Journal of Attention Disorders

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What is This?

Evolution of the Study of Methylphenidate and Its Actions on the Adult Versus Juvenile Brain

Kimberly R. Urban[1] and Wen-Jun Gao[1]

Abstract

Objective: Methylphenidate (MPH) is the most often prescribed medication for treatment of ADHD. However, many of its specific cellular and molecular mechanisms of action, as well as developmental consequences of treatment, are largely unknown. This review provides an overview of current understanding of MPH efficacy, safety, and dosage in adult and pediatric ADHD patients, as well as adult animal studies and pioneering studies in juvenile animals treated with MPH. **Method:** A thorough review of the current literature on MPH efficacy and safety in children, adults, and animal models was included. Results of studies were compared and contrasted. **Results:** While MPH is currently considered safe, there is a lack of knowledge of potential developmental consequences of early treatment, as well as differences in drug actions in the developing versus mature brain system. **Conclusion:** This review emphasizes the need for further research into the age-dependent activities and potency of MPH, and a need for tighter control and clinical relevance in future studies. *(J. of Att. Dis. 2012; XX(X) 1-XX)*

Keywords

psychostimulant, juvenile, ADHD, prefrontal cortex, methylphenidate

Introduction

ADHD is a commonly diagnosed pediatric behavioral disorder, with current estimates ranging from 3% to 5% of the population globally (Nair, Ehimare, Beitman, Nair, & Lavin, 2006). Symptoms, which can persist well into adulthood, include inattentiveness, hyperactivity, and impulsivity, often existing in a comorbid state with other behavioral disorders or mood disorders such as depression and/or anxiety (Bauermeister et al., 2007; Hazell, 2010; Hofvander, Ossowski, Lundstrom, & Anckarsater, 2009). If left untreated, effects can be devastating, affecting the ability of the affected individual to function in a classroom or job setting, and to establish and maintain social relationships (Barkley, Fischer, Smallish, & Fletcher, 2004; Castellanos & Tannock, 2002; Solanto, 1998; J. M. Swanson et al., 2007). It is thought that ADHD results from a deficit in the neurotransmitters dopamine and norepinephrine, and that symptoms arise from a specific prefrontal cortical hypoactivity of these neurotransmitter circuits (Arnsten, 2006; Ohno, 2003; Russell, 2003). ADHD is currently treated with a variety of pharmacological and behavioral therapies, but it is generally accepted that psychostimulants provide the most efficacious line of treatment (Wigal, 2009). Of this class of drugs, methylphenidate (MPH, Ritalin ©) is the most widely prescribed and researched example (Challman & Lipsky,

2000). MPH was approved for the treatment of ADHD in the 1960s and has exploded in usage over the last two decades (Bogle & Smith, 2009; Safer, Zito, & Fine, 1996). It has been used not only as a treatment for ADHD but also for narcolepsy, substance dependence, and cognitive enhancement in healthy individuals (Agay, Yechiam, Carmel, & Levkovitz, 2010; Cakic, 2009; Elkashef et al., 2008; Franke et al., 2011; Goodman, 2010; Gorelick, Gardner, & Xi, 2004; Grabowski et al., 1997; Karila et al., 2008; Outram, 2010). Functionally, MPH blocks the activity of the dopamine and norepinephrine transporters (NETs), raising the levels of these neurotransmitters in the brain (Berridge et al., 2006; Kuczenski & Segal, 2001, 2002, 2005). Much of the current literature focuses on animal research studies using wide ranges of doses (often far beyond what could be considered clinically relevant), varying brain regions of focus, and behavioral or molecular studies in adult animals. Clinically, MPH is prescribed largely to children and adolescents; therefore, the recent trend is for research involving

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young children and juvenile animals. However, the dosages of MPH used in these studies are highly variable, and recent evidence suggests that the juvenile brain may have a differential sensitivity to MPH compared with the adult brain, highlighting the need for age-dependent dose–response curves and a deeper understanding of the potential developmental ramifications of early life psychostimulant treatment. This review focuses on collecting and organizing the large body of research on clinical usage of MPH in human children, an overview of the adult animal studies, and recent findings in juvenile animals. Its goals are to (a) highlight the disparities within the animal studies in experimental designs and dose paradigms, (b) describe the developmental changes of the prefrontal cortex (PFC) and the rationale for differential studies in juvenile animals, and to (c) present a case for the importance of further examination of the effects of MPH treatment in juveniles and the development of an applicable, relevant dose–response curve.

MPH Efficacy in Human Children

MPH has been prescribed for the treatment of ADHD since the 1960s and is known to exert its therapeutic effects via a blockade of dopamine and NETs in the brain, particularly in the PFC, the main region of deficit in ADHD patients (Arnsten, 2006, 2009; Arnsten & Dudley, 2005; Berridge et al., 2006; Kuczenski & Segal, 2001, 2002, 2005). MPH is effective and well tolerated in human adults, with few reported side effects in clinically relevant doses (Buitelaar et al., 2011). Although ADHD affects children and adults, this review will focus on studies of human children and compare the large body of knowledge on efficacy in human children with the relative scarcity of research in juvenile animal models.

Immediate-release MPH formulations are given at doses in the range of 5 to 30 mg, twice daily, for up to 60 mg per day (Kidd, 2000). Extended or controlled-release formulations are given at 10 to 40 mg once daily, whereas oral MPH is recommended at 18 to 54 mg once daily (Anderson & Keating, 2006; Kowalik, Minami, & Silva, 2006). Finally, a transdermal patch formulation of MPH provides 10 to 30 mg over a 9-hr period (Anderson & Scott, 2006). The ideal dose can vary largely between individuals; thus, most patients are started at the lowest clinical dose and titrated upward until symptoms are resolved. In addition, weaning off periods are often implemented to assess symptom resolution and limit the development of negative side effects (Kidd, 2000). MPH is given orally, and is absorbed rapidly, reaching peak blood plasma levels in 1 to 3 hrs, at which point peak behavioral modification is also noted (Dollery, 1991; J. M. Swanson et al., 1998). The drug is also rapidly metabolized and excreted, with a short half-life of approximately 2 to 3 hr (a range of 1-5 hr) in children and 3 to 4 hr in adults (Kimko, Cross, & Abernethy, 1999).

