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Targeting the Nicotinic Cholinergic System to Treat Attention-Deficit/Hyperactivity Disorder: Rationale and Progress to Date

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Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common, chronic neurobehavioral disorder related to clinically significant levels of inattention, hyperactivity and/or impulsivity. ADHD begins in childhood and symptoms persist into adulthood for the majority of those with the disorder. Associated features of ADHD include emotion dysregulation and cognitive impairments which contribute to the considerable functional impairments in this disorder. Current approved treatments are reasonably effective however a significant need remains for new pharmacotherapies, both for individuals who do not achieve a full therapeutic response and for symptoms that are under-treated including cognition and emotion regulation. The striking relationship between ADHD and cigarette smoking and the known effects of nicotine on cognition has spurred research into the therapeutic potential of nicotinic agents for ADHD. Although there are no approved medications for ADHD that target nicotinic acetylcholine receptor (nAChR) function, results from many trials of nicotinic drugs are available and reviewed in this article. ADHD symptoms were reduced in the majority of published studies of nicotine and novel $\alpha 4\beta 2$ nicotinic agonists in adult ADHD. The drugs were generally well tolerated, with mild to moderate side effects reported, which were largely consistent with cholinergic stimulation and included nausea, dizziness, and gastrointestinal distress. Within-subject crossover study designs were used in the majority of positive studies. This design may be particularly useful in ADHD trials because it minimizes variability in this notoriously heterogeneous diagnostic group. In addition, many studies found evidence for a beneficial effect of nicotinic stimulation on cognitive and emotional domains. Thus, targeting nAChRs in ADHD appears to have modest clinical benefit in adult ADHD. Continued refinement of nAChR agonists with greater specificity and fewer side effects may lead to even more effective nAChR agonists for ADHD. Future clinical trials in ADHD should include direct measures of neuropsychological performance and emotion regulation.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common, chronic neurobehavioral disorder affecting 5% of children and adolescents worldwide [1]. Up to 65% of diagnosed children continue to experience significant symptoms in adulthood [2]. Symptoms of ADHD

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include developmentally inappropriate levels of inattention, hyperactivity and impulsivity that result in clinically significant impairments across multiple settings. Difficulties functioning in academic, occupational and recreational activities and conflict in personal relationships are typical of ADHD, and in 2007 the cost (i.e. healthcare, education, and juvenile justice) of ADHD was estimated to be $42 million dollars in the United States alone [3].

The syndrome of disordered attention, hyperactivity, and impulsivity has been noted throughout history beginning in 1798 with a chapter titled On Attention and its Diseases by Sir Alexander Crichton [4]. The Diagnostic and Statistical Manual of Mental Disorders (DSM) has classified syndromes including Hyperkinetic Reaction of Childhood in DSM-II [5]; Attention Deficit Disorder with or without hyperactivity in DSM-III [6]; and Attention-Deficit/Hyperactivity Disorder in DSMIII-R; DSM-IV and DSM-5 [7-9]. In 2013, the 5th edition of the DSM was released [9], and while the DSM-5 ADHD workgroup suggested modifications to increase the diagnostic weight of impulsivity/impulsive decision making, particularly in adults, no changes were made to the symptoms used to diagnose ADHD [10]. However, other changes suggested by the workgroup have been incorporated in DSM-5 including a lower symptom threshold for those 18 and older – 5 instead of 6 of the 9 symptoms in one or both clusters – the replacement of subtypes with presentation specifiers (predominantly inattentive, predominantly hyperactive/impulsive and combined), increased age of onset (now 12 years), and the inclusion of level of severity (from mild to severe) representing the number of symptoms and amount of impairment [9]. These changes were driven by research identifying weaknesses in previous diagnostic criteria [11, 12]. For example, a recent review concluded that while DSM-IV ADHD subtypes were a convenient way for clinicians to describe the behaviors associated with ADHD, the subtypes did not empirically identify stable and discrete subgroups of patients [11]. The heterogeneity within ADHD is further complicated by changes in symptom presentation within individuals over time, such as the finding that while hyperactivity symptoms tend to decline with age, impairments related to impulsivity and impulsive decisions tend to increase in adolescence and adulthood [10].

In addition to the diagnostic criteria, several associated features of ADHD impact functioning and add to the complexity of this neurobehavioral syndrome. These include disordered emotion regulation and impaired cognitive function [9]. Emotion regulation can be defined as the ability to flexibly modulate emotional states in response to the environment to enhance performance [13]. Emotion dysregulation is not specific to ADHD, but cuts across many psychiatric disorders including both internalizing and externalizing disorders [14]. Difficulty with emotion regulation was a primary symptom in the DSM-II syndrome but moved to an associated feature beginning in DSM-III. In ADHD, emotion dysregulation is often experienced as irritability, temper outbursts, and mood lability [14-16]. Large epidemiological studies report that 38% of children with ADHD have high mood lability [17] and these rates are estimated to be higher (34-70%) in adults [14]. The importance of emotional symptoms on overall function in ADHD has been demonstrated. For example, emotional problems have larger negative effects on well-being and self-esteem than do hyperactivity and/or inattention [18], and difficulties with emotion regulation make a unique contribution to functional impairment in ADHD [19]. Current pharmacotherapies,

both stimulant and non-stimulant, may increase emotional problems including emotional lability, irritability and sadness [20-23], although studies designed to rigorously examine emotional effects of ADHD treatments are rare. It has recently been suggested that a two-pronged pharmacological approach may be useful to treat both ADHD symptoms and emotion dysregulation [14] – making emotion regulation an important pharmacological target for drug development in ADHD.

Cognitive performance deficits, particularly in executive functions (EF) have been reported in ADHD for decades (for review see [24-26]) but do not occur in all individuals with the disorder. The most consistent cognitive deficits are seen in response inhibition and variable speed of responding, with deficits in broad cognitive control and arousal noted as well [27]. Recent work has begun to explore how executive dysfunction may relate to ADHD symptoms, for example it has been shown that inattentive but not hyperactive/impulsive symptoms are related to deficits in EF [28, 29]. However, more recent work has demonstrated that cognitive weaknesses are not specific to ADHD subtype, but rather vary with overall illness severity [27], suggesting that symptoms may not map directly onto neuropsychological deficits. Studies in both children and adults have demonstrated that among individuals with ADHD greater cognitive impairment is associated with greater functional impairment [30, 31]. Cognitive symptoms are difficult to treat in ADHD and often remain even when behavior improves [30, 32, 33]. Thus, treating cognitive dysfunction in ADHD is an important goal of novel treatments.

