Acute Transdermal Nicotine Improves Cognitive Deficits in Children, Adolescents, and Young Adults with Attention Deficit Hyperactive Disorder

Tiana Rose Leilani Ahue

Pacific University
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Abstract

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Results: A total of 11 articles were screened for relevance. After this review, 2 articles met inclusion criteria. One study showed improvements of learning problems associated with ADHD after a 7 day transdermal nicotine application. The second study revealed improvements in impulse control and other cognitive deficits after a 45-minute transdermal nicotine administration.

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Keywords
Transdermal Nicotine, Nicotine, ADHD, Attention Deficit Hyperactive Disorder

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Tiana R.L Ahue

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Faculty Advisor: Mark Pedemonte, MD
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

Background: Attention deficit hyperactive disorder (ADHD) is described as a neurobiological syndrome affecting approximately 5% of children and adolescents as reported by the American Academy of Pediatrics in 2008. Problems in school are often a key clinical finding for children with ADHD. Children with ADHD are associated with low academic grades and poor academic performances. Current pharmacological treatments, like psychostimulants, help to decrease core behavioral symptoms and increase academic productivity, but overall performance on standardized tests are often unaffected. Previous research has shown those with ADHD are two times more likely to smoke cigarettes and initiate cigarette smoking at an earlier age in comparison to those without ADHD. Nicotine has proven beneficial with improvement of symptoms, moods, and cognitive functioning in studies containing both smoking and non-smoking adults with ADHD. This review will look at the effects of acute transdermal nicotine on cognitive functioning in children, adolescents, and young adults with attention deficit hyperactive disorder.

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Keywords: Attention deficits hyperactive disorder, transdermal nicotine, cognitive problems, adolescents, and young adults
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[Redacted for privacy]
# Table of Contents

Biography .......................................................................................................................... 2
Abstract ............................................................................................................................... 3
Acknowledgements ............................................................................................................. 4
Table of Contents ................................................................................................................. 5
List of Tables ....................................................................................................................... 6
List of Abbreviations ............................................................................................................. 6
Background ........................................................................................................................ 7
Methods .............................................................................................................................. 9
Results .................................................................................................................................. 9
Discussion .......................................................................................................................... 13
Conclusion ......................................................................................................................... 15
References ......................................................................................................................... 17
Table 1 Characteristics of Reviewed Studies ........................................................................ 19
List of Tables
Table 1  Quality Assessment of Reviewed Articles

List of Abbreviations
ADHD  Attention Deficit Hyperactive Disorder
CGI  Clinical Global Impression
CPRS  Conner’s Parent Rating Scale
DSM IV/V  The Diagnostic and Statistical Manual of Mental Disorders- 4\textsuperscript{th}/5\textsuperscript{th} edition
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BACKGROUND

Attention deficit hyperactive disorder (ADHD) is described as a neurobiological syndrome affecting approximately 5% of children and adolescents worldwide. ADHD is often associated with poor academic scores, increased grade retention, and low graduation rates. Pharmacological and behavior treatment modalities are associated with a reduction in symptoms and increase academic productiveness but without improvement in standardized test scores.

School-based problems are often a key clinical finding in initially identifying those with ADHD. The Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM V) defines ADHD as a persistent pattern of inattention and/or hyperactivity-impulsivity occurring before age 12 that interferes with functioning or development in two or more settings, (eg, home, school, or work) that has direct negative impacts on social, academic, or occupational functioning. A tool used to assist with the diagnosis of ADHD is called the Conner’s Comprehensive Behavior Rating Scale. It is a list of screening questions assessing for deficiencies in emotion, behavior, and academics witnessed by a parent, a teacher, and the child him or herself.

Even though, the diagnosis of ADHD is based primarily on subjective behavior problems, cognitive problems tend to be affected as well. A meta analysis performed in 2006 showed those with ADHD have problems with executive functioning. Prominent cognitive problems tend to be linked to behavior inhibition, working memory, regulation of motivation, motor control, and sustained attention, possibility contributing to overall low academic outcomes.
Currently approved pharmacological treatment modalities for ADHD involve psychostimulant medications such as methylphenidate (Ritalin), dexamethylphenidate (Focalin), or a combination dextroamphetamine-amphetamine (Adderall). Another issue with current psychostimulants is their potential addiction risk and cardiovascular risk. Therefore, careful monitoring and regular office visits are often needed to determine efficacy and safety.

Previous research on ADHD has determined adolescents with ADHD are two times more likely to become cigarette smokers and are more likely to initiate cigarette smoking at an earlier age than adolescents without ADHD. Current theories suggest that cigarette smoking, specifically nicotine administration, is a form of self-medication and therefore a potential drug therapy.