MPH is largely efficacious in relieving the symptoms of ADHD, particularly locomotor hyperactivity (Group, 2004; MTA Cooperative Group, 1999). However, how MPH affects cognition is less clear and depends on the task used to assess treatment (Swanson, Baler, & Volkow, 2011). In fact, few children with ADHD will show deficits in all tasks, and MPH treatment will not elicit improvements in all children (Britton, 2012; Swanson et al., 2011). Nevertheless, MPH treatment seems to provide consistent improvement in tasks that lack a major executive-function component such as complex reaction time, delayed matching-to-sample, and spatial recognition reaction time. In contrast, a significant effect of treatment is often lacking when tasks involving executive functions such as response inhibition, working memory, strategy, planning, and set-shifting are used (Rhodes, Coghill, & Matthews, 2006). Further muddying the results is that many of the complex executive-function tasks contain nonexecutive-function components, on which improvement is noted. Thus, one must be very careful to separate the components of the tasks to understand the true nature of MPH actions. For example, MPH is effective at improving performance on simple reaction time, task-switching paradigms, focused attention, word-matching, and go/no-go tasks in children with diagnosis of ADHD, given a mean dose of 12 to 15 mg MPH (Cepeda, Cepeda, & Kramer, 2000; de Sonneville, Njiokiktjien, & Bos, 1994; Kramer, Cepeda, & Cepeda, 2001; Malone & Swanson, 1993; Scheres et al., 2003; Tannock, Martinussen, & Frijters, 2000). However, MPH treatment did not improve spatial working memory (SWM) or pattern recognition or divided attention tasks (Konrad, Gunther, Hanisch, & Herpertz-Dahlmann, 2004; Mehta, Goodyer, & Sahakian, 2004; Trommer, Hoeppner, & Zecker, 1991). Interestingly, improvements noted on seemingly executive-function tasks such as sustained and focused attention can be attributed to a simple reduction in reaction time variability following stimulant treatment, rather than an increase in attention or focus (Malone & Swanson, 1993; Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005; Spencer et al., 2009; Tannock et al., 2000). For more detail on cognitive effects of MPH, see the review by J. Swanson et al. (2011).

Despite the apparent efficacy of stimulant treatment in the above-referenced large-scale studies, researchers must examine the MPH dosages used in published studies with care. These studies all examined a flat dosage—not titrated by weight. To put in perspective, for a 23-kg (50 lb) child, a 5-mg dose is equivalent to 0.2 mg/kg, a 15-mg dose is 0.65 mg/kg, and a 30-mg dose is 1.3 mg/kg. However, for a 50-kg (110 lb) teenager, those same doses become equivalent to 0.1, 0.3, and 0.6 mg/kg, respectively—a much lower per kg dosage than the younger child would be receiving. For example, in a study by Mehta et al. (2004), 0.5 mg/kg MPH in humans resulted in improved performance on the SWM and Tower of London (spatial logic) paradigms, and the attentional set-shifting task, but did not improve pattern

or spatial memory tasks. In another study, 0.3 and 0.6 mg/ kg MPH did not improve performance on a visual orienting task (Nigg, Swanson, & Hinshaw, 1997). However, when a much wider dose range was examined, 0.5 mg/kg up to a maximum of 30 mg, improvement was noted on visually guided saccade tasks (O'Driscoll et al., 2005). Lower doses of 0.15 and 0.3 or 0.25 and 0.5 mg/kg improved performance on sustained and focused attention tasks, and stop-signal reaction time tasks, but not on divided attention tasks in children (Konrad et al., 2004; Trommer et al., 1991). These studies are early attempts to not only examine the individual variation in response success as a function of weight but also raise the importance of task specificity. Tasks requiring quick visual motor responses appear much less sensitive to the effects of MPH than tasks requiring sustained focus, self-inhibition, or logical puzzle-solving. One theory is that the task-dependent nature of MPH effects may be a result of stimulant-induced increases in stereotypic behaviors; this would improve performance in tasks where perseverance (sustained attention) and reaction time (repetitive action) are required, but impair performance on tasks where cognitive flexibility (reversal of strategy) are instead required. Pietrzak, Mollica, Maruff, and Snyder (2006) provided a very thorough meta-analysis of controlled studies of MPH on various tasks and revealed that although higher doses of MPH improved performance on certain aspects such as attention, vigilance, and working memory, no additional improvements were seen in other tasks involving planning, cognitive flexibility, inhibitory control, naming, and reaction time over the effective lower doses. A take-home message from these dose–response and task-specific studies is that the optimal dose for cognitive improvement is lower than the optimal dose for eliciting behavioral effects of MPH (reduced locomotor activity, improved response inhibition); thus, no further cognitive improvement is noted at higher doses (Coghill, Rhodes, & Matthews, 2007; Sprague & Sleator, 1977; J. Swanson et al., 2011).

MPH in Healthy Individuals

A large proportion of the literature on mechanisms of action of MPH and dose–response curves comes from studies performed on normal human subjects. At first thought, this may seem a weakness—How could studying the actions of a drug on a normal population represent its effects on a diseased subset? However, as early as 1978, studies were emerging suggesting that reduced hyperactivity and impulsivity in stimulant-treated ADHD patients were not "paradoxical" effects but in fact also occurred in healthy individuals given the same doses (J. B. Rapoport, Zahn, Weingartner, Ludlow, & Mikkelsen, 1978). This fact, along with the lack of an accepted reliable animal model of the ADHD disease state, led to the acceptance of stimulant study in healthy humans (and normal animals; see Sections "Adult Animal Studies of

MPH" and "Juvenile and Adolescent Animal Studies"). Studying MPH effects in healthy individuals can provide valuable insight into the drug's mechanisms of action and therapeutic mechanisms as well as potentially highlight differences between ADHD-diseased and healthy brains. Higher doses (doses greater than those given to treat ADHD) increase locomotor activity and impair attention and performance on PFC-dependent cognitive tasks; however, lower doses (those within the therapeutically effective range) improve cognitive performance and reduce locomotor activity in healthy individuals (Arnsten & Dudley, 2005; Mehta, Sahakian, & Robbins, 2001; J. L. Rapoport et al., 1980). For example, MPH improved response inhibition in normal children on the go/no-go task and improved response inhibition, task set-shifting, vigilance, and working memory in healthy humans (Kratz et al., 2009; Mehta et al., 2000; Santosh & Taylor, 2000; Studer et al., 2010; Vaidya et al., 1998). Functional magnetic resonance imaging scanning has revealed that lower doses of MPH, that is, those within the range prescribed clinically, appear to selectively activate frontal brain regions while deactivating striatal regions in healthy adults and children. However, the drugs activate frontal and striatal regions in those individuals afflicted with ADHD, suggesting a deficit in frontostriatal connectivity or circuitry in ADHD (Mehta et al., 2000; Vaidya et al., 1998). The prefrontal hypofunction theory has been supported by many studies examining blood flow and brain volume in patients diagnosed with ADHD as compared with healthy controls, and revealed specific deficits in frontostriatal regions and reduced dopamine release (Curatolo, Paloscia, D'Agati, Moavero, & Pasini, 2009; Dickstein, Bannon, Castellanos, & Milham, 2006; Nikolaus, Antke, & Muller, 2009; Rubia et al., 2010).

