Efficacy of N-Acetylcysteine in the Treatment of Nicotine Dependence: A Double-Blind Placebo-Controlled Pilot Study

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\begin{abstract}
Relapse is the rule rather than the exception in smokers aiming to quit smoking. Recently, evidence has emerged that glutamate transmission plays an important role in relapse. N-acetylcysteine (NAC), a cysteine prodrug, restores glutamate homeostasis and appears to be a potential new treatment for substance dependence. In the current pilot study, the effects of NAC on short-term abstinence of smoking were investigated. Subjects were heavy smokers randomized to receive placebo (n = 12) or NAC 3,600 mg/day (n = 10) in a double-blind fashion during 3.5 days. Subjects were asked to stop smoking and report on nicotine craving, nicotine withdrawal symptoms, and cigarette smoking during treatment. At the end of the treatment, subjects were invited to smoke a cigarette and to rate the rewarding effect of this cigarette. There was no significant effect of NAC on craving (p = 0.23, d = 0.52) and only a statistical trend towards fewer withdrawal symptoms in the NAC condition (p = 0.07, d = 0.80). Interestingly, subjects receiving NAC rated the first cigarette after the abstinence period of 3.5 days as significantly less rewarding than subjects on placebo (p = 0.04, d = 0.85).
\end{abstract}

Key Words
Nicotine dependence, treatment · N-acetylcysteine · Smoking

It is concluded that the results of this pilot study are encouraging and suggest that NAC might be a promising new treatment option for relapse prevention in nicotine dependence.

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Introduction

Smoking tobacco is the single most important cause of preventable disease and mortality. In the Netherlands, one fourth of smokers attempt to quit smoking every year, but only 1–7% of these quitters reach prolonged abstinence [1]. Most smokers try to quit smoking without professional assistance, although there is evidence that pharmacologically supported interventions are effective in the prevention of relapse, e.g. nicotine replacement therapy (NRT) or treatment with bupropion or varenicline [2, 3].

Nicotine stimulates nicotine acetylcholine (nACh) receptors in the central nervous system, which in turn elevate the release of several neurotransmitters such as dopamine, glutamate, serotonin and GABA [4–7]. Traditionally, treatment strategies have focused on targeting the nACh receptors (NRT, varenicline) [8] or blocking the reuptake of dopamine and noradrenaline (bupropion) [9, 10]. However, these pharmacotherapies are only moder-
ately successful in smoking cessation and relapse is the rule rather than the exception [11]. Moreover, these interventions are often accompanied with unpleasant side effects [12, 13]. Therefore, there is a continued need for novel pharmacotherapies to support smoking cessation with fewer side effects, perhaps targeting different neurotransmitter systems in the brain.

In recent years, the role of glutamate transmission in substance dependence has been more extensively investigated. Especially from preclinical work, evidence has emerged for the involvement of glutamate in relapse [14–17]. In a study of Baker et al. [18], relapse to cocaine-seeking behavior was linked to decreased basal concentrations of extracellular glutamate which, in turn, provided less tonic activation of the group II metabotropic glutamate (mGluR2/3) receptors that normally inhibit presynaptic glutamate release. Furthermore, synaptic glutamate transmission mediates the primary reinforcing effects of nicotine in rat models: stimulating mGluR2/3 receptors, which inhibits synaptic glutamate release, reduces the rewarding effects of nicotine [19]. Moreover, increasing extracellular glutamate attenuates symptoms associated with nicotine withdrawal [20]. In the brain, the basal levels of extracellular glutamate are maintained by the exchange of extracellular cystine for intracellular glutamate and this extracellular glutamate stimulates mGluR2/3 receptors which are important for regulating synaptic glutamate release. Restoring basal concentrations of extracellular glutamate and thereby increasing tonic activation of the mGluR2/3 receptors could therefore be an important target for treatment of nicotine dependence. Indeed, administration of N-acetylcysteine (NAC), a cysteine prodrug, restored extracellular glutamate concentrations and prevented relapse to drug-seeking behavior in rats previously treated with cocaine [21] and heroin [22]. In humans, pilot studies have shown that NAC decreases cue-induced craving for cocaine [23], pathological gambling [24], number of cigarettes smoked [25], and marijuana use and craving [26]. NAC is currently used for treatment of acetaminophen overdose, prescribed for pulmonary conditions, and sold over-the-counter as a mucolytic agent and nutritional supplement. NAC appears to be well tolerated; even at very high doses side effects are rare [27, 28]. These characteristics of NAC provide an advantage over the current pharmacotherapies for nicotine dependence. However, more double-blind placebo-controlled studies are needed to evaluate its potential clinical effect in smoking cessation.

