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Neuronal nicotinic receptor agonists for the treatment of attention-deficit/hyperactivity disorder: Focus on cognition

Timothy E. Wilens [a,*], *Michael W. Decker* [b,1]

[a] *Massachusetts General Hospital, Pediatric Psychopharmacology Research Unit, Yawkey Center for Outpatient Care-YAW 6A, 32 Fruit St., Boston, MA 02114, United States*

[b] *Neuroscience Drug Discovery, Global Pharmaceutical Research and Development, Dept. R4N5, Bldg. AP-9A/3, 100 Abbott Park Rd., Abbott Park, IL 60064-6125, United States*

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ABSTRACT

Attention deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed neurobehavioral disorder in children and adolescents, and in about half of these patients, significant symptomology continues into adulthood. Although impulsivity and hyperactivity are the most salient features of ADHD, cognitive deficits, particularly impairments in attention and executive function, are an important component, particularly in adolescents and adults, with over 90% of adults seeking treatment for ADHD manifesting cognitive dysfunction. Currently available medications treat the core ADHD symptoms but typically do not adequately address cognitive aspects of ADHD, underscoring the need for new therapeutics. Dopamine and norepinephrine are hypothesized to be particularly important in ADHD, but there is emerging evidence that cholinergic neurotransmission, particularly involving neuronal nicotinic acetylcholine receptors (nAChRs), may play a role in the pathophysiology of ADHD. Nicotine has demonstrated procognitive effects in both humans and experimental animals and has produced signals of efficacy in small proof-of-concept adult ADHD trials. Although adverse effects associated with nicotine preclude its development as a therapeutic, a number of novel nAChR agonists with improved safety/tolerability profiles have been discovered. Of these, ABT-418 and ABT-089 have both demonstrated signals of efficacy in adults with ADHD. Notably, tolerability issues that might be expected of a nAChR agonist, such as nausea and emesis, were not observed at efficacious doses of ABT-089. Further understanding of the effects of novel neuronal nAChR agonists on specific aspects of cognitive functioning in ADHD is required to assess the full potential of this approach.

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed neurobehavioral disorder in children and adolescents [1]. Worldwide, the prevalence of ADHD is from 6 to 8% [2]. In about 50% of these patients, significant symptomology continues into adulthood [3,4]. Because of its associated morbidity and disability in children, adolescents, and adults, ADHD is a major clinical and public health problem with significant financial cost, stress to families, impact on academic and vocational activities, as well as negative effects on self-esteem [3,5–15].

* *Corresponding author*. Tel.: +1 617 726 1731; fax: +1 617 724 3742.
E-mail addresses: twilens@partners.org (T.E. Wilens), michael.w.decker@abbott.com (M.W. Decker).
[1] Tel.: +1 847 937 2422; fax: +1 847 937 9195.

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ADHD is often characterized by a triad of attentional, hyperactive, and impulsive symptom clusters [16]. Although the most salient symptoms of ADHD are impulsivity and hyperactivity, cognitive deficits, particularly impairments in attention and executive function, are an important component of ADHD for many patients [17–23]. The earlier view of ADHD as primarily a hyperactive disorder [24,25] has been amended more recently to include a heightened emphasis on the associated cognitive dysfunction [26,27], with increased appreciation of the long-term influence that cognitive deficits in ADHD may have on morbidity [9,10,28]. The attentional cluster of symptoms of ADHD includes inattention, distractibility, shifting activities, forgetfulness, poor attention to detail, poor follow through, and organizational difficulties. Highlighting the critical importance of core cognitive symptoms in ADHD are consistent findings that these deficits persist [29,30], despite reductions in hyperactivity and impulsive symptoms over time [9,10,28,31]. Consistent with this observation, the presence of cognitive dysfunction is particularly common in adolescents and adults with ADHD, with over 90% of adults seeking treatment for ADHD manifesting cognitive dysfunction [31,32]. Moreover, those individuals with pronounced cognitive deficits in ADHD (e.g., particular learning disabilities or dysfunction on multiple tests of neuropsychological functioning) are at heightened risk for more academic and occupational difficulties [33].