The discovery that MPH can benefit cognitive performance in healthy individuals and those with cognitive deficit sparked a large body of research into the drug's applicability as a cognitive enhancer. MPH is frequently sold "black market" at schools and universities and has been used and/or abused by graduate and medical students, military personnel, doctors, and lawyers—Any high-stress position where cognitive ability is highly valued comes with a risk for stimulant abuse (Banjo, Nadler, & Reiner, 2010; Butcher, 2003; Franke et al., 2011; Goodman, 2010). This frequent off-label usage stresses the need for a deeper understanding of its actions and effects on the brain (Banjo et al., 2010).

MPH Side Effects in Humans

MPH is largely considered a "safe" treatment for ADHD, as long as dosage and efficacy are tightly monitored. However, there can be significant side effects. The Food and Drug Administration (FDA) reports the following common side effects: nervousness, insomnia, loss of appetite and weight,

nausea, dizziness, tachycardia, and heart palpitations (Buchhorn et al., 2012; Davis et al., 2012; Huang, Tsai, & Guilleminault, 2011; Lu, Kuang, & Chou, 2006; Stiefel & Besag, 2010). Other less common but serious side effects include retardation of growth rate in young children, seizures, and blurred vision. Psychiatric changes including paranoia, depression, and hallucinations have also been reported in rare cases (Charach, Figueroa, Chen, Ickowicz, & Schachar, 2006; FDA, 2007; National Institutes of Health, 2007; Schertz & Steinberg, 2008; Spensley & Rockwell, 1972; Tavakoli & Gleason, 2003). In some cases, deaths have been reported from cardiac arrest (McCarthy, Cranswick, Potts, Taylor, & Wong, 2009; Schelleman et al., 2011). These incidences of sudden death have been reported in children with no preexisting cardiac problems and are far more common in children taking stimulants than in adults (Gould et al., 2009; Kuehn, 2009). Therefore, evidence points to a potential differential effect of MPH, or at least heightened occurrence of MPH-mediated side effects, in children and adolescents versus adults. As with any pharmaceutical intervention, care must be taken to weigh the risks against the potential benefit of successful treatment, and in many cases, it is deemed that benefit will outweigh the risk. However, when one reviews the existing research literature, it becomes apparent that the medical and scientific communities know far less about the mechanisms of this drug than is largely believed.

Adult Animal Studies of MPH

MPH therapeutic effects and mechanisms of action have been examined for decades in animal models. One of the most common animal models of psychostimulant research is the rat. Rats, although primitive compared with humans and other primates, possess all the major neurotransmitter systems and pathways that humans do and possess a PFC with prelimbic and infralimbic regions. A PubMed search reveals the earliest article on MPH in the rat to be a 1963 study using operant conditioning to distinguish between effects and drug response to caffeine, MPH, and methamphetamine. Under fixed-interval testing, animals were far more sensitive to MPH and methamphetamine than to caffeine, and higher doses of those two stimulants also abolished temporal sensitivity, leading to indiscriminate fast responding. However, methamphetamine was more sensitive to a fixed-number test than caffeine or MPH. All drugs resulted in animals showing impulsive responding, and this increased with drug dosage (Mechner & Latranyi, 1963). MPH was also found to increase avoidance responding in adult rats, with increased correct responses at lower doses and impulsive responding following higher doses (Gauron & Rowley, 1975; Stretch & Skinner, 1967). These early studies reveal the inverted U-curve dose–response to MPH as well as its selective behavioral effects.

Another area of behavioral research historically focused on in MPH studies is locomotor activity, as the primary symptom of hyperactivity is increased "fidgeting" and the inability to remain still when required to. Psychostimulants produce an inverted-U dose–response curve of locomotor activity in animals and humans, such that low doses decrease, but high doses increase, spontaneous locomotor activity. Most studies have noted that a single acute dosing of MPH results in moderate, dose-dependent increase in locomotor activity (doses greater than 2.5 mg/kg, intraperitoneal [i.p.] or subcutaneous [s.c.]), whereas doses of 1 mg/kg and lower had no effect (Askenasy, Taber, Yang, & Dafny, 2007; Berridge & Robinson, 1995; Crawford, McDougall, Meier, Collins, & Watson, 1998; Eckermann et al., 2001; Gaytan, al-Rahim, Swann, & Dafny, 1997; Gaytan, Ghelani, Martin, Swann, & Dafny, 1996, 1997; Gaytan, Yang, Swann, & Dafny, 2000; McNamara, Davidson, & Schenk, 1993; Segal & Kuczenski, 1999; Shuster, Hudson, Anton, & Righi, 1982). With doses greater than 10 mg/kg, stereotypic behaviors begin to outweigh locomotor activity (Gaytan, al-Rahim, et al., 1997; Kuczenski & Segal, 2001, 2005). In addition, MPH appears to have a significant effect on social behavior and interaction in the rat, a normally social animal. Doses exceeding 1.0 mg/kg (i.p.) caused rats to avoid each other in an open-field locomotor test, despite increased overall locomotor activity (Arakawa, 1994). MPH also decreased social investigation of novel rats only in females, while increasing overall locomotor activity in both sexes. This demonstrates that there may be a sex-specific effect of MPH on socialization behaviors (Thor & Holloway, 1986). Furthermore, there appears to be a circadian-dependent effect as well; both baseline locomotor activity and stereotypic behaviors were found to occur at a naturally greater rate during the dark period than the light period; therefore, drug-induced effects would be more clearly distinguishable from baseline during light periods (Gaytan, al-Rahim, et al., 1997; Gaytan et al., 1996; Gaytan et al., 2000; Gaytan, Ghelani, et al., 1997). Sensitization to locomotor-activating doses is not seen when MPH is administered during the dark cycle (Askenasy et al., 2007). This may be due to a ceiling effect, as the dark cycle is the normal period of activity for nocturnal rodents such as rats. These studies emphasize the importance of considering circadian phase-specific responses when administering psychostimulants and call into question rat studies that do not address the nocturnal nature of rat models.