Current approved treatments for children and adults with ADHD include psychostimulant formulations and the non-stimulants atomoxetine, clonidine and guanfacine, with psychostimulants being the current first line treatment option [29, 30]. The approved medications are effective in treating the core symptoms of inattention, impulsivity and hyperactivity in many patients [34]. However, approximately 25-30% of adults with ADHD do not have an adequate response to current approved treatments [35]. In addition, several trials of psychostimulants have reported symptom improvement but no change in neuropsychological function (reviewed in [36]) and other studies have found an increase in emotional difficulties for some patients receiving current ADHD medications [20, 21, 23]. Taken together, while current pharmacological treatments control behavioral symptoms for many individuals, there remains a significant need for new treatment strategies in ADHD, including treatments aimed at cognitive dysfunction and emotion dysregulation as these are not adequately treated with existing pharmacotherapies.

The proposal that alterations in nicotinic acetylcholine receptor (nAChR) function may contribute to symptoms in ADHD, and that stimulation of these receptors may relieve symptoms has been explored for over two decades [37-40], however there are no approved nAChR medications for ADHD. Clinical studies, both initial treatment trials and acute laboratory studies, suggest that stimulating nAChRs can alleviate symptoms and improve executive function in ADHD [36, 38, 41-48]. Below we review clinical trials in ADHD of drugs that modulate nAChR function including trials of nicotine, novel nicotinic agonists, and cholinesterase inhibitors. Studies were included in this review if they administered a treatment for at least 24 hours, and measured ADHD symptoms as a primary outcome. Thus

several laboratory studies of the acute effects of nicotine and nicotinic agonists are not reviewed.

Table 1 includes randomized placebo-controlled trials (RPCT) of nicotinic agonists that used a clinician rating of ADHD symptoms as a primary outcome. Table 2 includes additional clinical trials of nicotinic agents administered for at least 24 hours.

2. Trials of Nicotine

2.1 RPCTs of Nicotine

While multiple studies of transdermal nicotine in ADHD show short-term (proof of concept) improvements in ADHD symptoms [38, 41, 44, 45, 49, 50], only two RPCTs using a clinician rated outcome (as opposed to self report) have been reported; one in adults and one in children with ADHD. Levin and colleagues [51] examined the effects of 4 weeks of double blind treatment with placebo, transdermal nicotine, methylphenidate, or transdermal nicotine plus methylphenidate on adult ADHD symptoms assessed by the Clinical Global Impression scale. This was a between groups study with forty subjects enrolled (10 per drug treatment group) and 34 subjects included in the analysis of the primary outcome variable. Results found initial (day 1) improvements in clinical global impression associated with nicotine alone, however this effect did not persist across the four week trial. Neither methlyphenidate alone nor nictoine plus methylphenidate improved clinical global impression over placebo at any time point. The authors suggest that the lack of efficacy of methylphenidate may indicate that the study was underpowered. Cognitive function (variability in response time) was improved with nicotine alone and nicotine in combination with methylphenidate during both acute and chronic phases of this study. A reduction in subject rated depressive symptoms was seen on day 15 in the nicotine and nicotine plus methylphenidate groups; and on day 21 in the methylphendiate alone group. Side effects of transdermal nicotine in the non–smoking subjects included transient dizziness, lightheadedness and nausea, which resolved within 1 hour of patch administration.

A small randomized placebo controlled between groups study of 10 (5 per group) children (ages 8-13) examined the effects of transdermal nicotine (7 mg) on ADHD symptoms assessed using the Connors Parent Rating Scale (CPRS; [52]) and the Clinical Global Impressions [46]. In this study 7 days of transdermal nicotine improved the Learning Problems subscale of the CPRS, which measures inattention and academic problems. The hyperactivity, conduct problems, psychosomatic, impulsive and anxiety subscales did not show improvement, nor did the clinical global impressions. There was no neuropsychological testing or mood ratings, and daytime side effects (nausea, dizziness, itching under the patch) led to dose reduction in most of the subjects [46].

2.2 Other Trials of Nicotine

Gehricke and colleagues [53] examined the effects of 2 days of transdermal nicotine or placebo treatment both with and without psychostimulants in 10 (abstinent) cigarette smokers with ADHD. Subjects reported on their mood and symptoms using an e-diary and these ratings were the primary endpoint of the study. Results inidcated that nicotine alone, psychostimulants alone, and nicotine plus psychostimulants signficinatly improved self-

reported ADHD symptoms including difficulty concentrating, and daydreaming/zoning out compared to placebo. Subject rated impatience was reduced in the combined nicotine plus psychostimulant treatment compared to placebo, and no change in depression ratings were found. This study did not measure neuropsychological performance, and side effects were not reported. The results of this study should be interpreted cautiously due to limitations including open label dosing and the manipulation inducing acute nicotine withdrawal prior to dosing. Thus it is unknown if the effects are related to alleviation of nicotine withdrawal or improvement in ADHD symptoms.

Gehricke and colleagues [42] conducted a larger study in smokers (n=52) and non-smokers (n=27) with ADHD using an e-diary to collect self-ratings of ADHD symptoms. Subjects were treated for two days with double-blind 7 mg nicotine/placebo patch. Side effects including nausea and dizziness were seen, with greater side effects in the non-smokers. Significant reductions in ADHD symptoms were seen in the nicotine compared to placebo condition. Mood rating showed improvement (decreased anger, nervousness and stress) associated with nicotine administration in both smokers and non-smokers with ADHD. Neuropsychological tests were not administered in this study.

2.3 Summary

Taken together, initial studies of transdermal nicotine with and without psychostimulants provide mixed support for the hypothesis that nicotinic stimulation alleviates ADHD symptoms. Several experimental studies show “proof of concept” symptom reduction using acute dose schedules while the one RPCT in adults using a clinician rating as a primary outcome saw initial but not sustained improvement. This raises the possibility that tolerance may develop to the clinical effects of nicotine. This could occur due to receptor desensitization which occurs particularly at low concentrations of nicotine [54]. However, in a large trial of transdermal nicotine in mild cognitive impairment (6 months) there was no evidnece of tolerance to the beneficial effects of nicotine [55] suggesting that tolerance to the cognitive effects of nicotine does not develop. Further, the Levin and colleagues study [51] which found initial but not sustained effects of nicotine failed to find sustained benefit of methylphenidate raising the possibility that the study design was insufficient to see sustained benefit of either drug. Trials of longer duration are needed in adult ADHD to determine if clinical benefits can be sustained with repeated drug administration, and studies are needed in children to determine if there is a tolerable dosing schedule for children.