Deficits in executive function represent an important component of the cognitive dysfunction in ADHD [17,18,32,34–37]. Executive function generally refers to ''mental control'' processes that are ''proactive'' and include interference control, effortful and flexible organization, and strategic planning, which includes anticipatory, goal oriented ''preparedness to act'' [17,38]. Executive function is self regulatory and goal oriented [18] and encompasses important aspects of working memory [18,39]. Welsh and Pennington [36,38] have defined executive function clinically as ''the ability to maintain an appropriate problem solving set for attainment of a future goal'' that includes an intention to inhibit a response or to defer it to a later more appropriate time, a strategic plan of action sequences, and a mental representation of the task, including the relevant stimulus information encoded in memory and the desired future goal-state [36]. Children and adults with ADHD show greater sensitivity to interference on the Stroop Color Naming task [40–42] and impaired impulse control. Similarly, ADHD patients have greater deficits in immediate and delayed recall in tasks that require use of organization strategies than on learning and recall tasks that require less active organization [17,43,44]. Although batteries that include tests such as Wisconsin Card Sort, Matching Familiar Figures Test, Tower of Hanoi, Go No-Go, Stroop, and Matching Memory Test are useful in assessing executive function deficits in ADHD [29,32,36,43,45,46], there are currently no *individual* tests with adequate sensitivity and selectivity for identifying executive function deficits in ADHD [36,41,47].

While cognitive dysfunction in general, and executive function deficits more specifically, in ADHD have consistently been demonstrated, the magnitude of the impairment varies across individuals [37,43,47–51]. However, individuals with ADHD characterized by prominent executive function deficits have increased risk for functional impairment over time [30,52]. For example, using an operational definition of impaired executive function based on a neuropsychological battery of executive function tests, 56% of ADHD children and adolescents had executive function deficits [49]. These individuals had significantly higher rates of academic difficulties and poorer overall global functioning than their ADHD peers without executive function deficits. Similarly, ADHD adults with prominent executive function deficits have higher rates of impairment in occupational and academic settings, and a subset of adults with ADHD have dysfunction in executive function [43] so great that they may present a divergent trajectory of ADHD resulting in more severe morbidity such as learning disability and academic failure [53] and high risk for mortality.

Among the various treatment options for ADHD, pharmacotherapy is fundamental in the treatment of the disorder across the lifespan [54]. Stimulant medications, such as methylphenidate and amphetamine, and the nonstimulant atomoxetine, are used for treating ADHD in both children and adults. Acutely, these medications address the core ADHD symptoms and some of the commonly associated features [55–63]. For example, stimulants can reduce motoric overactivity, impulsivity, and inattentiveness (for review see [57–59,61,64–66]). However, even with currently available treatments, residual symptoms are present. Stimulants, for instance, typically do not adequately address cognitive aspects of ADHD, including executive function [30,34,67]. After treatment with adequate doses of stimulants, 25–30% of adults with ADHD are nonresponders according to clinical impression or ADHD symptom checklist scores [68]; and of the responders, half still manifest clinically relevant residual symptoms. Moreover, while short-term stimulant and nonstimulant treatment can improve performance in specific tests of executive function [59,69–81], there are a number of clinical [80,82,83] and anecdotal reports of continued compromise leading to impaired functioning in multiple domains. For example, three controlled clinical trials of stimulants in adult ADHD demonstrated robust improvement of the observed behaviorally defined ADHD symptoms of attention and hyperactivity/impulsivity, but failed to signal improvement in neuropsychological tests of executive function (Continuous Performance Task, Wisconsin Card Sort, Stroop word test) [84]. Interestingly, organization, the DSM ADHD symptom most related to executive function, demonstrated the least robust change within the attentional symptom cluster with treatment.

Longer-term treatment studies also signal the importance of cognitive symptoms of ADHD and reflect continued cognitive dysfunction despite treatment. In two independent longitudinal studies of ADHD adolescents and young adults, those with neuropsychological impairment at baseline were at higher risk for continued neuropsychological impairment four years later [30,33,52], and medication had little influence on either neuropsychological profiles at follow-up or long-term functional outcomes [30,49,52]. Despite the inherent limitations of a naturalistic design (i.e. lack of randomization), these two longitudinal studies underscore the relative intractability of the cognitive deficits of ADHD and the need for new strategies to address these aspects of ADHD both short- and

long-term. In the following section, we provide a brief summary of the interface of ADHD and the nicotinic cholinergic system, the cognitive characteristics of nicotinic agents, and the potential role of neuronal nicotinic agents in the treatment of ADHD.