The aim of the current pilot study is to investigate the effect of treatment with NAC on short-term abstinence in cigarette-smoking students. We hypothesized that treatment with NAC would have a beneficial effect on self-reported craving and withdrawal symptoms and on the rewarding effect of nicotine.

Methods

Subjects

Twenty-three undergraduate students who smoked at least 15 cigarettes per day participated in the current study. All students were recruited from the University of Amsterdam. Exclusion criteria were: (a) on medication other than oral contraception; (b) trying to get pregnant or nursing; (c) suffering from a neurological, medical, or psychiatric illness; (d) experiencing severe stomach problems or ulcers, and (e) dependent on other substances than nicotine.

Subjects received study credits for completing the study and an additional 20 euro. The study was approved by the Ethics Committee of the University of Amsterdam and written informed consent was obtained from all participants.

Study Design and Procedure

After screening, subjects were randomly assigned to either NAC or placebo during 4 consecutive days. Subjects agreed to refrain from smoking during the treatment. Breath carbon monoxide concentration was measured at baseline and consecutive treatment days using a calibrated Micro + Smokerlyzer (Bedfont Scientific Ltd, Rochester, UK) to objectively verify self-reported smoking behavior. A CO value of <10 parts per million (ppm) was the criterion to confirm smoking abstinence during treatment. The first 3 days, a dose of 1,800 mg NAC or placebo was given twice daily in a double-blind fashion, resulting in a total dose of 3,600 mg/day. This dose was chosen because Mardikian et al. [29] found in cocaine-dependent patients that higher doses (2,400 and 3,600 mg/day) of NAC resulted in higher retention rates than lower doses (1,200 mg/day) while both higher and low doses were safe and well tolerated. Since the treatment period in the current study was only 4 days, we chose the highest dose (3,600 mg/day) for a maximum effect. On the fourth day, subjects received only one dose of 1,800 mg or placebo in the morning because final assessments took place in the early afternoon. Treatment duration was set at 3.5 days, because previous studies with a 3-day administration of NAC in cocaine-dependent subjects [23, 27] already resulted in a greater reduction in withdrawal symptoms and craving in diminished cue reactivity within the NAC condition compared to placebo.

Subjects visited the university every morning during the 4 days of treatment. The first dose was given in the morning and the second dose was given to take in at home later. On the first day, baseline data on cigarette, alcohol, and drug use for the last 3 months were collected using the Timeline Follow-Back method [30]. The Fagerström Test for Nicotine Dependence (FTND) [31] was administered to measure the level of nicotine dependence. In addition, at baseline and on the subsequent days, participants were asked about side effects, craving using the Questionnaire for Smoking Urges-Brief (QSU-Brief) [32] and withdrawal symptoms were assessed using the Minnesota Nicotine Withdrawal Scale (MNWS) [33]. The QSU-Brief [32] (Dutch translation) is a 10-item
self-report questionnaire rated on a 7-point scale. The QSU-Brief is adapted from the QSU [34] and consists of two subscales: ‘desire and intention to smoke’, and ‘reduction of negative affect and withdrawal symptoms’. These subscales have adequate psychometric properties [32, 35]. The Dutch translation of the MNWS is a self-report questionnaire consisting of 8 items rated on a 5-point scale resulting in a total score for withdrawal symptoms. Subjects were asked whether they smoked, or used alcohol or drugs the previous day during each visit. At the end of the last treatment day, subjects were asked to smoke a cigarette and to rate the rewarding effect of that cigarette using a visual analogue scale (VAS; range 1–100) with the question: How rewarding did you find smoking this cigarette?

Statistical Analyses

Data were checked for a normal distribution. Only age was not normally distributed and therefore log transformed before further analyses. The effect of NAC versus placebo on outcome (craving, withdrawal, and reward) was tested using analysis of variance (ANOVA) with treatment condition as a between-subjects factor. Effect sizes were calculated using Cohen’s $d$: 0.2–0.4 indicating small effect; 0.5–0.7 indicating medium effect, and $\geq 0.8$ indicating large effect [36]. In addition, associations between the outcome measures were examined using Pearson’s correlation analyses. The level of significance was set at $\alpha = 0.05$ (two-sided), with no correction for multiple testing.