It is interesting that in the RPCT where there was not a sustained clinical benefit of nicotine on ADHD symptoms, there were long-lasting positive effects on mood and cognition. Decreases in depressive symptoms, impatience and negative mood were seen both acutely and chronically as were improvements in sustained attention. This raises the possibility that nAChR stimulation may improve the dysregulations of mood and cognitive deficits that are frequently features of ADHD.

3. Trials of Cholinesterase Inhibitors

3.1 RPCTs of Cholinesterase Inhibitors

There has been one RPCT of galantamine in adult ADHD [56]. This study was a 12 week, parallel group trial in adults with ADHD (24 per group) using Clinical Global Impressions as the primary indicator of clinical efficacy. This study found galanatime to be well tolerated; however there was no reduction of ADHD symptoms seen with this drug. No measures of mood or cognition were included in this study [56].

3.2 Other Trials of Cholinesterase Inhibitors

The anti-cholinesterase drug donepezil has been reported in a case series [57] of children, and an open label trial of children and adults [58] to reduce ADHD symptoms when used as an adjunctive treatment to psychostimulants. In a retrospective case series of children who did not achieve satisfactory clinical benefit from psychostimulants, in all cases there was a reduction in CGI illness severity ratings [57]. This was followed by an open label trial of donepezil as an adjunct to psychostimulant treatment in 7 children and 6 adults with ADHD [58]. This trial failed to replicate the initial positive report and concluded that adding donepezil to psychostimulant treatment is not well tolerated with side effects including gastrointestinal distress and irritability. Neuropsychological testing was not done and mood was not measured in this study [58].

3.3 Summary

These studies suggest that anti-cholinesterase drugs, while efficacious in treating other disorders, are unlikely to be a useful treatment for ADHD. This may be due to the non-specificity of these drugs, leading investigators to examine sub-type specific agonists of α4β2nicotinic receptors for treatment of ADHD.

4. Trials of α4β2 Agonists

4.1 RPCTs of α4β2 Agonists

Several specific agonists at α4β2 nicotinic receptors have been developed and tested as primary treatments for ADHD. These include ABT-089, ABT-418, ABT-894, AZD1446 and AZD3480. Results from five RPCTs of ABT-089 in ADHD (3 in adults and 2 in children) are available. A small within subjects crossover study in adult ADHD (n=11) found significantly improved symptoms measured by the Conner's Adult ADHD Rating Scale – Investigator (CAARS-INV), the primary clinical endpoint of this study [48]. This study additionally found improved CGI and improvement on neuropsychological tests of two domains of executive function (working memory and impulsive responding) compared to placebo. Ratings of anxiety and depression were low at baseline and were unchanged by the drug. ABT-089 was well tolerated with only mild/moderate side effects reported that were not dose limiting [48]. A large (n=171) multi-center crossover trial of ABT-089 in adults [59] found a reduction on the primary endpoint, the CAARS-INV total score. Neuropsychological testing was not included in this study. Although independent measures of emotion regulation/mood were not included in this trial, subject ratings were significantly lower on the impulsive/emotional lability and self-concept problems scales of the Conner's

Adult ADHD Rating Scale – Self (CAARS-S) during ABT-089 treatment periods compared to placebo. ABT-089 was well tolerated with the incidence of adverse events similar between ABT-089 and placebo [59]. A parallel group study of ABT-089 compared to placebo in 137 (of 159) complete subjects did not find any evidence of efficacy measured by the CAARS-INV total score or CGI although as a pilot study, the trial was not statistically powered to detect such an effect [60]. Neuropsychological testing was not completed, and mood was not assessed. This study reported that the total score on the CAARS-S was not changed, however it did not report individual CAARS-S subscales (including those measuring impulsive/emotional lability and self-concept). Adverse event rates were similar between the two doses of ABT-089 and placebo in this study [60]. Two multicenter between groups studies have been conducted in children with ADHD [61]. The first study (total n=274; with n=271 in the primary outcome analysis) tested 4 doses of ABT-089, atomoxetine, and placebo during 8 weeks of treatment; and used the ADHD-RS-IV (HV) as the primary outcome measure. There was no significant effect of ABT-089 compared to placebo on ADHD symptoms, while there was a significant reduction in symptoms seen in the atomoxetine treatment group compared to placebo. In the second study, 119 subjects (n=115 in the efficacy analysis) were randomized to receive one of two doses of ABT-089 or placebo for a 6 week treatment period and the ADHD Rating Scale –IV Home Version (ADHD-RS-IV (HV)) was the specified primary outcome measure. In this study there was no significant effect of either dose of ABT-089 compared to placebo on ADHD symptoms [61]. Neither study included neuropsychological testing or measures of mood. Across both studies there were no side effects of ABT-089 seen with greater frequency than placebo [61]. Thus, in studies of ABT-089, two of the three trials in adults with ADHD showed significant clinical benefit, while neither study in children found evidence of efficacy.

Four other $\alpha 4\beta 2$ nicotinic agonists have been examined in RPCTs for treating ADHD. The clinical effects of ABT-418 were examined in a pilot (n=32) crossover trial of three weeks of treatment, in adults with ADHD, using improvement in either CGI or ARS as pre-specified clinical endpoints [47]. The study met both endpoints with significantly reduced symptoms and improved CGI ratings compared to placebo. Symptoms of anxiety and depression were not significantly affected by the drug, and neuropsychological performance was not examined in this study. Side effects of ABT-418 included dizziness, nausea and skin irritation, with 6 of 29 subjects having a dose adjustment to manage side effects [47]. A multi-center trial of ABT-894used a mixed design with subject assigned to one of four doses of ABT-894 or atomoxetine (as an active comparator) and placebo during two randomly assigned 4 week treatment periods [62]. Two hundred and two adults with ADHD completed the trial, with 196 included in the efficacy analysis, where the CAARS-INV Total Score was the pre-specified primary endpoint. Statistically significant improvements were found on the CAARS-INV total ADHD symptoms subscale and CGI related to the highest dose of ABT-894 (4 mg twice daily [BID]) and atomoxetine. All of the CAARS-S subscales (including problems with self-concept and impulsivity/emotion lability) were improved with ABT-894 treatment. Neuropsychological performance was not examined in this study. ABT-894 was well tolerated with no dose-limiting side effects seen. Nausea was seen in 12.1% of subjects across all doses of ABT-894 compared to 2.2% with placebo and 20.0% with atomoxetine [62]. The authors noted reduced frequency of side effects with BID dosing