2. Cholinergic neurotransmission and ADHD

Although the pathophysiological underpinnings of ADHD are not fully understood, neuropsychological and neuroimaging studies indicate that abnormalities in frontal and fronto-striatal networks represent important underlying neural substrates and that catecholamine dysregulation plays a critical role [40,85–92]. The cognitive deficits in ADHD are consistent with the hypothesis that ADHD is a developmental brain disorder with primary deficits in the prefrontal cortex and/or subcortical (e.g., striatal) regions projecting to the frontal lobes [19,25,85,93–96]. Dopamine and norepinephrine are the most prominent catecholamines hypothesized to be critical in ADHD modulation [40,85–92].

In addition, there is emerging evidence that cholinergic dysregulation (in particular, of nicotinic cholinergic systems) may play a role in the pathophysiology of ADHD [97]. Both clinical and epidemiological samples of humans indicate that ADHD is associated with an increased risk and earlier age of cigarette smoking [98–100]. Epidemiological data indicates that a higher risk of smoking correlates directly with more ADHD symptoms [100]. Furthermore, maternal smoking during pregnancy (independent of ADHD) increases the risk for ADHD in the offspring [101], an effect that can be modeled in experimental animals exposed to nicotine in-utero [102,103].

Pharmacological enhancement of the cholinergic system can improve a host of cognitive processes. As comprehensively reviewed by Levin et al. [104] and Potter et al. [97], a vast preclinical literature derived from laboratory models supports nicotine and other nicotinic agonists' role in improving performance on cognitive processes, including learning, spatial and working memory, processing speed and ability, inhibition, selective accuracy, detection, and overall attention. In general, using the preclinical paradigms, the effects of nicotine appear to persist with chronic administration [104].

A substantial literature has also identified cognitive improvements associated with nicotine administration in human, non-ADHD subjects [104]. For example, improvement in cognition has been reported in studies of adults receiving nicotine by gum [105], cigarette consumption [106], nicotine patch [107,108], and subcutaneous injection [109]. Nicotine has also been shown to improve rapid visual information processing [106], reaction time [107,109], and vigilance [110]. More broadly, activation of neuronal nicotinic acetylcholine receptors (nAChRs) has been shown to improve temporal memory [111], attention [106,107,109,112], cognitive vigilance [105,106,109], and executive function. In one study, improvement in attention by the continuous performance test (CPT) was most notable in adults with relatively lower compared to higher levels of attention [108].

Although therapeutic intervention using nicotine is limited by cardiovascular and gastrointestinal toxicities, ''proof-of-principle'' clinical evaluations have demonstrated its cognitive-enhancing effects in ADHD [113,114], as well as in other conditions characterized by cognitive impairment, such as Alzheimer's disease [109,115] and schizophrenia [116,117]. For example, in a short controlled trial in 17 adults with ADHD, nicotine patches produced a modest reduction in ADHD symptoms with a concomitant reduction in reaction time on the Continuous Performance Task (CPT) [118]. A preliminary brief crossover study of 10 adult smokers with ADHD receiving a nicotine patch, methylphenidate, or the combination of the nicotine patch and methylphenidate showed improvement in self-report of ADHD symptoms with the patch or stimulant that exceeded placebo conditions [119]. Similarly, a small study using the nicotine patch in adolescents with ADHD demonstrated positive neuropsychological effects on ADHD that were reminiscent of those elicited using methylphenidate [114]. In addition to its salutary effects on cognitive function, nicotine may have therapeutic effects in a number of disorders showing high comorbidity with ADHD, e.g., depression, anxiety, and Tourette's syndrome [120]. These aggregate findings have provided the impetus to identify compounds that reproduce the potentially therapeutic effects of nicotine but not the side effects. Not all nAChR agonists produce the same pattern of beneficial and adverse effects, so it is likely that these diverse effects of nicotine are mediated by actions at different receptor subtypes [121], and recent advances in our understanding of the molecular biology and pharmacology of neuronal nAChRs have identified potential strategies for developing better therapeutics [120,122].