Results

Sample

Of the 23 subjects, 1 was excluded due to cannabis use during the experiment leaving 22 subjects for analysis. None of the subjects reported smoking during the experiment and this was confirmed by breath carbon monoxide concentrations lower than 10 ppm. Five subjects in the placebo condition reported mild stomachache, while in the NAC condition 2 subjects reported mild stomach problems. No other side effects were reported.

Sample characteristics for the NAC ($n = 10$) and the placebo group ($n = 12$) are presented in Table 1. At baseline, the total sample smoked 17.5 cigarettes on average per day and had a mean FTND score of 3.45 out of 10 which is indicative for a low level of dependence. There was a trend towards more alcohol consumption during the experiment in the placebo group compared with the NAC group ($t = 1.97, df = 13.27, p = 0.07$), therefore this variable was included as a covariate in subsequent analyses.

Outcomes

Table 2 shows the scores for the two groups on the QSU-Brief, the MNWS and the VAS for reward at the last day of treatment. NAC treatment was not significantly associated with craving (QSU-total score: $F = 1.54, df = 1, p = 0.23, d = 0.52$; QSU-Factor 1: $F = 1.69, df = 1, p = 0.21$; QSU-Factor 2: $F = 0.37, df = 1, p = 0.55$), but there was a trend towards fewer withdrawal symptoms in the NAC compared to the placebo group ($F = 3.85, df = 1, p = 0.07; d = 0.80$). Participants in the NAC group rated the first cigarette after the abstinence period as significantly and considerably less rewarding than participants in the placebo group ($F = 4.70, df = 1.21, p = 0.04; d = 0.85$). Additional correlation analyses between outcome measures revealed a significant positive association only between the subjective rewarding effect of the cigarette and level of craving at the last treatment day ($R(22) = 0.70, p < 0.01$).
Discussion

In the current pilot study, we examined the short-term effects of NAC treatment on craving, withdrawal, and the rewarding effect of the first cigarette after a brief period of smoking cessation. NAC was associated with a large (non-significant: \( p = 0.07 \)) effect on withdrawal and a large (and significant) effect on nicotine reward after a very short treatment of 3.5 days including only seven doses of 1,800 mg NAC. To our knowledge, this is the second study investigating the effects of NAC on smoking cessation. In a randomized double-blind trial in 29 heavy smokers, Knackstedt et al. [25] compared 4 weeks of 2,400 mg NAC per day (\( n = 14 \)) with 4 weeks of placebo (\( n = 15 \)) and found a significant reduction in the number of smoked cigarettes in the NAC condition, but no significant effects on self-reported craving and withdrawal symptoms. However, because most subjects continued smoking during treatment, it was not likely for them to show withdrawal symptoms. Together, these data suggest that NAC in high dosages is safe and can reduce withdrawal and nicotine reward in smokers and subsequently reduce the probability of relapse to previous smoking levels.

Most people who attempt to quit smoking relapse within 5–10 days [37, 38]. Major contributors to this early relapse are withdrawal symptoms [39, 40]. Withdrawal symptoms emerge within the first hours after the last cigarette [41]. The easiest way to relieve these symptoms is to start smoking again. Our results suggested a tendency towards fewer withdrawal symptoms after 3.5 days of treatment with NAC. Reduction of these early withdrawal symptoms could be of major importance in preventing relapse. In addition, administration of NAC was associated with a smaller rewarding effect of smoking a cigarette after almost 4 days of abstinence compared to placebo. NAC restores extracellular glutamate concentrations which in turn stimulates mGluR2/3 receptors [21]. It is found that the stimulation of group II mGluR receptors inhibits synaptic glutamate transmission and diminishes the rewarding effects of nicotine [19]. This could have resulted in the diminished reward of smoking in the current study. In addition, the smaller rewarding effect of smoking a cigarette in the NAC condition could be related to the reduction in withdrawal symptoms observed in the same condition, because more severe withdrawal symptoms would result in higher relief after smoking, which might be interpreted as reward. However, in the current study we did not find an association between the subjective rewarding effect of smoking and withdrawal symptoms at the last day of treatment or the reduction in withdrawal symptoms over the course of treatment. Instead, there was a relationship between the rewarding effect of the cigarette and levels of craving at the last day of treatment. Treatment with NAC, however, did not affect self-reported craving levels.