of ABT-894 and suggested that BID dosing or an extended release formulation may improve the side effect profile without compromising therapeutic dosing [62]. A third novel nicotinic agonist, AZD1446 was tested in 79 adults with ADHD in a multi-center mixed design with each subject receiving two doses of AZD1446 and placebo during a two week treatment period in a random order [63]. This study did not find significant improvement on the CAARS-INV Total ADHD Symptoms score (the primary clinical endpoint) or CGI [63]. The highest dose of AZD1446 was associated with significant improvement on a test of executive function (Groton maze learning) in non-smoking subjects. There were no significant drug related effects on the CAARS-S sub-scales that measure impulsivity/ emotion lability or self-concept. Side effects associated with AZD1446 included nausea and headache, however most side effects were mild/moderate and did not require intervention [63]. Finally, two weeks of treatment with AZD3480 and placebo was tested in a crossover trial of 30 (24 complete) adults with ADHD using the CAARS-INV total ADHD symptoms subscale as a primary endpoint [64]. This study found significant improvements on the CAARS-INV with the highest dose of AZD3480 (50 mg) tested. Neuropsychological improvements were seen in response inhibition on the Stop Signal Task, and the impulsivity/ emotional lability subscale of the CAARS-S was improved with both doses of AZD3480 tested. Side effects of AZD3480 were mild/moderate and similar in type and number to those seen with placebo [64].

In summary, four different α4β2 nicotinic agonists have shown efficacy in the majority (5 of 7) of RPCTs in adult ADHD, with tolerable side effect profiles. Several of these agonists have shown evidence of improved neuropsychological performance and self-reported mood, areas of impairment in ADHD that are not well treated with existing pharmacotherapies. However, many studies do not systematically measure neuropsychological performance or mood directly thus our understanding of the clinical benefit of nAChR agonists in these domains is limited. Trials in children (ABT-089 in two separate studies) showed no clinical benefit although the drug was well tolerated at the doses tested.

5. Discussion

Overall there are 13 studies of nicotine and/or α4β2 agonists of at least 24 hour duration that measured ADHD symptoms as an outcome. Of these studies 9 reported statistically significant reduction in symptoms, and 4 trials were negative. Generally, studies that used a within-subjects design were more successful than studies using between group comparisons (7 of 8 crossover studies and 2 of 5 between group studies met the primary endpoint). It should also be noted that 3 of the between group studies were in children (1 positive and 2 negative). The simplest explanation for this would be that the effect sizes related to nicotinic agonists are small, and are not detectable in crossover studies limiting the clinical utility of nicotinic agonists. While only four studies reported effect sizes, the range of effect sizes (. 29, .45, .76, .74) are comparable to the effect sizes reported in a meta-analysis of ADHD treatments [65]. That study found the average effect size for efficacy measured by the CAARS-INV for non-stimulant medications was .39, and for stimulant formulations was . 76. Thus it is unlikely that the effects of nicotinic agonists are not clinically meaningful. An alternate explanation for the difference in findings in crossover and parallel group designs may relate to the heterogeneity within the categorical diagnosis of ADHD. DSM-IV

diagnostic criteria (used by all of the reviewed studies) require 6 of 9 clinically significant symptoms in at least one ADHD domain (inattentive and hyperactive/impulsive) resulting in over 3000 different potential symptom combinations within the diagnosis of ADHD [66]. Given this, it may be that nicotinic agonists are effective for a subgroup of individuals, perhaps with a specific symptoms profile, however detecting these effects may be particularly difficult in between group studies. The simplest way to examine this would be to look at diagnostic subtype, however studies of psychostimulant and non-stimulant treatments for ADHD do not show differential efficacy by ADHD subtype [67-70]. This is not surprising given the considerable overlap of symptoms within each diagnostic subtype. Thus, examining individual differences in response to medications using a more objective measure, such as cognitive performance may improve detection of clinically significant effects. Indeed, in a recent study of AZD3480 [64], the authors found that baseline cognitive performance and not baseline symptoms were related to treatment response (improved symptoms).

The available literature suggests that stimulating α4β2 nicotinic receptors has benefits to core aspects of cognition affecting many individuals with ADHD. Improvement in cognition with stimulation of α4β2 nAChRs has been seen across many different cognitive outcome measures including response inhibition, variability in reaction time, and executive function. Additionally, multiple studies have noted acute effects of nicotine on cognition in ADHD [38, 44, 45, 49], strengthening the findings of improved cognition in clinical trials with multiple outcome measures. Review of these clinical trials also suggests that cognitive function may be more sensitive than global symptom measures at detecting effects of nicotinic agents. It has been proposed [64] that integrating clinical and cognitive models of ADHD may be useful in designing clinical trials to understand both the therapeutic potential of an agent and the neurobiological mechanism by which the symptoms of ADHD improve.

Nicotine has an inverted U dose-response curve [71] and thus it is possible that some drugs with significant therapeutic potential may produce negative results by testing doses that are both too high and too low to detect clinical effects. This highlights the importance of early stage dose ranging studies prior to large clinical trials. In addition to the inverted U dose-response curve, stimulating nAChRs produces well known rate dependent effects on behavior [72]. This, along with the heterogeneity within the ADHD diagnosis makes it challenging to effectively test nAChR agonists in ADHD. Future studies that characterize the relationship between cognitive, emotional, and behavioral symptoms of ADHD, and describe how these contribute to functional impairments are needed to understand the individual variability in treatment response to nAChR agents. The rate dependency of nicotinic agents is markedly different from the psychostimulants which have more consistent effects across subject groups [73, 74]. Thus, using trial designs and measures developed in trials of psychostimulants may not be appropriate.