Due to the controversy of the clinical relevance of injected MPH (the drug is taken orally by humans), researchers have recently returned to experimenting with orally administered MPH in the rat. MPH is given in a sucrose or water suspension for rats. The animals must drink the liquid containing the drug; therefore, there are inherent problems with this method. Rats must be water deprived to induce motivation to drink or the drug must be injected via a gavage syringe

into the throat, and the exact amount of drug ingested can prove more challenging to monitor. These procedures would cause additional confounding effects such as hunger, stress, or pain. Furthermore, the ingested MPH is subject to the harsh digestive enzymes and acidic environment of the gastrointestinal tract and less is absorbed into the bloodstream, requiring a higher initial dose. Gerasimov et al. (2000) demonstrated the differing absorption rates between i.p. and oral MPH on rat nucleus accumbens dopamine levels as well as on locomotor activity. MPH (i.p.) at doses of 5 and 10 mg/kg resulted in approximately twofold higher dopamine levels as well as locomotor activity; a comparatively low dose of 2 mg/kg i.p. injection also resulted in locomotor activation, whereas oral administration of 2 mg/kg did not (Gerasimov et al., 2000).

MPH has been found to affect neuronal activity in the ventral tegmental area (VTA), locus coeruleus, as well as PFC, in a dose-dependent manner. Therapeutically relevant doses of MPH (0.25, 0.5, or 1 mg/kg i.p., or 2 or 4 mg/kg oral) resulted in a decrease of the signal-to-noise ratio of the excitatory phasic discharge while increasing the signal-to-noise ratio during inhibitory phasic discharge (Devilbiss & Berridge, 2006). Therefore, the locomotor calming and cognitive-enhancing aspects of the drug are likely due to the combination of locus coeruleus modulation along with increased catecholamine release and uptake to the PFC. Indeed, the increased catecholamine levels appear to exert their cognitive-enhancing effects via a combination of adrenergic alpha-2 and dopaminergic D1 receptor actions (Arnsten & Dudley, 2005).

Several other oral MPH studies delve deeper into the potential ramification of systemic effects of MPH usage. It was found that at doses of 5, 10, and 20 mg/kg oral, MPH induced corneal cell degenerations and abnormalities (Gozil et al., 2008). These changes indicate that MPH usage within the therapeutic range and above may cause ocular damage and impair vision; therefore, it is important to keep treatment to the minimum effective dose. MPH was also found to induce destruction of cardiac tissue; again, the doses of 5, 10, and 20 mg/kg oral solution were examined (Take et al., 2008). For a summary of adult rat studies, refer to Table 1.

Juvenile and Adolescent Animal Studies

The studies conducted in adult animals have provided novel insights into the mechanistic actions and potential side effects of MPH. However, because MPH is mostly used to treat children with ADHD and the periadolescent period is a period of great vulnerability to stress/experience-induced PFC dysfunctions, it is particularly important to investigate the drug's effects on juvenile and adolescent animals (rats < postnatal day (PD) 40, before pubertal development has begun). It is not hard to imagine that the adult brain may react differently to MPH treatment than would a juvenile, still developing brain. This late prefrontal cortical development is of particular relevance to the development of ADHD; levels of norepinephrine and dopamine peak in the locus coeruleus at PD 7 and decline through PDs 21, 35, and beyond in pigs, and likely follow a similar pattern in rats and human children at equivalent developmental milestones (Kanitz et al., 2011). This development and remodeling of the neurotransmitter systems implicated in ADHD reveals a period of vulnerability during which insults to the system could change the developmental course and cause lasting alterations in the neurotransmitter levels. Due to this developing system, it is likely that MPH may have differential or heightened effects on a juvenile or adolescent brain as compared with an adult brain.

In fact, a small, recently emerging body of research has begun to demonstrate the differential actions of MPH on juvenile versus adult animals, as summarized in Table 2.

Juvenile animal studies thus far seem largely to have concentrated on a dosage of around 2 mg/kg i.p, and these studies have produced often conflicting results. Brandon, Marinelli, Baker, and White (2001) found that 2 mg/kg i.p. MPH, given for 7 days at PD14, enhanced the rewarding effects of young adult (PD56) cocaine administration while not inducing locomotor sensitization. However, several other studies found that 2 mg/kg MPH, given daily (i.p.) for 14 days, attenuated the self-administration and rewarding effects of cocaine (Andersen, Arvanitogiannis, Pliakas, LeBlanc, & Carlezon, 2002; Bolanos, Barrot, Berton, Wallace-Black, & Nestler, 2003; Carlezon, Mague, & Andersen, 2003). In fact, Bolanos' study found that juvenile MPH administration reduced the rats' responsiveness not only to cocaine but also to other natural rewards such as sucrose, sex, and novelty-induced activity, and these effects lasted well into adulthood (Bolanos et al., 2003). Crawford et al. (2010) found that juvenile (PD11-PD20) treatment with MPH resulted in increased cocaine self-administration during adulthood but did not alter conditioned place-preference. This suggests that it is specifically the rewarding value of the drug that is enhanced, whereas the drug-associated cue value is not altered. Yet another study found that 2.5 mg/kg i.p. for 7 days resulted in cross-sensitization to amphetamine in regard to locomotor activation (Yang, Swann, & Dafny, 2003). The 2 mg/kg i.p. dose in juvenile rats has also been associated with an increase in anxiety-related behaviors. Given daily for 16 days to adolescents, it was found to increase anxiety-related behaviors in the open-field test and ethanol self-administration persevering into adulthood (Vendruscolo, Izidio, Takahashi, & Ramos, 2008). Although these studies provide somewhat conflicting information on MPH effects on drug usage, some of these discrepancies can be explained by considering that assessment of drug-seeking behaviors was performed at different circadian time points, varying paradigms were used for assessment, and the range of MPH doses was different across these studies.

