (Kollins et al., 2020). The RCT included preregistration at ClinicalTrials.gov, an active digital control group, double-blinded outcomes, and a large sample size ($N = 348$). Participants were to play the CT videogame at home, named AKL-T01 in the study (i.e., EndeavorRXTM), for five 5-min sessions per day 5 days per week for 4 weeks (actual sessions completed $M = 83.2$ out of 100 prescribed). Significant treatment gains were reported on the Test of Variables of Attention (TOVA; Lark et al., 2016; preregistered as primary outcome at ClinicalTrials.gov), a CPT, compared to participants in the control group. However, the treatment did not yield improvements in (a) parent-reported ADHD symptoms, as indexed by the ADHD-Rating Scale (ADHD-RS; DuPaul et al., 2016); or (b) parent- or clinician-reports of impairment, as indexed by the Impairment Rating Scale (IRS) and the Clinical Global Impressions (CGI). Lack of effects on these measures indicates that any changes in child behavior were undetectable by parents and clinicians. Nevertheless, Kollins et al. (2020) argued that the TOVA is “mimicking one component of the classroom situation in which children are required to remain seated and engaged in a tedious, repetitive task, suggesting ecological validity of the TOVA test for real-world settings in which children with ADHD often struggle” (p. e175). This conclusion warrants scrutiny because CPTs such as the TOVA are only weakly associated with observations of classroom attention (Rappport et al., 2009). In fact, observations of child *behavior* while completing a CPT predicts their classroom behavior better than CPT performance itself (Borger et al., 1999; Weis &

Totten, 2004). Thus, it is unsurprising that small gains on the TOVA test failed to translate to changes in “real world” behavior in the RCT. Indeed, although near transfer to a laboratory measure (TOVA) was observed, far transfer to ADHD symptoms and impairment was not. Given that this was a meticulously designed RCT, lack of far transfer is noteworthy. Furthermore, effect sizes of near transfer were small. Although Kollins and colleagues did not report effect sizes, the TOVA data provided in the article indicate a Cohen’s d of 0.28. *This indicates 92% overlap in posttest group distributions of TOVA scores for treated versus control participants.* Changes this small, although detectable statistically, are not “visible to the naked eye of a careful observer” (Cohen, 1992, p. 156).

How does the evidence for CT compare to the evidence for other psychosocial treatments?

The most recent review by the SCCAP (Evans et al., 2018) identifies two psychosocial (i.e., non-medication) treatment approaches as well-established: (1) behavior management (including BPT, behavioral classroom management, and behavioral peer interventions) and (2) organization skills training depending on the age of the child. The AAP treatment guidelines provide strong recommendations for behavior management, training interventions, and FDA-approved medication treatment for children and adolescents with ADHD (Wolraich et al., 2019). Based solely on the conclusions of these two professional organizations, there are plenty of effective alternatives to CT.

Behavior management interventions for youth with ADHD involve working with parents and teachers to craft optimal environments in which youth with ADHD thrive. These environments include structure/routines, clear expectations, praise for appropriate behaviors, and consistent, nonphysical consequences for rule-breaking and aggression. Behavioral interventions for children yield improvements in ADHD symptoms and associated impairment, as measured by parent- and teacher-ratings, and by independent observers. Yet, even for these interventions, conclusions based on meta-analyses differ in relation to the magnitude and consistency of effects (Fabiano et al., 2015). Behavior management interventions for adolescents, which are less

studied, involve the adolescent to a greater extent (as opposed to parents or teachers), and include behavioral contracting, motivational interviewing, and communication training (Sibley et al., 2016). Given relatively less research on behavior management for adolescents and mixed outcomes, it is classified as “possibly efficacious.”

Organization skills training (OST) involves direct instruction, practice, and coaching in use of new or replacement behaviors designed to address ADHD symptoms and associated impairments (e.g., in academics). Youth are taught to organize materials and time, and to practice frequently with performance feedback over an extended period. Improvements in parent-reports, teacher-reports, and objective indices of academic functioning are observed (Evans et al., 2016; Langberg et al., 2018); however, variability in findings has emerged across studies. Two factors that determine efficacy appear to be the: (1) amount of practice and performance feedback provided; and (2) degree to which the content of training matches real-world behaviors and domains of impairment. Given that ADHD is in large part a disorder of performance, effective training interventions provide many repetitions with performance feedback for functional behaviors that are required by settings in which individuals are impaired.