The side effect profile of nicotinic agonists is generally favorable with side effects related to cholinergic stimulation most common (nausea, dizziness, stomach upset). Most studies reported mild/moderate side effects that were manageable with the exception of studies in children in which side effects were dose limiting. The study of ABT-894 [62], found reduced frequency of side effects and higher plasma drug levels using BID dosing. While

BID dosing may raise compliance problems in patients with ADHD [75, 76] there is evidence that compliance is greater with extended release formulations of medications for ADHD [76]. Thus, developing an extended release nicotinic agonist may allow greater therapeutic benefit with fewer side effects

Literature indicating that cigarette smokers are more impulsive than non-smokers [77-81], raises the concern that nicotinic treatments for ADHD may have deleterious behavioral effects in those with milder forms of ADHD. This is particularly relevant as the diagnostic threshold for adults diagnosed with ADHD has been lowered in DSM-5. Within the smoking literature, it has been suggested that increased impulsivity is a pre-existing vulnerability to smoking and not a consequence of nicotine administration [79, 82, 83]. The literature on nicotine administration in healthy volunteers demonstrates mixed results with reports of improved, impaired and no change in various types of performance [42, 84-89]. For example, in separate studies, nicotine has been shown to decrease and increase reward responsiveness in non-smokers [86, 89]. Similarly nicotine has been shown to have no effect on risk taking in healthy subjects [89], and to reduce risk taking in those with high baseline risk taking [90]. This is consistent with the rate-dependent effects of nicotine across cognitive and emotional domains [72]. For example, Wignall & de Wit found beneficial effects of nicotine on interference control in underperforming participants [89]. There is little evidence for significant behavioral or cognitive impairments following nicotine administration in control subjects, suggesting that the likelihood of causing behavioral/cognitive dysfunction in sub-threshold ADHD is not high.

6. Conclusion

Behavioral targets for novel ADHD treatments include core symptoms of inattention, hyperactivity and impulsivity as well as emotion regulation and cognitive function. Trials of nicotine and novel nicotinic agonists show evidence for symptom improvement in adult ADHD. In addition improvements in cognitive function, emotion lability, self-esteem, irritability, and depressive symptoms have been reported. These promising results suggest that future studies should capture changes in neuropsychological performance and mood associated with new treatments. However, understanding how these improvements relate to ADHD symptoms is lacking.

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References

1. Polanczyk G, et al. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007; 164(6):942–8. [PubMed: 17541055]
2. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol Med. 2006; 36(2):159–65. [PubMed: 16420712]
3. Pelham WE, Foster EM, Robb JA. The economic impact of attention-deficit/hyperactivity disorder in children and adolescents. J Pediatr Psychol. 2007; 32(6):711–27. [PubMed: 17556402]

4. Lange KW, et al. The history of attention deficit hyperactivity disorder. Atten Defic Hyperact Disord. 2010; 2(4):241–55. [PubMed: 21258430]
5. American Psychiatic Association. Diagnostic and Statisical Manual of Mental Disorders (DSM-II). 2nd Edition ed.. American Psychiatric Association; Washington, DC: 1968.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-III). 3rd Edition ed.. American Psychiatric Association; Washington, DC: 1980.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Revised 4th ed.. American Psychiatric Association; Washington, DC: 2000.
8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th edition ed.. U.S. Government Printing Office; 1994.
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 5 2013. American Psychiatric Association; Arlington, VT:
10. Castellanos, FX. [2014 April] DSM-5 ADHD and Disruptive Behavior Disorders Work Group. 2009. Available from: http://www.DSM-5.org/progressreports/pages/0904dsm-vadhdanddisruptivebehaviordisordersworkgroup.aspx
11. Willcutt EG, et al. Validity of DSM-IV attention deficit/hyperactivity disorder symptom dimensions and subtypes. J Abnorm Psychol. 2012; 121(4):991–1010. [PubMed: 22612200]
12. Lahey BB, Willcutt EG. Predictive validity of a continuous alternative to nominal subtypes of attention-deficit/hyperactivity disorder for DSM-V. J Clin Child Adolesc Psychol. 2010; 39(6): 761–75. [PubMed: 21058124]
13. Thompson RA. Emotion regulation: a theme in search of definition. Monogr Soc Res Child Dev. 1994; 59(2-3):25–52. [PubMed: 7984164]
14. Shaw P, et al. Emotion dysregulation in attention deficit hyperactivity disorder. Am J Psychiatry. 2014; 171(3):276–93. [PubMed: 24480998]
15. Stringaris A. Irritability in children and adolescents: a challenge for DSM-5. Eur Child Adolesc Psychiatry. 2011; 20(2):61–6. [PubMed: 21298306]
16. Sobanski E, et al. Emotional lability in children and adolescents with attention deficit/hyperactivity disorder (ADHD): clinical correlates and familial prevalence. J Child Psychol Psychiatry. 2010; 51(8):915–23. [PubMed: 20132417]
17. Stringaris A, Goodman R. Mood lability and psychopathology in youth. Psychol Med. 2009; 39(8): 1237–45. [PubMed: 19079807]
18. Wehmeier PM, Schacht A, Barkley RA. Social and emotional impairment in children and adolescents with ADHD and the impact on quality of life. J Adolesc Health. 2010; 46(3):209–17. [PubMed: 20159496]
19. Barkley RA, Fischer M. The unique contribution of emotional impulsiveness to impairment in major life activities in hyperactive children as adults. J Am Acad Child Adolesc Psychiatry. 2010; 49(5):503–13. [PubMed: 20431470]
20. Amiri S, et al. Modafinil as a treatment for Attention-Deficit/Hyperactivity Disorder in children and adolescents: a double blind, randomized clinical trial. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(1):145–9. [PubMed: 17765380]
21. Biederman J, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. Clin Ther. 2007; 29(3):450–63. [PubMed: 17577466]
22. Spencer TJ, et al. Efficacy and safety of mixed amphetamine salts extended release (Adderall XR) in the management of attention-deficit/hyperactivity disorder in adolescent patients: a 4-week, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther. 2006; 28(2):266–79. [PubMed: 16678648]
23. Wigal SB, et al. A laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children with attention deficit/hyperactivity disorder. J Atten Disord. 2005; 9(1):275–89. [PubMed: 16371674]
24. Barkley RA. Attention-deficit/hyperactivity disorder, self-regulation, and time: toward a more comprehensive theory. J Dev Behav Pediatr. 1997; 18(4):271–9. [PubMed: 9276836]
25. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull. 1997; 121(1):65–94. [PubMed: 9000892]

26. Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. Journal of Child Psychology & Psychiatry & Allied Disciplines. 1996; 37(1):51–87.
27. Nikolas MA, Nigg JT. Neuropsychological performance and attention-deficit hyperactivity disorder subtypes and symptom dimensions. Neuropsychology. 2013; 27(1):107–20. [PubMed: 23148496]
28. Nigg JT, et al. Executive functions and ADHD in adults: evidence for selective effects on ADHD symptom domains. J Abnorm Psychol. 2005; 114(4):706–17. [PubMed: 16351391]
29. Martel M, Nikolas M, Nigg JT. Executive function in adolescents with ADHD. J Am Acad Child Adolesc Psychiatry. 2007; 46(11):1437–44. [PubMed: 18049293]
30. Fischer M, et al. The adolescent outcome of hyperactive children diagnosed by research criteria: II. Academic, attentional, and neuropsychological status. J Consult Clin Psychol. 1990; 58(5):580–8. [PubMed: 2254504]
31. Seidman LJ. Neuropsychological functioning in people with ADHD across the lifespan. Clinical Psychology Review. 2006; 26(4):466–85. [PubMed: 16473440]
32. Seidman LJ, et al. Toward defining a neuropsychology of attention deficit-hyperactivity disorder: performance of children and adolescents from a large clinically referred sample. J Consult Clin Psychol. 1997; 65(1):150–60. [PubMed: 9103744]
33. Gualtieri CT, Johnson LG. Medications do not necessarily normalize cognition in ADHD patients. J Atten Disord. 2008; 11(4):459–69. [PubMed: 17934180]
34. Wilens TE, et al. Pharmacotherapy of adult attention deficit/hyperactivity disorder: a review. J Clin Psychopharmacol. 1995; 15(4):270–9. [PubMed: 7593710]
35. Spencer, et al. A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005; 57(5):456–63. [PubMed: 15737659]
36. Wilens TE, Decker MW. Neuronal nicotinic receptor agonists for the treatment of attention-deficit/hyperactivity disorder: focus on cognition. Biochem Pharmacol. 2007; 74(8):1212–23. [PubMed: 17689498]
37. Potter AS, Newhouse PA, Bucci DJ. Central nicotinic cholinergic systems: a role in the cognitive dysfunction in attention-deficit/hyperactivity disorder? Behav Brain Res. 2006; 175(2):201–11. [PubMed: 17081628]
38. Levin ED, et al. Nicotine effects on adults with attention-deficit/hyperactivity disorder. Psychopharmacology (Berl). 1996; 123(1):55–63. [PubMed: 8741955]
39. Singh A, Potter A, Newhouse P. Nicotinic acetylcholine receptor system and neuropsychiatric disorders. IDrugs. 2004; 7(12):1096–103. [PubMed: 15599803]
40. Wilens TE, Spencer TJ, Biederman J. A review of the pharmacotherapy of adults with attention-deficit/hyperactivity disorder. J Atten Disord. 2002; 5(4):189–202. [PubMed: 11967475]
41. Conners CK, et al. Nicotine and attention in adult attention deficit hyperactivity disorder (ADHD). Psychopharmacol Bull. 1996; 32(1):67–73. [PubMed: 8927677]
42. Gehricke JG, et al. Effects of transdermal nicotine on symptoms, moods, and cardiovascular activity in the everyday lives of smokers and nonsmokers with attention-deficit/hyperactivity disorder. Psychol Addict Behav. 2009; 23(4):644–55. [PubMed: 20025370]
43. Poltavski DV, Petros T. Effects of transdermal nicotine on attention in adult non-smokers with and without attentional deficits. Physiol Behav. 2006; 87(3):614–24. [PubMed: 16466655]
44. Potter AS, Newhouse PA. Acute nicotine improves cognitive deficits in young adults with attention-deficit/hyperactivity disorder. Pharmacol Biochem Behav. 2008; 88(4):407–17. [PubMed: 18022679]
45. Potter AS, Newhouse PA. Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder. Psychopharmacology (Berl). 2004; 176(2):182–94. [PubMed: 15083253]
46. Shytle RD, et al. A pilot controlled trial of transdermal nicotine in the treatment of attention deficit hyperactivity disorder. World J Biol Psychiatry. 2002; 3(3):150–5. [PubMed: 12478880]
47. Wilens TE, et al. A pilot controlled clinical trial of ABT-418, a cholinergic agonist, in the treatment of adults with attention deficit hyperactivity disorder. Am J Psychiatry. 1999; 156(12): 1931–7. [PubMed: 10588407]

48. Wilens TE, et al. ABT-089, a neuronal nicotinic receptor partial agonist, for the treatment of attention-deficit/hyperactivity disorder in adults: results of a pilot study. Biological Psychiatry. 2006; 59(11):1065–70. [PubMed: 16499880]
49. Potter AS, Bucci DJ, Newhouse PA. Manipulation of nicotinic acetylcholine receptors differentially affects behavioral inhibition in human subjects with and without disordered baseline impulsivity. Psychopharmacology (Berl). 2012; 220(2):331–40. [PubMed: 21969123]
50. Potter AS, Ryan KK, Newhouse PA. Effects of acute ultra-low dose mecamylamine on cognition in adult attention-deficit/hyperactivity disorder (ADHD). Hum Psychopharmacol. 2009; 24(4): 309–17. [PubMed: 19475630]
51. Levin ED, et al. Effects of chronic nicotine and methylphenidate in adults with attention deficit/hyperactivity disorder. Experimental & Clinical Psychopharmacology. 2001; 9(1):83–90. [PubMed: 11519638]
52. Conners CK, et al. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol. 1998; 26(4):257–68. [PubMed: 9700518]
53. Gehricke JG, et al. The reinforcing effects of nicotine and stimulant medication in the everyday lives of adult smokers with ADHD: A preliminary examination. Nicotine Tob Res. 2006; 8(1):37–47. [PubMed: 16497598]
54. Giniatullin R, Nistri A, Yakel JL. Desensitization of nicotinic ACh receptors: shaping cholinergic signaling. Trends Neurosci. 2005; 28(7):371–8. [PubMed: 15979501]
55. Newhouse P, et al. Nicotine treatment of mild cognitive impairment: a 6-month double-blind pilot clinical trial. Neurology. 2012; 78(2):91–101. [PubMed: 22232050]
56. Biederman J, et al. A double-blind comparison of galantamine hydrogen bromide and placebo in adults with attention-deficit/hyperactivity disorder: a pilot study. J Clin Psychopharmacol. 2006; 26(2):163–6. [PubMed: 16633145]
57. Wilens TE, et al. Adjunctive donepezil in attention deficit hyperactivity disorder youth: case series. J Child Adolesc Psychopharmacol. 2000; 10(3):217–22. [PubMed: 11052411]
58. Wilens TE, et al. An open trial of adjunctive donepezil in attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2005; 15(6):947–55. [PubMed: 16379515]
59. Apostol G, et al. Efficacy and safety of the novel alpha(4)beta(2) neuronal nicotinic receptor partial agonist ABT-089 in adults with attention-deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled crossover study. Psychopharmacology (Berl). 2012; 219(3):715–25. [PubMed: 21748252]
60. Bain EE, et al. A randomized pilot study of the efficacy and safety of ABT-089, a novel alpha4beta2 neuronal nicotinic receptor agonist, in adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2012; 73(6):783–9. [PubMed: 22795204]
61. Wilens TE, et al. Safety and efficacy of ABT-089 in pediatric attention-deficit/hyperactivity disorder: results from two randomized placebo-controlled clinical trials. J Am Acad Child Adolesc Psychiatry. 2011; 50(1):73–84. e1. [PubMed: 21156272]
62. Bain EE, et al. A randomized, double-blind, placebo-controlled phase 2 study of alpha4beta2 agonist ABT-894 in adults with ADHD. Neuropsychopharmacology. 2013; 38(3):405–13. [PubMed: 23032073]
63. Jucaite A, et al. A randomized, double-blind, placebo-controlled crossover study of alpha4beta 2* nicotinic acetylcholine receptor agonist AZD1446 (TC-6683) in adults with attention-deficit/hyperactivity disorder. Psychopharmacology (Berl). 2014; 231(6):1251–65. [PubMed: 23640072]
64. Potter AS, et al. AZD3480, a novel nicotinic receptor agonist, for the treatment of attention-deficit/hyperactivity disorder in adults. Biol Psychiatry. 2014; 75(3):207–14. [PubMed: 23856296]
65. Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. J Clin Psychiatry. 2010; 71(6):754–63. [PubMed: 20051220]
66. Joober R. On the simple and the complex in psychiatry, with reference to DSM 5 and Research Domain Criteria. J Psychiatry Neurosci. 2013; 38(3):148–51. [PubMed: 23601364]