Nicotine is a tertiary amine compound found naturally in tobacco. Nicotine binds to the nicotinic cholinergic receptors found in multiple areas of the brain, the autonomic ganglia, and neuromuscular junctions. When activated it stimulates a release of neurotransmitters, including acetylcholine, norepinephrine, dopamine, serotonin, B endorphins, and others. The nicotine cholinergic receptor activation in the adrenal medulla releases epinephrine and other B endorphins. A study performed on 11 adult patients with ADHD found nicotine therapies to have similar neurochemical effects to other stimulant-like mediations by lowering striatal dopamine transporters in the brain. Nicotine administration through cigarette smoking is known to increase cardiovascular risk mainly due to its stimulant like effects, but the administration of transdermal nicotine has not been proved to be associated with any serious or rare complications.
A study performed by Levin et al\textsuperscript{16} showed a subjective and clinical reduction in ADHD symptoms and an increase in cognitive functioning associated with a nicotine therapy in both smoking and non-smoking adults. Attempting to treat the symptoms at an earlier age would help provide an alternative treatment modality to children and adolescents with ADHD. This review will assess if acute transdermal nicotine treatments could potentially increase cognitive functioning and decrease symptoms in children, adolescents, and young adults with ADHD.

**METHODS**

An exhaustive search of available literature was performed using Medline- OVID, Web of Science, and Google Scholar. Keywords included in the search were nicotine patch, transdermal nicotine, ADHD, attention deficit hyperactivity disorder, cognitive functioning, and symptom improvement. The search was limited to include only studies done on humans, in the English language, and on children, adolescents, or young adults in the subject demographics. Other articles were assessed for further information. Using the GRADE criteria, all relevant articles were assessed for quality\textsuperscript{17}.

**RESULTS**

A total of 11 articles were screened for relevance. After this review, 2 studies\textsuperscript{18,19} met inclusion criteria. Both articles were randomized control trials, in the English language, performed on humans 25 years of age or younger. See Table 1.

**Shytle et al.**

This was a double blind, randomized controlled trial\textsuperscript{18} testing the effects of a 5 mg/16 hour daily transdermal nicotine patch versus a placebo patch in 10 children and adolescents between the ages of 8 and 13 years of age, who meet the DSM IV criteria for ADHD. Potential participants currently taking psychoactive drugs and those with drug, alcohol, or tobacco abuse or dependence within 6 month from the start of the trial and were excluded. The study was performed over a 7 day period and subjects were
instructed to apply a new transdermal patch daily. Subjects and the parents of subjects were also instructed to keep a diary assessing for compliance. Participants were instructed to remove the patch if they experienced abnormal side effects, specifically nausea or dizziness. If the patch was removed due to side effects, subjects were informed to apply a new patch the next day. A 48-item Conner’s Parent Rating Scale (CPRS) and the Clinical Global Impression (CGI) Scale were used to assess for symptomatological changes at baseline, day 0 and day 7. The Conner’s Parent Rating Scale was divided into 6 subgroups: conduct problems, learning problems, psychosomatic, impulsivity, anxiety, and hyperactivity.\(^\text{18}\)

Shytle et al study found the nicotine group to be statistically significant in improvement of “learning problems,” a subset of an item in Conner’s Parent Rating Scale. Although the nicotine group showed improvements in all the other subgroups, none were found to be statistically significant. The Clinical Global Impression Scale assessment was inconclusive in showing any differences between the 2 groups after a 7-day period. Along with the benefits of nicotine, the treatment group reported elevated levels of side effects. Eighty percent of the treatment group reported nausea and 60% reported stomach aches and local skin irritation associated with the transdermal nicotine administration.\(^\text{18}\)

The biggest limitation mentioned by the authors of this study was the possible compromise of blinding. The treatment group was noted to have high percentage of side effects, including nausea, stomach aches, local irritation under the patch, and dizziness. Although attempts were made to keep the placebo transdermal application similar in size and smell, Shytle et al was unable to predict the treatment groups’ side effects. With the associated side effects profile dominating the treatment group, it could have been easy for the researcher to determine which subjects were a part of the treatment group, thus compromising the overall blinding of this study.\(^\text{18}\)

\textbf{Potter and Newhouse}
This was a randomized, controlled, double blind pilot study comparing the effects of behavior inhibition, delay aversion, and recognition memory after application of a 45 minute 7 mg transdermal nicotine patch versus a placebo in young adults diagnosed with attention deficit hyperactive disorder. This study compared 15 non-smoking subjects between the ages of 18-24, diagnosed with ADHD-C, a sub-type of ADHD, based on the DSM IV criteria. Prior to each study day, subjects were to abstain from taking any prescribed ADHD medication for at least 3 half-lives of the medication, which was verified subjectively. Subjects were also required to pass an expired carbon monoxide level of < 10 ppm to ensure non-smoking status. Subjects were assessed twice at least 2-10 days apart, by two different investigators, once with a 7 mg nicotine patch and once with the placebo patch.