There is far less evidence for CT than the two well-established non-medication treatments outlined above. This does not mean that BPT, teacher training, and organization training work for all youth. There are a variety of reasons for variability in treatment response, including heterogeneity in causes and presentation of ADHD (see above) and provision of treatments in a manner that does not adhere to established guidelines (i.e., poor fidelity). For example, in schools many students receive services that are referred to as organization skills training, but rather than following training procedures prescribed by manualized evidence-based interventions, educators “organize” student’s materials for them. Similarly, BPT provided by someone who is not expert in behavioral treatments can lead to parents inadvertently reinforcing the very behaviors targeted for extinction. In addition, unique characteristics of children and families can diminish success of otherwise effective treatments. Finally, youth respond variably, even to effective

treatments. Close examination of almost any clinical trial reveals participants in the treatment condition who did not respond. Nevertheless, treatments classified as effective are more likely to help clients than treatments with little or no evidence. Thus, when selecting treatments, starting with those with the most robust empirical evidence gives clinicians, children, and families the best chance for success.

Beyond well-established treatments, there are many psychosocial interventions with far more evidence for effectiveness than CT – many of which are classified as “possibly” or “probably” efficacious and therefore not yet well-established (Evans et al., 2018). Thus, CT is low on the list of possible treatments that are likely to work for children and adolescents who present with ADHD. Nevertheless, EndeavorRX™ received FDA clearance and many well-established treatments have not.

What does it mean that a treatment has FDA clearance?

The lack of meaningful evidence for the effectiveness of EndeavorRX™, coupled with FDA clearance, presents a paradox. It is common for providers and the public alike to mistake FDA clearance as proof that a product had been vetted for effectiveness and is endorsed for its stated use. In a recent press release regarding EndeavorRX™, Jeffrey Shuren, M.D., J.D., director of the FDA Center for Devices and Radiological Health, stated: “The FDA is committed to providing regulatory pathways that enable patients’ timely access to safe and *effective* innovative digital therapeutics” (Food and Drug Administration (FDA), 2020, *italics added*). It is understandable that professionals and the lay public are confused about what, if anything, distinguishes FDA clearance from empirical support for a treatment.

FDA clearance and designations of empirical support for treatments differ markedly in their definitions of “effective” (see Figure 1). In part, there are different goals when seeking FDA clearance versus establishing a treatment as evidence-based. FDA clearance is focused on ensuring safety before a product is marketed to the public. Although the FDA requires “clinical evidence” before clearing a device for marketing, data included in FDA premarketing applications are

insufficient for classifying a treatment as evidence-based by professional organizations such as SCCAP or AAP. Given these differences in purpose and definitions of “effective,” it is unsurprising that processes for obtaining FDA clearance and establishing a treatment as evidence-based differ.

The FDA approval process for studying and marketing medical devices is described on the FDA website (www.fda.gov) and summarized here. The first step is to register the product as a medical device. A medical device is an instrument, apparatus, machine, or other similar article that is (1) recognized in the National Formulary or U.S. Pharmacopoeia; (2) intended for use in diagnosis or treatment of a disease or other condition; or (3) intended to affect functioning without involving chemical action or metabolization (i.e., it is non-pharmacologic). Medical devices are further classified into three classes. Class I presents minimal potential for harm to the user (e.g., elastic bandages). Class II presents moderate risk of harm to the user (e.g., videogame treatments such as EndeavorRX™). Class III sustains or supports life, is implanted, or presents potential high risk of illness or injury (e.g., implantable pacemakers). Device classification depends on the *intended use* of the device, but also on *indications for use*. For example, the intended use of EndeavorRX™ is to improve attention via a digital therapy device, and indications for use include children diagnosed with ADHD.

The class to which a device is assigned determines the type of premarketing application required for FDA clearance. Class I and II devices generally require a 510(k) for marketing. This is a premarketing submission made to the FDA demonstrating that the device is safe and effective. Effectiveness is documented by proving substantial equivalence to a legally marketed device (predicate device). When no predicate device exists, the De Novo regulatory pathway for low- to moderate-risk devices of a new type can be used, as was the case for EndeavorRX™. A De Novo application needs to document (1) probable benefits of the device compared to probable or anticipated risks when the device is used as intended; (2) controls to ensure reasonable assurance of safety and effectiveness; and (3) any clinical and/or nonclinical data that are relevant to ensure reasonable assurance of

safety and effectiveness. Because devices in the De Novo pathway are low- to moderate-risk, they “*may not need to confer as substantial a benefit to patients in order to have a favorable benefit-risk profile*” (FDA, 2019, italics added). An FDA-cleared device from the De Novo pathway can then become a predicate device to which future devices are compared in the 510(k) premarket notification process. Thus, another CT product can now seek FDA clearance based on EndeavorRX™ already being cleared.