The finding of no effect of NAC on self-reported craving is similar to the findings of Knackstedt et al. [25] in smoking and LaRowe et al. [23] in cocaine dependence. However, whereas withdrawal symptoms increase dramatically immediately after cessation, craving is often found to be higher during ad libitum smoking than after cessation [42, 43]. Researchers distinguish between tonic craving and episodic craving provoked by cues related to drug use termed cue-induced craving. In contrast to tonic craving, cue-induced craving can occur within several hours after cessation [44]. Cue-induced craving can continue to occur for long periods of time after quitting [43] and predicts relapse [45]. A cue-induced craving paradigm was not incorporated in the current study. However, in a double-blind cross-over study (\( n = 15 \)), LaRowe et al. [23] reported that NAC had no effect on craving but...

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**Table 2. Efficacy measures at the last day of treatment (t4)**

<table>
<thead>
<tr>
<th>Measure t4</th>
<th>Placebo group (( n = 12 ))</th>
<th>NAC group (( n = 10 ))</th>
<th>( F (df) )</th>
<th>( p ) value</th>
<th>( d ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean SD</td>
<td>mean SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QSU Total score</td>
<td>35.92 14.88</td>
<td>28.70 11.81</td>
<td>1.54 (1)</td>
<td>0.23</td>
<td>0.52</td>
</tr>
<tr>
<td>Factor 1 score</td>
<td>24.17 9.72</td>
<td>18.90 8.33</td>
<td>1.69 (1)</td>
<td>0.21</td>
<td>0.58</td>
</tr>
<tr>
<td>Factor 2 score</td>
<td>6.50 3.48</td>
<td>5.90 2.47</td>
<td>0.37 (1)</td>
<td>0.55</td>
<td>0.20</td>
</tr>
<tr>
<td>MNWS</td>
<td>14.25 7.98</td>
<td>8.60 6.02</td>
<td>3.85 (1)</td>
<td>0.07</td>
<td>0.80</td>
</tr>
<tr>
<td>VAS reward cigarette</td>
<td>65.58 24.70</td>
<td>42.60 29.02</td>
<td>4.70 (1)</td>
<td>0.04</td>
<td>0.85</td>
</tr>
</tbody>
</table>
that it did decrease the desire to use cocaine in response to cocaine cues in cocaine-dependent subjects. Perhaps NAC is more effective in reducing intense episodic craving provoked by drug cues than in the reduction of tonic background craving.

A major benefit of NAC is that it is a readily available treatment option, as it is sold over-the-counter in contrast to bupropion and varenicline, which are only available as (often not reimbursed and expensive) prescription medications. Smokers may find over-the-counter aids more acceptable than prescription drugs as most smokers who attempt to quit do so without professional assistance or use nicotine replacement products [12]. Advantages of NAC over replacement therapies are that it does not contain nicotine and has fewer side effects. In the current study, no serious side effects were reported, only 2 subjects in the NAC condition reported mild stomachache as opposed to 5 subjects in the placebo condition. This corresponds to previous findings that high dosages of NAC are well tolerated in cocaine-dependent subjects [27] and pathological gamblers [24].

Some limitations of the current pilot study need to be addressed. First, FTND scores in the current sample pointed to low levels of nicotine dependence, therefore overall ratings of craving and withdrawal reported by our subjects might be lower than in treatment samples. However, it is noteworthy that even lower FTND scores have been reported in population samples of current smokers [46, 47]. Second, the findings of decreased withdrawal symptoms showed only a trend towards significance despite the large effect size. This is in all likelihood due to our small sample size resulting in modest statistical power. In addition, the length of NAC treatment was relatively short and a longer period of treatment might be needed to reach steady-state levels of NAC. Therefore, double-blind placebo-controlled studies with larger sample sizes and longer treatment periods are needed to confirm our findings. Another limitation is that the subjects were asked to quit smoking for only 3.5 days and were expected to smoke a cigarette at the end of treatment. Studies with subjects seeking treatment directed at long-term abstinence are required.

We conclude that the current study together with the study of Knackstedt et al. [25] is suggestive for higher dosage of NAC as a promising and easily accessible medical aid for smoking cessation.

References


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