Table 1. MPH Effects on Adults

Reference	Species/strain	Age at dosing	Age at testing	Dosing	Treatment effect
Arnsten and Dudley (2005)	Male SD rats	Young adult, 240-260 g	Same	1-3 mg/kg, oral, dissolved on cracker, acute single dose	1-2 mg/kg improved delayed alternation performance, whereas 2-3 mg/kg caused perseveration and errors. Enhancing effects of low-dose MPH blocked by α2 and D1 receptor blockers
Arakawa (1994)	Male Wistar rats	8 weeks old	Same	0.008, 0.04, 0.2, 1, or 5 mg/kg i.p., acute single dose	High-dose MPH increased overall movement but decreased social exploration and interaction. Fleeing distance increased, but chasing distance decreased
Berridge et al. (2006)	Male SD rats	Adult, 290-370 g	Same	0.25-1 mg/kg i.p.; 2 mg/kg oral, acute	These low doses of MPH increase NE and DA efflux within PFC without significantly affecting levels in other cortical regions
Devilbiss and Berridge (2006)	Male SD rats	Adult, 300-450 g	Same	0.25-1 mg/kg i.p., 2 or 4 mg/kg oral, single dose	MPH enhanced inhibitory phasic discharge, while inhibiting the excitatory phasic discharge, comparable between oral and i.p.
Eckermann et al. (2001)	Male SD rats	Adult, 180-190 g	2 weeks later	2.5 mg/kg i.p., Day 2, Day 4-9, Day 14 or Day 15	Valproate (50 mg/kg) blocked behavioral sensitization to repeated and challenge dose MPH, indicating GABA involvement in drug actions
Gaytan, al-Rahim, Swann, and Dafny (1997)	Male SD rats	Adult	2 weeks later	0.6, 2.5, or 10 mg/kg s.c., then 5 days; 2.5 mg/kg, challenge, after 5 days	Augmented response to challenged doses was only observed in lower doses—0.6 and 2.5 mg/kg. Tolerance to 10 m/kg apparent. Forward ambulation more sensitized than rearing
Gaytan, Ghelani, Martin, Swann, and Dafny (1997)	Male SD rats	Adults	Same	0.6, 2.5, 10, or 40 mg/kg s.c., single dose	10 mg/kg had greatest increase in locomotor activity, whereas 40 mg/kg caused stereotypic behavior. Smaller stereotypic effect during dark than light phase of light cycle, no difference in locomotor activity
Gaytan, Yang, Swann, and Dafny (2000)	Male SD rats	Adult	2 weeks later	0.6, 2.5, or 10 mg/kg s.c., then 5 days; 2.5 mg/kg, challenge after 5 days	Sensitization more robust during light phase, but nocturnal forward ambulance increase persisted after drug cessation. Dose-dependent and time-of-day-dependent sensitization.
Gauron and Rowley (1975)	Male albino rats	P47 and P87	P65 and P105	0.5, 1.5, or 4.5 mg/kg s.c. for 18 days	No difference in avoidance learning acquisition, but MPH-treated groups made more correct responses. Those started on MPH at PD 87 showed more correct responses than those started at P47
Gerasimov et al. (2000)	Male SD rats	Adult, 200-300 g	Same	2, 5, or 10 mg/kg i.p.; 2, 5, or 10 mg/kg oral gavage	2 mg/kg i.p. and 5 mg/kg oral increase locomotion and DA levels, drug effects are due to central neurotransmitter bioavailability. The i.p. route gave levels twice as high as the oral route, greater bioavailability
Kuczenski and Segal (2001)	Male SD rats	Adult, 325-350 g	15 days later	0.5-1 mg/kg i.p., twice daily for 11 days; 2.5 mg/kg, 4 days later	Treatment with even lowest doses resulted in augmented response to later challenge dose, indicating that behavioral sensitization occurs to low-dose MPH treatment

(continued)

Table 1. (continued)

Reference	Species/strain	Age at dosing	Age at testing	Dosing	Treatment effect
McNamara, Davidson, and Schenk (1993)	Male SD rats	Adult, 300-400 g	1 week later	5, 10, or 20 mg/kg i.p. for 7 days	Drug-induced locomotor increased, became smaller over subsequent days, 1 or 5 mg/kg failed to produce tolerance even after 7 days
Mechner and Latranyi (1963)	Male albino rats	Adult	15 weeks later	6, 12, 24, or 48 mg/kg oral, 15 weeks	MPH had a caffeine-like effect under fixed-number testing but a methamphetamine-like effect under fixed interval
Stretch and Skinner (1967)	Male hooded rats	PD 90-PD 95	6 months later	2, 4, 8, or 16 mg/kg i.p., acute with 3-4 days between doses	4 and 8 mg/kg increased avoidance responding closer to impending shock than signal onset; stimulants may increase responding when response rats are low but shocks are few, and suppress responding when response rate is high but accompanied by frequent shock
Sproson, Chantrey, Hollis, Marsden, and Fonel (2001)	Male hooded Listar rats	Adult, 190-230 g	Same	4 mg/kg i.p., twice daily for 4 days	No effect on subsequent social interaction

Note: SD = Sprague-Dawley; MPH = methylphenidate; D1 = dopamine D1 receptor; i.p. = intraperitoneal; NE = norepinephrine; DA = dopamine; PFC = prefrontal cortex; GABA = gamma-aminobutyric acid; PD = postnatal day; SC/s.c. = subcutaneous.

Behavioral sensitization to MPH has also been noted in rats treated with MPH as juveniles. Rats that were given a week of 0.6, 2.5, or 10 mg/kg i.p. MPH, allowed 3 days of washout, and then challenged with another dose at the concentration previously given showed stronger behavioral sensitization and locomotor activity when they had previously been given MPH as juveniles (Yang, Swann, & Dafny, 2010). In contrast, juvenile treatment did not change baseline locomotor activity or behavior and the differences were notable only following a challenge dose (Yang et al., 2010). In addition, individual genetics (strains or species in animal models) seem to play a role in the MPH actions as well. When the same treatment protocol was applied to three different strains of juvenile rats—Sprague-Dawley (SD), Wistar/Kyoto (WKY), and spontaneously hypertensive (SHR), it was noted that although all three groups exhibited comparable baseline activity, the SHR rats were significantly less sensitize to the locomotor-activating effects of MPH than the WKY strains (Yang, Swann, & Dafny, 2006). Effects of higher doses on behavioral and adaptational measures have also been examined. Previous studies indicated that 4 mg/kg MPH (i.p.) for 4 days had no lasting effect on social interaction, whereas 10 mg/kg for 3 weeks resulted in cross-sensitization of stress and dopamine-related responses in the PFC and nucleus accumbens (Jezierski, Zehle, Bock, Braun, & Gruss, 2007; Sproson, Chantrey, Hollis, Marsden, & Fonel, 2001).