3. Neuronal nicotinic acetylcholine receptor pharmacology

Neuronal nAChRs are ligand-gated ion channels, each composed of five subunits surrounding a cation pore (see Fig. 1). Twelve distinct neuronal nAChR subunits have been identified in vertebrates ($\alpha2$–$\alpha10$, $\beta2$–$\beta4$). Although the specific subunit compositions of native neuronal nAChRs have not yet been fully elaborated, a number of different subunit combinations form functional recombinant neuronal nAChRs in vitro, each with distinctive pharmacological and electrophysiological properties [123,124]. The two most abundant neuronal nAChRs in the CNS can be differentiated by their relative affinities for nicotine and α-bungarotoxin (α-BTX). Receptor subtypes with high affinity for nicotine and cytisine, but low affinity for α-BTX, contain combinations of α and β subunits; whereas neuronal nAChRs with low affinity for nicotine, but high affinity for α-BTX, are predominantly homomeric $\alpha7$ nAChRs. The most common high-affinity nicotine binding sites in brain are $\alpha4\beta2^*$ nAChRs. A small number of $\alpha3\beta4^*$ neuronal nAChRs with high affinity for nicotine are found in brain, but these receptors are more abundant in the autonomic nervous system where they likely play a role in many of the adverse effects of nicotine [125].

Neuronal nAChRs are found in a variety of brain regions important for cognitive processes (for comprehensive reviews, see [126,127]). The $\alpha4\beta2^*$ receptors, which may also sometimes include other subunits (e.g., $\alpha5$), are the most broadly distributed and are found in the cortex and in

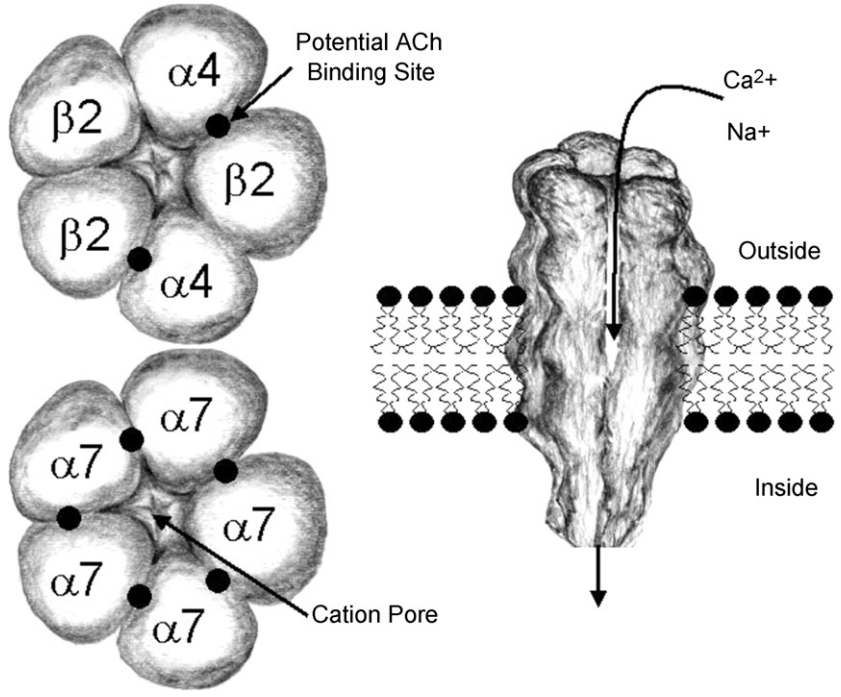

Fig. 1 – Neuronal nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels, each composed of five subunits surrounding a cation pore. The cartoons on the left provide a view of the receptor from above (looking down into the channel pore), whereas the illustration on the right provides a cut-away side view. In vertebrates, 12 subunits have been identified: nine α subunits (α2–α10) and three β subunits (β2–β4). However, not all possible subunit combinations form functional receptors. For example, β subunits can only form functional receptors if combined with α subunits, and α2–α6 subunits require the presence of β2 or β4 subunits, with the further requirement that α5-containing receptors have additional α subunits. α4β2-containing (designated α4β2*) nAChRs are the most common subtype in brain and have high affinity for nicotine. The example in the figure contains only α4 and β2 subunits, but there is also evidence that some α4β2* receptors contain other subunits as well (e.g., α6 or α5) which can alter their pharmacological and electrophysiological properties. α7–α10 subunits do not need to be combined with β subunits to form functional nAChRs. The most common of these subunits is α7, which appears to form a homopentomeric nAChR in vivo. This α7 nAChR is the second most abundant nAChR in brain and has low affinity for nicotine but higher permeability to Ca^{2+} and faster desensitization kinetics than the α4β2* nAChR.