It is also important to distinguish between “approval” and “clearance.” FDA approval indicates that benefits of a device outweigh known risks for its intended use. FDA clearance indicates that a manufacturer demonstrated that their product is *substantially equivalent* to a similar, legally marketed device with existing clearance or approval. The FDA grants approval to Class III devices, not to Class I or II devices. Because Class III devices are associated with significantly higher risk, approval requires premarket approval (PMA) as opposed to 510(k), and safety and efficacy must be demonstrated through clinical evidence – a more rigorous review than for Class I or II devices. Because EndeavorRX™ is a Class II device and thus poses lower risk of use, developers simply had to demonstrate that its use provided more benefits than risks. This does *not* translate to being an “evidence-based treatment.” Therefore, given the process outlined herein, it is understandable how EndeavorRX™ received FDA clearance without evidence of meaningful clinical benefit.

Conclusions regarding evidence and FDA clearance

Despite the fact that EndeavorRX™ received FDA clearance (not FDA approval) for the treatment of children with ADHD, there is no evidence that using this game will result in any benefit in terms of their functioning and presenting problems. FDA clearance for a Class II device does not indicate or suggest that there is adequate evidence supporting its effectiveness for children with ADHD. There are many psychosocial treatments with much more evidence of effectiveness than there is for EndeavorRX™ or any other CT. Although FDA

clearance of EndeavorRX™ garnered significant media attention, clinicians (a) are in a critical position to help their clients be educated consumers and (b) have an ethical obligation to provide treatments with the best-established efficacy. *Treating children with ADHD with EndeavorRX™ or any other currently commercially available CT is not supported by science at this time.*

The role of FDA clearance and approval may need to be reconsidered in relation to non-pharmacological treatments for youth with ADHD. Many clinicians and clients are not aware of the distinction between FDA approval and FDA clearance (indeed, many of the authors of this manuscript were not previously aware of this!). As a result, when people see that the FDA has publicly stated support for a treatment (clearance or approval), many are likely to assume that the treatment is *both* safe and effective, when in reality it may only be the former. The primary study for EndeavorRX™ indicates that there is no evidence to support that parents will notice any improvement in the presenting problems of their child as a result of this treatment (Kollins et al., 2020). Thus, FDA support for this treatment could be misleading to parents and clinicians who assume that this implies effectiveness. This erodes trust in the FDA at a time where our society must depend on them to know whether they should take treatments and vaccines for COVID-19.

Helping parents understand their treatment options

Given media attention, FDA clearance, and likely marketing activity, many parents of youth with ADHD may ask clinicians to prescribe EndeavorRX™ or another CT. There is certainly appeal to these treatments as they are likely to be enjoyable and engaging to youth, require little to no time of parents, and are easy for clinicians. In fact, some investigators have argued that treatments that are “safe, easy, cheap and sensible” (SECS) do not need the same level of evidence supporting their effectiveness as other treatments (Arnold et al., 2011). But when these eye-catching options compete with well-established treatments, the risk is that consumers will make unwise decisions that are not grounded in science.

Before considering how to have this discussion with parents, clinicians need to consider whether they are willing to provide this treatment and for whom they would consider prescribing it. The limited research on EndeavorRXTM indicates that parents are not likely to see any improvement in their child's symptoms of ADHD, school functioning, peer functioning, family functioning, or executive functioning as a result of this treatment (Kollins et al., 2020). The only gains reported were on another computer task. Given this, clinicians should consider whether there are situations in which they are willing to prescribe a treatment they know is unlikely to be effective instead of prescribing other, established treatments that are far more likely to help.

Once a clinician decides how to consider EndeavorRXTM and other CTs for potential treatment of youth with ADHD, it is time to plan how to have discussions on this topic with families and other professionals (e.g., educators, referral sources, media outlets). We recommend that clinicians: (1) emphasize factual information about strengths, costs, and limitations of treatment options; (2) review specific treatment goals to determine which treatment(s) are most likely to be beneficial for the child; and (3) conduct an informal analysis of goals, barriers, and availability, leading to a decision about next steps.

A reasonable and consumer-oriented discussion of the research evidence will ensure that parents are adequately informed of their options. Clients benefit most when this discussion is presented clearly, in lay language so they understand their choices. Some families may find it valuable to learn about important elements of conducting scientific studies of treatments that were reviewed earlier in this manuscript. Using guidelines for presenting science to the public based upon methods such as those studied at the Alan Alda Center for Communicating Science at Stony Brook University (<https://www.aldacenter.org>) may be helpful. Clinicians are encouraged to avoid strident arguments against CT as these may inadvertently strengthen preexisting commitment to the intervention rather than reduce it (Ferrero et al., 2020). Furthermore, overly dismissive approaches that suggest CT is foolish may be perceived as disrespectful of not only the idea, but also the person considering the idea. As described in this paper,

there are many reasons to believe that CTs have potential. Continued development and scientific evaluation of CT to help individuals with ADHD is an active area of research and there are indications that a CTs may be developed that is effective either as a standalone treatment or as a part of effective multimodal treatments. Finally, such conversations are best accomplished using clinical skills such as active listening, effective questioning, and encouragement of contemplation (Bago et al., 2020).