Other studies support this notion that although early treatment may not induce lasting overt behavioral changes, it can indeed alter susceptibility to stress and resulting oxidative damage well into adulthood, both in the PFC, striatum, and hippocampus—brain areas notably altered in human patients diagnosed with ADHD and other psychological disorders (Martins et al., 2006; Torres-Reveron et al., 2009). Yet another potentially negative effect of juvenile MPH treatment that has been noted is a dose-dependent disruption of diurnal behavior and circadian rhythms. When 0.6, 2.5, or 10 mg/kg i.p. was given to 40-day-old female rats for 11 days, a long-term increase of diurnal locomotor activity was noted at 2.5 and 10 mg/kg doses (Lee et al., 2009). These effects were also seen in adolescent (PD 40) male rats, but in this study, only the 10 mg/kg dose elicited significant effects (Algahim, Yang, Burau, Swann, & Dafny, 2010).

Oral administration (the most clinically analogous route of administration) of MPH to juvenile rats has also demonstrated dose dependency and therapeutic benefits as well as potential risks and damage. Doses of 0.75 to 3 mg/kg oral in adolescent rats (P40) were found to decrease locomotor activity, increase hippocampal norepinephrine but not nucleus accumbens dopamine release, and prevent cross-sensitization to other stimulants (Kuczenski & Segal, 2002). In younger rats (P25-P39), doses of 0.4 to 2 mg/kg were found to have a minimal effect on VTA dopamine activity,

Table 2. MPH Effects on Juveniles and Adolescents

Reference	Species/strain	Age at dosing	Age at testing	Dosing	Treatment effect
Adriani et al. (2006)	Wistar rats	PD 30-PD 46	Adult, >PD 60	2 mg/kg i.p. for 14 days	Improved efficiency in choice tasks, heightened sensitization to cocaine, genes upregulated for Kainate 2 receptor, 5-HT7R, and α1b adrenergic receptor
Algahim, Yang, Burau, Swann, and Dafny (2010)	Spraque-Dawley rats	PD 40	PD 51	0.6, 2.5, or 10.0 mg/kg i.p. for 11 days	Only 10 mg/kg dose elicited changes in diurnal activity measured as increased locomotion in open-field assay
Andersen, Arvanitogiannis, Pliakas, LeBlanc, and Carlezon (2002)	SD rats	PD 20	PD 35	2 mg/kg i.p., for 14 days	Attenuated reward to subsequent cocaine administration
Andersen, Napierata, Brenhouse, and Sonntag (2008)	SD rats	PD 20	PD 35	2 mg/kg i.p., twice daily for 2 weeks	Modulates reward-related behaviors and cerebral blood flow by decreasing D3 receptors
Bolanos, Barrot, Berton, Wallace-Black, and Nestler (2003)	SD rats	PD 20	PD 36	2 mg/kg i.p., for 16 days	Attenuated reward to subsequent cocaine, enhanced stress responsivity/reactivity
Brandon, Marinelli, Baker, and White (2001)	Male SD rats	PD 28	PD 35	2 mg/kg i.p., for 7 days, 5 or 10 mg/g i.p., for 5 or 7 days	5-10 mg/kg MPH enhanced psychomotor responses to cocaine, but 2 mg/kg dose only increased cocaine self-administration; MPH increased value of low-level enforcers
Brandon, Marinelli, and White (2003)	Male SD rats	PD 28	PD 35	2, 5, or 10 mg/kg i.p., for 5 or 7 days	Minimal effect on VTA DA neuronal activity, altered VTA DA neuronal activity, no change in autoreceptor sensitivity
Brandon and Steiner (2003)	Male SD rats	PD 28	PD 35	2, 5, or 10 mg/kg i.p., acute. 10 mg/kg i.p., for 7 days	Induction of c-fos and zif268 at doses > 2 mg/kg in striatum
Britton and Bethancourt (2009)	Male Wistar rats	PD 27	PD 55 or PD 76	2, 3, or 5 mg/kg, oral, for 4 or 7 weeks	Little or no enduring effects on anxiety-related behaviors
Carlezon, Mague, and Andersen (2003)	SD rats	PD 20	PD 35	2 mg/kg i.p., for 14 days	Attenuated reward to subsequent cocaine administration
Chase, Carrey, Brown, and Wilkinson (2005b)	Male SD rats	PD 38, PD 25	PD 38 or PD 39	1 to 5 mg/kg s.c., single dose or 1, 2, or 10 mg/kg s.c., for 14 days	Attenuated c-fos induction with >2 mg/kg pretreatment
Dow-Edwards, Weedon, and Hellmann (2008)	SD rats	PD 22	PD 59	1 or 3 mg/kg, oral, from PD 22-PD 59	3 mg/kg improved performance on the radial arm maze and increased locomotor activity and error number
Gozil et al. (2008)	Female Wistar rats	Prepubertal	Same	5, 10, or 20 mg/kg oral, single dose	Dose-dependent degeneration of epithelial cornea cells, including apoptotic markers and crystolysis
Gray et al. (2007)	Male SD rats	PD 7	PD 35	5 mg/kg i.p., twice daily for 4 weeks	55% increase in TH, 60% more Nissl-stained cell, and 40% decrease in NET in PFC. Changes also found in hippocampus and striatum

(continued)

Table 2. (continued)