subcortical structures, including thalamic and monoamine nuclei that modulate cortical processes. The α7 nAChRs are also found in many of these same regions, with the exception of the thalamus, which has little or no expression of α7. The α7 subtype is particularly prominent in the hippocampus where it is expressed at higher levels than is α4β2*. Other nAChR subtypes are found in the brain but have much more restricted distributions. For example, α6-containing and α3-containing nAChRs are associated with catecholamine neurons, and a high concentration of α3β4* nAChRs are present in the pineal body. The localization of nAChRs in regions, such as amygdala, frontal cortex, midbrain DA nuclei (VTA), and the dorsolateral thalamus, is consistent with the cognitive effects of nAChR agonists. Agonists at neuronal nAChRs can act postsynaptically to improve cognitive function but can also increase the release of a number of neurotransmitters involved in cognitive function [128]—including NE (norepinephrine), 5-HT (serotonin), DA (dopamine), GABA (gamma aminobutyric acid), glutamate, and ACh itself [127,129].

Cholinergic pathways originating in the basal forebrain project diffusely to the cerebral cortex [130]. ACh appears to be particularly important for normal cognitive function, including processes mediated by the prefrontal cortex that are affected in ADHD, such as attention, working memory, and executive function. In rats, performance in a sustained attention task is accompanied by increased ACh release in the prefrontal cortex [131]. ACh release in the prefrontal cortex becomes even more prominent when demands on attention are increased, and performance on attention tasks can be impaired by experimental disruption of cholinergic function [131,132]. Additionally, nAChR stimulation can modulate dopaminergic neurotransmission [133,134]. Nicotine produces a concentration dependent release of dopamine from superfused slices of rat striatum [133], and nicotine has been shown to have a effects on striatal presynaptic dopamine transporters in adults with ADHD [135]. However, as discussed below, not all neuronal nAChR agonists reproduce the effects of nicotine on dopamine release.

Neurotransmitter release is generally believed to mediate many of the effects of neuronal nAChR agonists [121], but effects on MAP kinase signaling may also play an important role [136]. More recent research has also identified a role for nAChRs in the regulation of phosphorylation of DARPP-32 (dopamine and cAMP-regulated phosphoprotein of molecular mass of 32 kDa). The phosphorylation state of DARPP-32, in turn, plays a role in modulating responses of ionotropic glutamate receptors important in learning and memory [137].

Although the precise neuronal nAChR subtypes mediating the cognitive-enhancing effects of neuronal nAChR agonists have not yet been fully elucidated, both α7 and α4β2* nAChRs appear to play significant roles. A variety of selective α7 agonists have demonstrated efficacy in learning and memory tasks in animals [138–142] and antisense knockdown of the α7 subunit can impair spatial learning in the Morris water maze [143]. However, there is some evidence that α4β2* nAChRs play a more critical role in attention than do α7 nAChRs. For example, α4β2*-preferring nAChR agonists are more efficacious than α7 agonists in the 5-choice serial reaction time task (5-CSRTT) in rats, a sustained attention task modeled after the CPT used in humans [144].

Antagonist and gene knockout studies also support a role for α4β2* nAChRs in cognition. Dihydro-β-ethroidine (DHβE), an antagonist that shows preferential affinity for β2-containing neuronal nAChRs, can disrupt cognitive performance in rodents [145]. Consistent with these observations, genetically altered mice lacking the β2 subunit exhibit a small but reliable impairment in contextual fear conditioning under baseline conditions that optimize wild type mouse performance, and the memory-enhancing effects of nicotine on contextual fear conditioning are absent in the β2 knockout mice [146]. Similarly, the ability of nicotine to improve memory in the inhibitory avoidance task is also absent in β2 knockout mice, although in this case the β2 knockout mice actually show somewhat better performance than wild type mice under baseline conditions [147]. β2 Knockout mice perform normally in the Morris water maze as young adults but show accelerated age-related deficits in this task [147]. Despite their adequate performance in the water maze, young adult β2 knockout mice demonstrate behavioral rigidity and locomotor exploratory patterns suggestive of impaired prefrontal ''executive'' function [148]. Furthermore, nicotine-induced improvements in sustained attention in normal rats performing the 5-CSRTT appear to be mediated through actions at α4β2* receptors in the prefrontal cortex [149,150]. Thus, α4β2* receptors in the prefrontal cortex likely play an important role in prefrontal executive function, a cognitive domain particularly affected in ADHD. The involvement of α4β2* nAChRs in attention is also supported by genetic data in that an association between an intron mutation in the gene coding for the α4 subunit and ADHD characterized by severe inattention has been reported [151].

