Boosting impulse control in addiction: Pharmacological neuroimaging studies
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PART III

CHAPTER 5

EFFICACY OF N-ACETYLCYSTEINE IN THE TREATMENT OF NICOTINE DEPENDENCE: A DOUBLE-BLIND PLACEBO-CONTROLLED PILOT STUDY

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ABSTRACT

BACKGROUND 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, 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 N-acetylcysteine on short-term abstinence of smoking were investigated.

METHODS Subjects were heavy smokers randomized to receive placebo (n=12) or N-acetylcysteine 3600 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.

RESULTS There was no significant effect of N-acetylcysteine on craving ($p=0.23$, $d=0.52$) and only a statistical trend towards fewer withdrawal symptoms in the N-acetylcysteine condition ($p=0.07$, $d=0.80$). Interestingly, subjects receiving N-acetylcysteine rated the first cigarette after the abstinence period of 3.5 days as significantly less rewarding than subjects on placebo ($p=0.04$, $d=0.85$).

CONCLUSION It is concluded that the results of this pilot study are encouraging and suggest that N-acetylcysteine might be a promising new treatment option for relapse prevention in nicotine dependence.
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 (Stivoro 2010). 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 (Agboola et al. 2010; Mills et al. 2009).

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 (Calabresi and Di Filippo 2008; Jones et al. 1999; Picciotto et al. 2000; Picciotto 2003). Traditionally, treatment strategies have focused on targeting the nACh receptors (NRT, varenicline) (Mihalak et al. 2006) or blocking the reuptake of dopamine and noradrenaline (bupropion) (Ascher et al. 1995; Learned-Coughlin et al. 2003). However, these pharmacotherapies are only moderately successful in smoking cessation and relapse is the rule rather than the exception (Zaniewska et al. 2009). Moreover, these interventions are often accompanied with unpleasant side effects (Cahill et al. 2008; Hughes et al. 2007). Therefore, there is a continued need for novel pharmacotherapy’s 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 (Cornish and Kalivas 2000; Di Ciano and Everitt 2001; McFarland et al. 2003; McFarland et al. 2004). In a study of Baker et al. (2003a), 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 (Liechti et al. 2007). Moreover, increasing extracellular glutamate attenuates symptoms associated with nicotine withdrawal (Kenny et al. 2003). 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 (Baker et al. 2003b) and heroin (Zhou and Kalivas 2008). In humans, pilot studies have shown that NAC decreases cue-induced craving for cocaine (LaRowe et al. 2007), pathological gambling (Grant et al. 2007), number of cigarettes smoked (Knackstedt et al. 2009), and marijuana use and craving (Gray et al. 2010). 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 (LaRowe et al. 2006; Miller and Rumack 1983). 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 d) 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 four 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 three days, a dose of 1800 mg NAC or placebo was given twice daily in a double-blind fashion, resulting in a total dose of 3600 mg a day. This dose was chosen because Mardikian et al. (2007) found in cocaine dependent patients that higher doses (2400 mg/day and 3600
mg/day) of N-acetylcysteine resulted in higher retention rates than lower doses (1200 mg/day) while both higher and low doses were safe and well tolerated. Since the treatment period in the current study was only four days, we chose the highest dose (3600 mg/day) for a maximum effect. On the fourth day, subjects received only one dose of 1800 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 three-day administration of N-acetylcysteine in cocaine dependent subjects (LaRowe et al. 2006; LaRowe et al. 2007) already resulted in a greater reduction in withdrawal symptoms and craving and in diminished cue reactivity within the NAC condition compared to placebo.