Reference	Species/strain	Age at dosing	Age at testing	Dosing	Treatment effect
Kidani, Ishimatsu, and Akasu (2010)	Male WKY rats	PD 7	Same	0.3-30 μM bath application to brain slices	>3 μM produced hyperpolarizing current, 1 μM increased amplitude of IPSP, 30 μM enhanced NE outward current in locus coeruleus
Kuczenski and Segal (2002)	SD rats	PD 40	PD 40 or PD 68	0.75 to 3 mg/kg oral, acute 0.75 to 3 mg/kg oral for 28 days	Decreased locomotor activity, increased hippocampus NE release, not accumbens DA release No locomotor sensitization; no cross-sensitization to subsequent methamphetamine, but induction of c-fos at doses >2 mg/kg
Lagace, Yee, Bolanos, and Eisch (2006)	Male SD rats	PD 18	PD 34	2 mg/kg i.p., twice daily for 16 days	Attenuates adult hippocampal neurogenesis
Lee et al. (2009)	Female SD rats	PD 40	PD 55	0.6, 2.5, 10 mg/kg i.p., for 11 days	2.5 and 10 mg/kg MPHs change the locomotor diurnal rhythm patterns in long-term effects
Martins et al. (2006)	Wistar rats	PD 25	PD 53	1, 2, or 10 mg/kg i.p., for 28 days	Dose-dependent increase in oxidative stress
McFadyen, Brown, and Carrey (2002)	Mice	PD 26	PD 33	0.6, 2.5, 10 mg/kg i.p., for 11 days	2.5 and 10 mg/kg MPHs change the locomotor diurnal rhythm patterns in long-term effects
Scaini et al. (2008)	Wistar rats	PD 25	PD 53	10 mg/kg i.p., acute or for 4 weeks	Increased creatine kinase activity, an enzyme involved in energy homeostasis
Take et al. (2008)	Female Wistar rats	Prepubertal	Prepubertal	5, 10, and 20 mg/kg i.p.	Dose-dependent changes to DA-mediated cardiac pathways, may damage the mitochondria to affect contraction and rhythm
Torres-Reveron et al. (2009)	SD rats	PD 7-PD 35	39 days after final dose	5 mg/kg i.p., for 4 weeks	Alters stress reactivity and increases hippocampal ectopic granule cells in adults
Vendruscolo, Izidio, Takahashi, and Ramos (2008)	SD rats	Adolescent	16 days later	2 mg/kg i.p., twice daily for 16 days	Increases anxiety-related behaviors and ethanol drinking in adults
Yang, Swann, and Dafny (2003)	SD rats	PD 35	PD 42	2.5 mg/kg i.p., for 7 days	Locomotor cross-sensitization to AMPH
Yang, Swann, and Dafny (2006)	Male Wistar-Kyoto, spontaneously hypertensive, and SD rats	PD 31	PD 42	0.6, 2.5, or 10 mg/kg i.p., for 6 days, 3 days washout	SHR rats less sensitive, mild locomotor activation at 2.5 mg/kg, significant at 10 mg/kg. SD and WKY show activation at 2.5 and 10 m/kg, shows strain-specific responses to MPH
Yang, Swann, and Dafny (2010)	SD rats	PD 41, PD 67	PD 50, PD 76	0.6, 2.5, or 10 mg/kg i.p., for 6 days, 3 days washout	Rats treated with paradigm as juveniles (P40-P50), then tested as adults showed greater sensitization than animals treated only as adults
Zhu, Weedon, and Dow-Edwards (2007)	SD rats	PD 22	PD 40	3.0 mg/kg, oral for 18 days	

Note: PD = postnatal day; i.p. = intraperitoneal; 5-HT = serotonin; MPH = methylphenidate; VTA = ventral tegmental area; DA = dopamine; s.c. = subcutaneous; TH = tyrosine hydroxylase; NET = norepinephrine transporter; PFC = prefrontal cortex; WKY = Wistar-Kyoto; IPSP = inhibitory postsynaptic potential; NE = norepinephrine; AMPH = amphetamine; SHR = spontaneously hypertensive rat; SD = Sprague-Dawley; D1 = dopamine D1 receptor.

but increased the firing of these neurons (Brandon, Marinelli, & White, 2003). Thus, these low doses of oral MPH may increase dopamine-related activity and pathways without causing a massive increase in the neurotransmitter levels or significantly changing reuptake receptor qualities. These low doses of oral MPH also appear to have very little effect on anxiety and anxious behaviors, unlike equivalent i.p.-injected doses (Britton & Bethancourt, 2009). The low oral doses also improve attentional and memory tasks, such as performance in the radial arm maze and the modified radial arm maze win-shift task (Dow-Edwards, Weedon, & Hellmann, 2008; Zhu, Weedon, & Dow-Edwards, 2007).

Juvenile rat studies, like the adult animal studies, have also delved into examining molecular mechanisms of MPH action in normal animals, although the body of literature is much smaller. One study noted that 2 mg/kg i.p. induced a significant increase in markers of oxidative stress as measured by the levels of reactive oxygen species and free radicals in various brain regions (Martins et al., 2006). Higher doses have also been found to induce higher levels of creatine kinase (10 mg/kg i.p. 4 weeks), an enzyme involved in the breakdown and consumption of adenosine triphosphate (ATP) as well as to attenuate the levels of c-Fos (a protein encoded for by the FOS gene) while raising FosB (FBJ murine osteosarcoma viral oncogene homolog B, a protein that is encoded by the FOSB gene) levels (1-10 mg/kg s.c. 14 days; Chase, Carrey, Brown, & Wilkinson, 2005a, 2005b; Scaini et al., 2008). This suggests that juvenile treatment of MPH may affect basal brain metabolism and deplete ATP. These higher doses also negatively affect the levels of dopamine and norepinephrine, as can be expected from adult animal studies and human brain scans. When 5 mg/kg i.p. was given to prepubertal rats for 4 weeks, it significantly decreased the levels of NET, while increasing tyrosine hydroxylase (markers of dopaminergic neurons and dopamine production) and Nissl-staining cells in the PFC, indicating that this dose strongly increases the levels of catecholamine neurotransmitters, while simultaneously decreasing their reuptake (Gray et al., 2007).

Few juvenile studies have attempted to consider the impact of circadian light/dark cycles as well as route of administration; however, there are several pioneering studies that have been published recently considering these issues. Rats at PD 22 to PD 23 were given 3 mg/kg MPH orally on a cracker during the dark phase of their light cycle and tested for anxiety, attention, and locomotor activity. The animals given the MPH showed increased time in the open arms of the elevated plus maze, indicating reduced anxiety, and improved performance in the multitrial attention task; however, they also showed increased locomotor activity (Zhu, Weedon, & Dow-Edwards, 2010). Previously, this group used the same dosage method from PD 22 to PD 40; these chronically treated rats showed improved spatial learning and memory during the first 7 days of treatment as

compared with controls and did not show increased locomotor activity at the conclusion of treatment. These results indicate that, when light/dark cycle is considered, and a clinically relevant dose and route of administration are used, MPH can reduce anxiety and improve attention and spatial learning in juvenile rats. There appears to be rapid adaptation to the locomotor-activating effects, as they are seen in acutely dosed rats but not chronically treated. This may indicate that cellular or molecular compensatory changes may be occurring that warrant further study.