Based on the evidence for the role of α4β2* nAChRs in cognitive function, this receptor subtype has been targeted in efforts to identify nAChR agonists with better safety profiles than nicotine, including a few compounds that have demonstrated cognitive enhancement in humans—e.g., ABT-418 and ABT-089 from Abbott, and ispronicline (TC-1734) from Targacept [152–159]. Two of these compounds—ABT-418 and ABT-089—have been tested specifically in ADHD.

4. Novel neuronal nAChR agonists and ADHD

ABT-418 was the first of these novel neuronal nAChR agonists to be evaluated in ADHD [157]. ABT-418 has ~3 nM affinity at the α4β2* nAChR and is a full agonist at this subtype in vitro, with potency comparable to that of nicotine, but it is less potent at the ganglionic subtype (α3β4*) than nicotine [160]. In preclinical studies, ABT-418 demonstrated efficacy and potency similar to that of nicotine in animal models of cognition, but had reduced toxicities [154]. Clinically, the compound was tested in a placebo-controlled, randomized trial, comparing a transdermal patch of ABT-418 (75 mg daily) to placebo in adults with DSM IV ADHD using a crossover design (two 3-week treatment periods separated by 1 week of washout). Of the 32 subjects enrolled in the study (88% male; mean age ± S.D., 40 ± 9 years), there were 29 completers. At the endpoint of each active arm, a significantly higher proportion of subjects were rated ''much to very much improved'' on a clinical global improvement scale of ADHD when treated with ABT-418 (40% versus 13% with placebo; $p = 0.026$). Progressively more symptom reduction was observed over the 3 weeks of treatment. As shown in Table 1, there were significant reductions in the inattentive symptom cluster, and in particular, among symptoms related to organization and planning – symptoms only nominally improved using similar methodology with other medications in ADHD. In contrast, impulsivity and hyperactivity were less robustly addressed by ABT-418.

Although safer than nicotine, ABT-418 did produce some nicotine-like side effects, such as dizziness and nausea. In addition, ABT-418 has a very short half-life requiring transdermal delivery, necessitating efforts to find another compound that would reproduce the cognitive effects of ABT-418 but with an improved preclinical therapeutic index and a better pharmacokinetic profile. This work culminated in the identification of ABT-089

ABT-089 has high binding affinity and selectivity for the α4β2* subtype ($K_i \sim 15$ nM for both human and rat versus K_i values $> 10{,}000$ nM for human and rat α7 nAChRs and > 1000 nM for the muscle type receptor expressed in Torpedo electroplax) [161]. However, ABT-089 is significantly less efficacious than nicotine or ABT-418 at α4β2* nAChRs in vitro, producing no cation ($^{86}Rb^+$) efflux from cells expressing recombinant human α4β2 nAChRs at concentrations up to 300 μM and achieving only 34% of the efficacy of nicotine at mouse α4β2* receptors, as reflected by cation ($^{86}Rb^+$) efflux from thalamus synaptosomes. However, ABT-089 has efficacy comparable to nicotine in evoking ACh release from rat hippocampal synaptosomes [161] and was as efficacious as nicotine and slightly more potent than nicotine in inducing ACh release from prefrontal cortex in rats after local application [162]. In contrast to its prominent effects on ACh release, ABT-089 is only about 70% as efficacious and 25-fold less potent than nicotine in inducing release of dopamine from striatal slices [161,163]. Moreover, in contrast to nicotine and ABT-418, which activate dopaminergic neurons in ventral tegmental area (VTA) slices, ABT-089 was inactive in this assay at concentrations up to 10 μM [161,163]. The reduced activity of ABT-089 at dopaminergic VTA neurons may be a reflection of its partial agonist profile, which is consistent with the