67. Tanaka Y, et al. A meta-analysis of the consistency of atomoxetine treatment effects in pediatric patients with attention-deficit/hyperactivity disorder from 15 clinical trials across four geographic regions. J Child Adolesc Psychopharmacol. 2013; 23(4):262–70. [PubMed: 23683141]
68. Solanto M, et al. Stimulant drug response in the predominantly inattentive and combined subtypes of attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2009; 19(6):663–71. [PubMed: 20035584]
69. Mattingly G, et al. Attention deficit hyperactivity disorder subtypes and symptom response in adults treated with lisdexamfetamine dimesylate. Innov Clin Neurosci. 2012; 9(5-6):22–30. [PubMed: 22808446]
70. Gorman EB, et al. Effects of methylphenidate on subtypes of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006; 45(7):808–16. [PubMed: 16832317]
71. Picciotto MR. Nicotine as a modulator of behavior: beyond the inverted U. Trends Pharmacol Sci. 2003; 24(9):493–9. [PubMed: 12967775]
72. Perkins KA. Baseline-dependency of nicotine effects: a review. Behavioural Pharmacology. 1999; 10(6-7):597–615. [PubMed: 10780501]
73. Rapoport JL, et al. Dextroamphetamine. Its cognitive and behavioral effects in normal and hyperactive boys and normal men. Archives of General Psychiatry. 1980; 37(8):933–43. [PubMed: 7406657]
74. Rapoport JL, Inoff-Germain G. Responses to methylphenidate in Attention-Deficit/Hyperactivity Disorder and normal children: update 2002. J Atten Disord. 2002; 6(Suppl 1):S57–60. [PubMed: 12685519]
75. Adler LA, et al. Medication adherence and symptom reduction in adults treated with mixed amphetamine salts in a randomized crossover study. Postgrad Med. 2011; 123(5):71–9. [PubMed: 21904088]
76. Adler LD, Nierenberg AA. Review of medication adherence in children and adults with ADHD. Postgrad Med. 2010; 122(1):184–91. [PubMed: 20107302]
77. Bickel WK, Odum AL, Madden GJ. Impulsivity and cigarette smoking: delay discounting in current, never, and ex-smokers. Psychopharmacology. 1999; 146(4):447–54. [PubMed: 10550495]
78. Doran N, et al. Impulsivity and smoking relapse. Nicotine Tob Res. 2004; 6(4):641–7. [PubMed: 15370160]
79. Krishnan-Sarin S, et al. Behavioral impulsivity predicts treatment outcome in a smoking cessation program for adolescent smokers. Drug Alcohol Depend. 2007; 88(1):79–82. [PubMed: 17049754]
80. Mitchell SH. Measuring impulsivity and modeling its association with cigarette smoking. Behav Cogn Neurosci Rev. 2004; 3(4):261–75. [PubMed: 15812110]
81. Ryan KK, Mackillop J, Carpenter MJ. The relationship between impulsivity, risk-taking propensity and nicotine dependence among older adolescent smokers. Addict Behav. 2013; 38(1):1431–4. [PubMed: 23006247]
82. Heffner JL, et al. Relationship between cigarette smoking and childhood symptoms of inattention and hyperactivity/impulsivity in alcohol-dependent adults without attention-deficit hyperactivity disorder. Nicotine Tob Res. 2010; 12(3):243–50. [PubMed: 20083646]
83. Kollins SH, McClernon FJ, Fuemmeler BF. Association between smoking and attention-deficit/hyperactivity disorder symptoms in a population-based sample of young adults. Archives of General Psychiatry. 2005; 62(10):1142–1147. [PubMed: 16203959]
84. Avila MT, et al. Effects of nicotine on leading saccades during smooth pursuit eye movements in smokers and nonsmokers with schizophrenia. Neuropsychopharmacology. 2003; 28(12):2184–91. [PubMed: 12968127]
85. Barr RS, et al. The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. Neuropsychopharmacology. 2008; 33(3):480–90. [PubMed: 17443126]
86. Barr RS, et al. A single dose of nicotine enhances reward responsiveness in nonsmokers: implications for development of dependence. Biol Psychiatry. 2008; 63(11):1061–5. [PubMed: 17976537]
87. Jubelt LE, et al. Effects of transdermal nicotine on episodic memory in non-smokers with and without schizophrenia. Psychopharmacology (Berl). 2008; 199(1):89–98. [PubMed: 18548234]

88. Martin-Solch C, et al. Changes in brain activation associated with reward processing in smokers and nonsmokers. A positron emission tomography study. Experimental brain research.Experimentelle Hirnforschung.Experimentation cerebrale. 2001; 139(3):278–286.