Subjects were then admitted to an outpatient clinical research facility, where a 7 mg transdermal nicotine patch or an identical appearing placebo patch was administered. Forty-five minutes later the patch was removed and each subject immediately continued on to a 4 part, computer based cognitive testing session in the following fixed order: 1) stop signal task, 2) the stroop task 3) the choice delay task, and 4) high-low imagery task.

1) The stop signal task tested behavior inhibition by asking subjects to respond to two visual “go” signals, the letter X and O and auditory stop signal. The test measures the speed of cognitive inhibition that translates to the ability to control a specific impulse.

2) The stroop task measures the ability of word reading, color naming, and interference. Interference measures the brains ability to keep focus with a specific task, while being cognitively distracted. In this test subjects are first asked to read a list of colors, ie, BLUE, RED, GREEN, written in black ink. The second task asked the subjects to read a list of colors BLUE, RED, GREEN, in their respective colored ink. The last task measures the speed at which the subject is able to read a list of colors, written in a colored ink different from the color of the
word, eg, the word BLUE written in green ink. The times between the three tasks are then compared.

3) The choice delay task test analyzes the subject’s ability to wait for a greater delayed reward. This task is performed by choosing between 2 arbitrary shapes, a circle or a square. Picking the circle gives the participant 5 points, picking the square credits the participant 15-points, but the circle is on a continuous 5-second delay and the square is on a variable delay, becoming increasingly longer if the subject continues to pick the square.

4) The high–low imagery task measures recognition memory. Subjects are presented with 14 words, 7 of high imagery (“Cat”) and 7 of low imagery (“idea”). The subjects are then presented with 28 words, the previous 14 high and low imagery words and 14 distracting words. They are informed to indicated if the word was from the first 14 original words or a new word to the set.

Following the cognitive testing, participants completed 3 self-report questionnaires: 1) profile of mood states, 2) visual analog battery, and 3) a physical symptom checklist. Clinical investigators also completed clinical global impression scores and visual analog battery scores for each participant following the completion of the cognitive task sessions. Each task and questionnaire coincided to a tangible score that was inputted into Microsoft Excel spreadsheets. Three subjects were excluded from the study due to side effects and, therefore, the data of only 12 subjects was compared.19

This study reported a statistically significant improvement in stop signal reaction time in the nicotine patch treatment group compared to the placebo group, showing an improvement in impulse control. Potter and Newhouse also reported the nicotine group to be associated with an increase in the number of delayed choices during the choice delay task. During the high-low imagery task, the nicotine treatment group showed an increase in the number of words correctly identified, suggesting a strong influence on acute learning. The subjective and objective questionnaires did not reveal any significant
drug related changes in comparison to the placebo group.\textsuperscript{19}

Potter and Newhouse noted multiple limitations to their study. One limitation that was addressed included how using a specific ADHD subtype made the results of the study hard to predict for other ADHD types. Another limitation mentioned was the possibility that nicotine receptors had been affected by previous exposure to stimulants. Participants in the study already taking stimulants were informed to allow for the clearing of 3 half lives of the medication before participating in the study. Potter and Newhouse addressed the uncertainty of a known connection between nicotinic receptor expressions in the presence of previously taken chronic stimulants, and therefore it is uncertain if similar effects would occur in subjects without a prior stimulant history.\textsuperscript{19}

Another limitation mentioned in the study was the fixed order of cognitive testing. The nicotine patch was administered for 45 minutes and then removed prior to the cognitive testing session in order to minimize the side effects of the nicotine. Therefore, the researchers mentioned nicotine plasma concentration could be assumed higher at the start of the testing, but there was no evidence to suggest a linear dose response. Potter and Newhouse suggest further studies should investigate for a possible relationship between plasma nicotine levels and cognitive functioning.\textsuperscript{19}