Despite the increasing usage of juvenile and adolescent rats in MPH research, no attempt has been made to determine whether there is a difference in the rate of metabolism of MPH between juvenile rats and adult rats. Given the higher basal metabolic and growth rates of juvenile rats, it would stand to reason that differences in the speed of metabolism and breakdown of pharmaceuticals such as MPH would be evident. Although no study has yet examined the specific metabolism of MPH in juvenile rats, it should be noted that adolescent rats (PD 40-PD 45) that received 10 mg/kg i.p. of MPH displayed increased brain glucose metabolism across most brain regions (Torres-Reveron, Weedon, & Dow-Edwards, 2010). This dosage is far beyond the clinical range (0.5-2 mg/kg i.p.), but it does suggest that MPH increases brain metabolic rate. Therefore, if metabolic rates differ between juvenile and adult rats, the dose–response curve and therapeutic range might differ as well. However, no studies have yet attempted to examine this. Given the inconsistencies of current juvenile rat MPH studies and the wide range of doses used in these studies, it is imperative to determine a proper therapeutic range for juvenile rats following injected and orally administered MPH as well as to determine the ideal time points following drug administration at which to conduct experiments to note maximal effects.

A recent study conducted by the authors found that MPH induced opposite effects following administration of 1 mg/kg (i.p.) in juvenile (P15-P25) SD rats as compared with adult (>P90) rats. Whole-cell patch clamp recording of Layer 5 prefrontal neurons in the PFC revealed a significant decrease in neuronal excitability (spike numbers) in juvenile rats, but an increase in adult rats. In juvenile rats, this decrease in excitability was associated with a marked increase in the amplitude of hyperpolarization-activated cyclic nucleotide-gated channel-mediated current as well as reduced excitatory synaptic transmission. Excitability and synaptic transmission recovered within 1 week following cessation of 1 mg/kg i.p. treatment but exhibited no recovery from 3 and 9 mg/kg treatment after even 10 weeks of washout (Urban, Gao, & Waterhouse, 2012). The 1 mg/kg and 3 mg/kg doses represent a range of doses used in many of the studies examined in this review article (see Table 2), whereas the 9 mg/kg dose is most representative of an abuse dose. However, published articles have used upward of 10

mg/kg MPH without indicating the lack of therapeutic relevance. Therefore, the extended recovery times and lack of recovery of neuronal activity from the highest dose indicate that MPH may induce lasting changes to prefrontal cortical circuitry when given during juvenile and adolescence.

Conclusion and Insights

In conclusion, the studies examined in this review indicate that juvenile MPH treatment may induce lasting molecular changes that alter energy consumption and metabolism, neurotransmitter levels and receptor functions, synaptic transmission and plasticity, ion channels, and gene transcription/ translation well into adulthood. Thus, treatment for even a short while during development may have lifelong ramifications. Therefore, it is imperative that the field of study move toward a deeper understanding of the differences between juvenile and adult brains in response to psychostimulant treatment as well as more thorough understanding of the etiology of ADHD and better diagnostic measures.

Many urgent questions remain to be answered. First, although our recent studies provide evidence that the juvenile brain may be much more sensitive to the effects of MPH and therefore juvenile animal research warrants a reexamination of the dose–response curve, which doses to examine for therapeutic relevance remains unclear. In addition, to the best of our knowledge, no studies exist that examine the rate of MPH metabolism in juvenile animals. It has been established that peak blood plasma levels occur 15-45 min following drug administration in adult rats; however, juvenile rats may have a disparate absorption and/or elimination rate due to the faster overall metabolic rate during the growth period (Wargin et al., 1983). Therefore, examination and development of a blood plasma level curve and elimination rate are imperative for conducting ideal future juvenile animal studies. Second, examination of potential lasting effects needs to be completed. Our lab has noted that PFC neuronal excitability recovers to control levels within 1 week following a 3-week regimen of daily 1 mg/kg i.p. MPH but remains depressed even 10 weeks after the same regimen of 3 and 9 mg/kg i.p. treatment (Urban et al., 2012). Do these results indicate a potential for permanent modification of innate cellular characteristics by chronic MPH treatment? How relevant is 3 or 9 mg/kg i.p. MPH to doses achieved by healthy individuals abusing MPH or using it as a cognitive enhancer? It is currently unclear. Third, a decrease in pyramidal neuron excitability could lead to impairments in learning and memory—executive functions of the PFC. How these behaviors could be affected by the doses of MPH currently used in animal research studies in juveniles is yet uncertain, as is the permanence of such effects. Future studies must meld together cellular/molecular and behavioral assays to examine the receptors and pathways involved in MPH's distinct effects on juvenile PFC.

Finally, there may be a distinct time-of-day effect of MPH administration and drug effect studies. When the drug is given during the light period of the light/dark cycle (rats' normal resting period), stereotypic behaviors dominate at doses 10 mg/kg and more, and animals sensitize to subsequent doses. However, sensitization to locomotor-activating doses is not seen when MPH is administered during the dark cycle (Askenasy et al., 2007). In humans, MPH is taken orally during the active period (light period) and no sensitization is noted, just as in rats treated during their active period, that is, during the dark period of the cycle. Humans that inject MPH during the night hours often report rewarding effects similar to intravenously or intranasally administered cocaine and amphetamine, along with a sensitization and symptoms of addiction. These phenomena are not reported when the drug is given orally during the daytime hours (Askenasy et al., 2007). Thus, the current experimental model of injecting MPH during the light period of the light/dark cycle may in fact be more closely representative of an abuse state than a therapeutic state. If this is the case, it would raise concerns about a large proportion of the accepted animal study research. Further examination of the differential effects of low- and high-dose MPH on adult and juvenile rats during various periods during the light/ dark cycle is therefore urgently needed.

These and other unknowns abound in the field of MPH research, and the concerns raised by our lack of understanding of the drug's differential effects on individuals of various ages and disease states perpetuate misunderstanding and overprescription of a drug that is assumed safe and "effective." The scientific community needs to piece out the answers to these urgent questions. Only then can we provide the optimal therapeutic benefit for individuals afflicted with ADHD or other related cognitive deficits, while minimizing the treatment-associated risks.

Declaration of Conflicting Interests

Funding

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