Table 1 – Effect of ABT-418 on specific symptoms of ADHD in adults

Symptom cluster	Baseline		End of treatment			
	Entire sample		Placebo		ABT-418	
	Mean	±S.D.	Mean	±S.D.	Mean	±S.D.
Hyperactivity						
Difficulty remaining seated	1.27	1.0	1.16	0.8	1.00	0.9
Fidgety	2.09	0.8	1.69b*	0.9	1.47b**	0.8
Difficulty working quietly	1.21	1.1	0.91	0.9	0.83b*	0.8
Talks excessively	1.61	1.0	1.50	0.9	1.53	0.9
Interrupts or intrudes	1.76	0.9	1.31b*	0.9	1.17b***	0.8
Blurts out answers	1.79	1.0	1.25b**	1.0	1.27b**	0.9
Difficulty waiting turn	1.48	1.0	1.25	1.0	1.13b*	1.0
Often "on the go"	1.94	1.1	1.72	1.0	1.53	1.0
Hyperactive/restless	1.85	1.1	1.69	1.0	1.23a*b*	0.9
Inattentiveness						
Difficulty sustaining attention	2.18	0.7	1.94	0.8	1.50b***	0.8
Difficulty following instructions	1.61	1.0	1.34	1.0	1.13b**	0.9
Easily distracted	2.42	0.6	2.03b*	0.8	1.57a*b***	0.8
Loses things	1.52	1.0	1.44	0.9	1.17b*	1.0
Doesn't listen	1.61	0.8	1.34	0.7	1.20b*	0.7
Trouble with details	1.64	1.0	1.50	0.8	1.13a**b**	0.8
Difficulties organizing	2.12	1.0	1.75	1.0	1.40a*b***	1.0
Avoidance of mental tasks	1.85	0.9	1.41b*	0.9	1.23b**	0.9
Often forgetful	1.67	1.0	1.72	0.9	1.20a*b*	0.9

Table 1 depicts the effects of a novel nicotinic agonist, ABT-418 (75 mg daily) compared to placebo in the treatment of adults with ADHD using a crossover design of two 3-week treatment periods separated by 1 week of washout in 32 adults. At the endpoint of each active arm (last observation carried forward), a significantly higher proportion of subjects were rated "much to very much improved" on a clinical global improvement scale of ADHD when treated with ABT-418 (40% vs. 13% with placebo; $p = 0.026$). Shown are the individual symptoms of ADHD as rated using the ADHD rating scale (0 = "not a problem"; 1 = "mild problem"; 2 = "moderate problem"; 3 = "severe problem"). Statistical significance: a vs. placebo, b vs. baseline.

* $p \leq 0.05$.

** $p \leq 0.01$.

*** $p \leq 0.001$.

observation that ABT-089 can attenuate the actions of nicotine in this assay when the compounds are applied together [161,163].

ABT-089 is efficacious in a variety of preclinical cognition models. Continuous infusions of the compound attenuated spatial learning deficits in aged rats in the Morris water maze and improved acquisition in a 2-platform spatial discrimination water maze in young adult rats with large septal lesions that disrupted cholinergic input to the hippocampus [155]. ABT-089 was efficacious at 1.3–4.0 μmol/kg/day but not at a higher dose of 13 μmol/kg/day, resulting in a U-shaped dose response curve. Similarly, daily injections of ABT-089 improved 2-platform water maze deficits induced by administration of the muscarinic antagonist scopolamine [153]. In contrast to the results obtained with ABT-089, the cholinesterase inhibitor, tacrine, was ineffective in the septal lesion model [164], probably owing to the low level of residual hippocampal cholinergic input in this model. Thus, although ABT-089 increases ACh release, its beneficial effects in the water maze do not appear to depend on residual hippocampal cholinergic tone [153,155].

ABT-089 also improved the performance of monkeys in a delayed matching-to-sample task that assesses short-term memory and attention [155]. In this task, correct identification of a target stimulus typically declines as a function of the delay between the study phase and the test phase, but this delay-dependent impairment can be attenuated by ABT-089, particularly when individualized dose-finding trials are used to identify the "best dose" for each monkey. These relatively modest effects of ABT-089 under standard conditions can be increased dramatically when the monkeys perform the task in the presence of a visual distractor stimulus introduced during delay intervals. Under these conditions, ABT-089 completely reinstated normal performance [165]. Methylphenidate is also active in the distractor model [166], although its effects are not as impressive as those obtained with ABT-089. The enhanced effects of ABT-089 in the presence of a distractor is consistent with data from rats demonstrating increased importance of frontal cholinergic input for cognitive performance in the presence of a distractor [131].