89. Wignall ND, de Wit H. Effects of nicotine on attention and inhibitory control in healthy nonsmokers. Exp Clin Psychopharmacol. 2011; 19(3):183–91. [PubMed: 21480731]

90. Ryan KK, Dube SL, Potter AS. Rate dependent effects of acute nicotine on risk taking in young adults are not related to ADHD diagnosis. Pharmacol Biochem Behav. 2013; 103(3):652–8. [PubMed: 23159875]

Key Points

1. Stimulation of α4β2 nicotinic cholinergic receptors reduces symptoms of adult ADHD with mild/moderate side effects in the majority of (though not all) published studies.
2. Challenges to drug development and dose selection for novel nicotinic agonists include the occurrence of cholinergic side effects, receptor desensitization at higher doses, and nicotinic receptor subtype specificity.
3. The heterogeneity of symptom presentations in adult ADHD likely contributes to the mixed results seen in the literature, and to the individual variability in response to nAChR agonists.
4. The literature suggests benefits of nAChR agonists on cognitive function including attention, response inhibition and cognitive control and emotional processes including mood lability, irritability and negative affect in ADHD however the clinical significance of these findings is unknown.

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Table 1

Randomized Placebo-Controlled Trials of Nicotinic Agonists that use a Clinician Rating of ADHD Symptoms as a Primary Outcome.

RPCT [reference #]	Sample Size[a]	Female	Age Mean (SD)	Research Design	Smoking Status	Duration of Treatment	Nicotinic Treatment	1° Clinical Endpoint	1° Clinical Measure Met (Y/N), Effect Size
Trials in Adults									
Levin et al., 2001 [51]	34	37.5%	19 – 56[b]	Between	Non-smokers	4 weeks	Nicotine	CGI	No, N/A
Wilens et al., 2006 [48]	11	45.5%	32.0 (10.15)	Within	Non-smokers	2 weeks	ABT-089	CAARS-INV	Yes, ES=.92
Apostol et al., 2012 [59]	171	32%	38.6 (11.34)	Within	Both	4 weeks	ABT-089	CAARS-INV	Yes, ES=.30
Bain et al., 2012 [60]	137	38%	35.9 (N/A)	Between	Both	8 weeks	ABT-089	CAARS-INV	No, N/A
Wilens et al., 1999 [47]	32	12%	40.3 (9.4)	Within	Both	3 weeks	ABT-418	CGI or ARS	Yes, N/A
Bain et al., 2013 [62]	196	47%	36.2 (11.85)	Within	Both	4 weeks	ABT-894	CAARS-INV	Yes, ES=.45
Potter et al., 2014 [64]	24	25%	44.3 (N/A)	Within	Non-smokers	2 weeks	AZD3480	CAARS-INV	Yes, ES (d)=.74
Jucaite et al., 2014 [63]	79	13%	33.7 (N/A)	Within	Both	2 weeks	AZD1446	CAARS-INV	No, N/A
Trials in Children									
Shytle et al., 2002 [46]	10	40%	10 (0.8)	Between	Non-smokers	7 days	Nicotine	CPRS and CGI	Yes, N/A
Wilens et al., 2011 [61][1]	271	34%	8.6 (N/A)	Between	Non-smokers	8 weeks	ABT-089	ADHD-RS-IV (HV)	No, N/A
Wilens et al., 2011 [61][2]	115	34%	8.5 (N/A)	Between	Non-smokers	6 weeks	ABT-089	ADHD-RS-IV (HV)	No, N/A

Abbreviations: RPCT = Randomized Placebo Controlled Trial; Between = between subjects; Within = within subjects; N/A = not available; CPRS = Conner's Parent Rating Scale; CGI = Clinical Global Impression; AISRS = ADHD Investigator Symptom Report Scale; CAARS-INV = Conner's Adult ADHD Rating Scale, Investigator; ADHD-RS-IV (HV) TS = ADHD Rating Scale-IV Home Version; ARS = ADHD Rating Scale

[a] Sample Size refers to number analyzed in the primary clinical measure (% Female and Age are from reported demographics)

[b] mean (SD) not available, reported age range

[1] Wilens et al., 2011 includes studies 1 and 2, here we report them individually

[2]Wilens et al., 2011 includes studies 1 and 2, here we report them individually

Table 2

Additional Clinical Trials of Nicotinic Agents in ADHD.

Study [reference #]	Sample Size[a]	Female	Age Mean (SD)	Research Design	Smoking Status	Duration of Treatment	Nicotinic Treatment	1° Clinical Endpoint	1° Clinical Measure Met (Y/N), Effect Size	Reason for Exclusion from Table 1
Gehricke [42]	52	29%	27 (7.9)	RPCT Within	Both	2 day	Nicotine	e-diary self-report[b]	Yes, N/A	No clinician rating of ADHD
Gehricke [53]	10	50%	25 (6.2)	RPCT Within	Abstinent Smokers	2 day	Nicotine	e-diary self-report[b]	Yes, N/A	No clinician rating of ADHD, abstinent smokers
Wilens [58]	13	31%	26 (18.6)[c]	Open label	unspecified	12 week	Adjunct Donepezil	CGI	No, N/A	Open label; Not a nicotinic agonist
Wilens [57]	5	0%	8 - 17	Case Series	Non-Smokers	8-26 weeks	Adjunct Donepezil	CGI	Yes, N/A	Retrospective case series (open label); not a nicotinic agonist
Biederman [56]	36	50%	35.9 (7.8)	RPCT Between	N/A	12 week	Galantamine	CGI	No, N/A	Not a nicotinic agonist

Abbreviations: RPCT = Randomized Placebo Controlled Trial; Between = between subjects; Within = within subjects; N/A = not available; CPRS = Conner's Parent Rating Scale; CGI = Clinical Global Impression; AISRS = ADHD Investigator Symptom Report Scale; CAARS-INV = Conner's Adult ADHD Rating Scale, Investigator; ADHD-RS-IV (HV) TS = ADHD Rating Scale-IV Home Version; ARS = ADHD Rating Scale

[a] Sample Size refers to number analyzed in the primary clinical measure (% Female and Age are from reported demographics)

[b] There was no specified primary endpoint – effects on ADHD symptoms were reported as positive (see original article)

[c] This study included both children and adults, however as the results did not differ by age they are reported together