**DISCUSSION**

The results from both\textsuperscript{18,19} articles demonstrated benefits of nicotine administration in children, adolescents and young adults with ADHD. Acute nicotine administration via transdermal nicotine patches in young adults with ADHD showed improvements in subjective symptomology, impulse control, and cognitive learning. The studies compared were both pilot studies and therefore had very small sample sizes. The Shytle el al. study\textsuperscript{18} had a sample size of 10 and the Potter and Newhouse study\textsuperscript{19} had a sample size of 15. Future larger randomized control trials using transdermal nicotine administration would allow for more accurate and convincing results.
Another limitation of the Shytle et al study\textsuperscript{18} was the high percentages of side effects, which increased the risk of unblinding participants and researchers. Eighty percent of the subjects in the treatment group reported nausea as a side effect to the medication, 60\% reported stomachaches, 40\% dizziness, and 40\% headaches. The frequency and duration of each side effect was also not reported in the overall study, and side effects were reported as a subjective binary (yes or no). Subjects were also informed to remove the patch if symptoms of nausea or dizziness occurred, which resulted in 4 out of 5 participants without a patch for at least 1 day and possibly 2 days. This lack of information could have altered the overall application time frame and therefore showed a more acute impact on ADHD symptoms, which coincides with other more recent studies, such as the Potter and Newhouse study.\textsuperscript{19}

One of the greatest limitations to the Potter and Newhouse study,\textsuperscript{19} as mentioned previously, was the overall sample size. Another limitation with the sample population was the lack of demographic information collected. The subject’s age and gender was recorded but not compared, and ethnic background demographics were not assessed. These limitations could make it difficult to extend the study’s findings to a population with diverse demographics, or to evaluate if the results of the study might be confounded by significant differences based on gender or race.

Secondly, as mentioned by Potter and Newhouse\textsuperscript{19}, the study design followed a very regimented order. The 4-part cognitive testing session was performed with the stop signal reaction test first, which was the only overall task that showed statistically significant improvements. Potter and Newhouse\textsuperscript{18} addressed the possibility that nicotine concentrations at the beginning of the cognitive testing sessions could have been higher. They suggested future studies should evaluate for a possible dose response in relation to cognitive deficits. If the cognitive testing order was randomized, it may have reduced a possibility of a nicotine dose response making the overall results of the study stronger.

The greatest and most daunting risks associated with using nicotine to treat ADHD, especially in
children and adolescents, are the overall side effects profile, addiction, and cardiovascular risk. However, previous studies\textsuperscript{13,15} have suggested that transdermal application of nicotine should be considered safe in the acute setting. Although some researchers believe short-term transdermal nicotine administration to be safe, long term or chronic use of transdermal nicotine has not been fully researched. Therefore further studies should continue to investigate the safety and efficacy of transdermal nicotine in children and adolescents with ADHD. Other research is currently investigating drugs that stimulate the nicotinic receptor, or nicotine agonist, that provide similar therapeutic benefits but without the overall side effects, addiction, and cardiovascular risk profile.

Current treatment modalities for children and adolescents with ADHD have been found to improve academic productivity equating to better grades, but standardized test scores remain unchanged.\textsuperscript{3} If an acute dose of nicotine could improve the cognitive deficits, impulse control, and learning problems associated with those diagnosed with ADHD, there could be a benefit to using nicotine administration to help academic performance and possibly improved standardized test scores in those with ADHD. Further research should continue to investigate if improvements in cognitive function translate to improvements in academic performance and standardized test scores.

Shytle et al\textsuperscript{18} and Potter and Newhouse\textsuperscript{19} suggested that stimulating the nicotinic cholinergic system with nicotine helps to decrease cognitive deficits in those with ADHD and should continue to be explored as a viable treatment modality in the future. Newer research has targeted stimulation of the nicotinic cholinergic receptors to help reduce symptoms and improve cognitive functioning but without the side effects and cardiovascular risks.

**CONCLUSION**

Based on the studies assessed, transdermal nicotine application in adolescents and young adults with ADHD improved symptomatic deficits in learning, recognition memory, delayed gratification, and
impulse control in an acute setting. However, the overall quality of evidence is very low mainly due to small sample sizes. At this point in time, new larger randomized control trials are needed to assess if transdermal nicotine administration could be a viable and safe alternative to current treatment modalities. Currently there is not enough research using transdermal nicotine on children, adolescents, and young adults with ADHD to suggest clinical use, but research has been directed to activate stimulation of the nicotinic cholinergic receptor to help improve cognitive deficits linked with ADHD without the associated risks.
References


### Table I. Quality Assessment of Reviewed Articles

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</thead>
<tbody>
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<td></td>
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<td>Limitations</td>
<td>Indirectness of evidence</td>
<td>Inconsistency of results</td>
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<td>Shytle et al</td>
<td>RCT</td>
<td>Serious a, b</td>
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a Risk of unblinding due to a high percentage of side effects in treatment group
b Subjective outcome
c Small sample size