Based on its promising preclinical profile, ABT-089 was more recently evaluated in a randomized, double blind, placebo-controlled phase 2a proof-of-concept study in adult ADHD [158]. The compound was administered orally (placebo, 2 mg, 4 mg, or 20 mg b.i.d.) using a crossover design with treatment periods of 2 weeks each and no washout periods between treatments. The study was terminated prematurely based on some preclinical data that have since been resolved, resulting in 11 subjects completing the entire study. Based on these limited data, ABT-089 produced significant improvements on the primary outcome measure, the Conner's Adult ADHD Rating Scale, including both attentional and

hyperactive/impulsive symptoms (1-tail p values of: 0.021, 0.047, and 0.056 for 2, 4, and 20 mg doses, respectively). Computerized neurocognitive test results revealed a significant improvement in spatial working memory (1-tail $p = 0.021$ at 20 mg and trends at 2 and 4 mg, $p = 0.074$ and 0.052, respectively) and a tendency to improve numeric working memory (1-tail $p = 0.091$ at 20 mg). ABT-089 also improved selective attention as measured by the CPT, reducing commission errors, which occur when a response is made to a non-target stimulus (1-tail p values of: 0.022, 0.009, and 0.007 for 2, 4, and 20 mg doses, respectively). In this study and in phase 1 studies, ABT-089 demonstrated very favorable tolerability and safety data consistent with its relatively benign safety profile in preclinical studies [153,167].

5. Conclusions

Longitudinal data continue to highlight the chronicity and clinical and public health importance of ADHD and its treatment throughout the lifespan. Increasingly recognized is the persistence of attentional dysfunction and cognitive deficits in ADHD and their role in creating additional sequalae associated with ADHD. Unfortunately, many of the treatments for ADHD result in residual cognitive symptoms. Hence, treatment strategies that include adequate treatment of the general ADHD triad, and more specifically the attentional-based and executive function symptoms of ADHD are needed. Because of the cardinal role of cognitive dysfunction in ADHD, such a therapeutic approach would improve not only cognitive/attentional/executive function specifically, but would likely address ADHD in general as well.

A large literature demonstrates the bidirectional overlap of ADHD and cigarette smoking/nicotine use. Nicotinic cholinergic neurotransmission plays an important role in attention and executive function processes, and nicotine has demonstrated procognitive effects in a number of animal studies, and pilot data indicates some degree of efficacy in small proof-of-concept adult ADHD trials. Although adverse effects associated with nicotine preclude its development as a therapeutic, a number of novel $\alpha4\beta2$ nAChR agonists with improved safety/tolerability profiles have been discovered. Of these, early proof-of-concept studies in humans have revealed signals of cognitive enhancement for ispronicline, ABT-418, and ABT-089. Varenicline, another partial agonist at the $\alpha4\beta2$ nAChR that is FDA approved for the treatment of cigarette cessation, remains untested in ADHD. To date, ispronicline has been targeted for Alzheimer's disease and studies in ADHD are not yet available. ABT-418 and ABT-089, on the other hand, have both preliminary signals of efficacy in adults with ADHD. Notably, ABT-089 did not produce tolerability issues that might be expected of a nAChR agonist, such as nausea and emesis, most likely because of its selectivity and partial agonist profile. Moreover, ABT-089 has the potential to produce cognitive improvement that is independent of effects on dopamine and the attendant concerns, such as abuse liability and insomnia, since preclinical data suggest that unlike nicotine, ABT-089 has minimal effects on dopaminergic transmission. It remains to be seen if partial compared to full $\alpha4\beta2$ agonists will have a differential overall and specific effect on neuropsychological functioning and behavioral symptoms of attention in ADHD and other psychiatric disorders. More information on the role of novel neuronal nAChR full and partial agonists on specific aspects of cognitive functioning in ADHD and other psychiatric disorders with associated cognitive impairment is necessary to evaluate the full potential of this approach.

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Conflict of interest

Dr. Timothy Wilens receives/d research support from, is/has been a speaker for, or is/has been on the advisory board for the following Pharmaceutical Companies: Abbott Laboratories, Ortho-McNeil, Eli Lilly and Company, National Institute on Drug Abuse (NIDA), Novartis Pharmaceuticals, and Shire Laboratories Inc. Dr. Michael Decker is an employee of Abbott Laboratories. Some of the compounds discussed in detail in the article are Abbott Compounds (ABT-418 and ABT-089).

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