In addition to discussing the relative merits of treatments, it is important to have parents clearly describe their treatment goals. Help them consider specific changes they wish to see at home, at school, and in social situations, and in what realm they wish to see change (e.g., behaviors, emotions, and/or thinking). It can also be helpful to have them describe their goals for the process of treatment. In other words, what amount of effort and stress can they accept to facilitate care? Parents and clinicians should identify and discuss logistical barriers (e.g., transportation, cost) and other realities that may interfere with or facilitate successful treatment. Once these are identified, it is important to review effective/efficacious treatments that align with their treatment goals. If a child is elementary school-age and the goal is reducing the frequency of oppositionality, hyperactivity, impulsivity, and inattention, then use of BPT to address problems at home and teacher consultation to help with problems at school (e.g., Daily Report Cards) are well established (Evans et al., 2018). If school performance including homework completion, organizational skills, and associated family conflict are primary concerns, consider school-based or school-focused treatments (Abikoff et al., 2013; Evans et al., 2016; Langberg et al., 2018; Sibley et al., 2016). In addition to psychosocial treatments, there are effective medication treatments that may improve many of these areas (Wolraich et al., 2019). A thorough discussion of the desired outcomes, patient preferences, available options, and barriers and facilitators of the treatment process is warranted before proceeding to the decision-making step.

The final step involves aligning the clients' goals with available treatments and deciding how to move forward. Most clinicians are familiar with this process when considering typical psychosocial treatments for youth with ADHD; however, consideration of CT can

complicate this process. For example, after having the discussion described above, some parents may still want to start with EndeavorRX™. They may trust the FDA clearance and distrust the clinician's description of the research, or maybe they promised their child that he would only have to play a videogame for treatment. Whatever the reason, this could put some clinicians in a position of referring a family to another provider if s/he is not comfortable providing a treatment that is unlikely to help. Other clinicians may go ahead and prescribe or offer EndeavorRX™ or other CTs for parents who choose that approach. They may assume that even if the treatment is ineffective, it is unlikely to do harm. This assumption is unfortunately inaccurate as when families spend their time, money, and hope on a service they believe will help their child and it provides no benefit, they often experience hopelessness and a disinclination to seek care in the future because they assume that they cannot be helped.












Working with parents to help them align their goals for treatment outcomes with the best available treatments is an important part of providing care. A careful discussion with families can be used to weigh these factors and various treatment options. Similar discussions will be needed when talking with providers (e.g., pediatricians, psychologists), educators, and interest groups such as Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD) because the attention around FDA approval for EndeavorRX™ has created considerable interest and excitement. Furthermore, practitioners and researchers may be asked to weigh-in on use of CT by referral sources, colleagues, media, and the public, so clinicians need to be well-informed, confident in his or her personal decisions regarding provision of this treatment, and able to express this information clearly and objectively to a variety of audiences.

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Andrea Chronis-Tuscano discloses that she gets royalties for a book "Supporting Caregivers of Children with ADHD" with Oxford University Press and Richard Gallagher discloses that he receives book royalties from Guilford Press and royalties from Multihealth Systems for the measure Children's Organizational Skills Scale. Eric Youngstrom discloses that he is the Executive Director of Helping Give Away Psychological Science and received royalties from the American Psychological Association. Michael Kofler reports

that his university submitted a non-provisional patent application for a neurocognitive interventions that he developed.

ORCID

Steven W. Evans  <http://orcid.org/0000-0002-7283-2274>
 Theodore P. Beauchaine  <http://orcid.org/0000-0002-0938-945X>
 Andrea Chronis-Tuscano  <http://orcid.org/0000-0001-9173-0073>
 Stephen P. Becker  <http://orcid.org/0000-0001-9046-5183>
 Anil Chacko  <http://orcid.org/0000-0002-3275-4726>
 Richard Gallagher  <http://orcid.org/0000-0002-6612-3463>
 Cynthia M. Hartung  <http://orcid.org/0000-0003-2210-8373>
 Michael J. Kofler  <http://orcid.org/0000-0002-8604-3647>
 Brandon K. Schultz  <http://orcid.org/0000-0001-9130-6723>
 Leanne Tamm  <http://orcid.org/0000-0001-6066-1669>
 Eric A. Youngstrom  <http://orcid.org/0000-0003-2251-6860>

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