Subjects visited the university every morning during the four 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 six months were collected using the Timeline Follow-Back method (Sobell and Sobell 1992). The Fagerström-Test for Nicotine Dependence (FTND; Heatherton et al. 1991) was administered to measure 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; Cox et al. 2001) and withdrawal symptoms were assessed using the Minnesota Nicotine Withdrawal Scale (MNWS; Hughes and Hatsukami 1986). The QSU-Brief (Cox et al. 2001) (Dutch translation) is a 10-item self-report questionnaire rated on a 7-point scale. The QSU-Brief is adapted from the QSU (Tiffany and Drobes 1991) and consists of two subscales: ‘desire and intention to smoke’, and ‘reduction of negative affect and withdrawal symptoms’. These subscales have adequate psychometric properties (Cappelleri et al. 2007; Cox et al. 2001). The Dutch translation of the MNWS is 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 to 0.4 indicating small effect; 0.5 to 0.7 indicating medium effect; and ≥ 0.8 indicating large effect (Cohen 1992). 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, one 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 two 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.

Table 1: Demographics and clinical characteristics at baseline

<table>
<thead>
<tr>
<th>Demographic variable at baseline</th>
<th>Placebo group (N=12)</th>
<th>NAC group (N=10)</th>
<th>t (df)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean 20.25 (SD 1.14)</td>
<td>Mean 21.40 (SD 2.07)</td>
<td>1.57 (13.43)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>Mean 17.33 (SD 1.92)</td>
<td>Mean 17.70 (SD 1.70)</td>
<td>-0.47 (20)</td>
<td>0.64</td>
</tr>
<tr>
<td>FTND</td>
<td>Mean 3.08 (SD 1.73)</td>
<td>Mean 3.90 (SD 1.34)</td>
<td>-1.23 (20)</td>
<td>0.23</td>
</tr>
<tr>
<td>Years smoking</td>
<td>Mean 5.57 (SD 1.66)</td>
<td>Mean 6.80 (SD 2.82)</td>
<td>-1.09 (20)</td>
<td>0.29</td>
</tr>
<tr>
<td>Alcohol in standard units/week</td>
<td>Mean 10.83 (SD 4.97)</td>
<td>Mean 7.60 (SD 4.93)</td>
<td>1.53 (20)</td>
<td>0.14</td>
</tr>
<tr>
<td>Total alcohol intake during treatment in standard units</td>
<td>Mean 6.08 (SD 5.99)</td>
<td>Mean 2.50 (SD 1.78)</td>
<td>1.97 (13.27)</td>
<td>0.07</td>
</tr>
<tr>
<td>QSU</td>
<td>Total score Mean 35.58 (sd 16.13)</td>
<td>Mean 34.90 (sd 10.20)</td>
<td>0.12 (20)</td>
<td>0.91</td>
</tr>
<tr>
<td>Factor 1 score</td>
<td>Mean 24.08 (sd 8.71)</td>
<td>Mean 24.20 (sd 6.90)</td>
<td>-0.03 (20)</td>
<td>0.97</td>
</tr>
<tr>
<td>Factor 2 score</td>
<td>Mean 6.92 (sd 5.12)</td>
<td>Mean 6.10 (sd 2.60)</td>
<td>0.20 (20)</td>
<td>0.85</td>
</tr>
<tr>
<td>MNWS</td>
<td>Mean 17.58 (sd 8.53)</td>
<td>Mean 17.10 (sd 10.44)</td>
<td>0.12 (20)</td>
<td>0.91</td>
</tr>
<tr>
<td>% maleª</td>
<td>42</td>
<td>40</td>
<td>χ²(1) =0.01</td>
<td>0.94</td>
</tr>
</tbody>
</table>

FTND: Fagerström-Test for Nicotine Dependence; QSU: Questionnaire on Smoking Urges; MNWS: Minnesota Nicotine Withdrawal Scale.
ªChi-square test of independence.

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. N-acetylcysteine treatment was not significantly associated with craving (QSU-total score: F=1.54, df=1, p=0.23, d=0.52; QSU-Factor1:
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).

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

<table>
<thead>
<tr>
<th>Measure</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>QSU</td>
<td>Mean: 35.92 SD: 14.88</td>
<td>Mean: 28.70 SD: 11.81</td>
<td>1.54 (1)</td>
<td>0.23</td>
<td>0.52</td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor 1 score</td>
<td>Mean: 24.17 SD: 9.72</td>
<td>Mean: 18.90 SD: 8.33</td>
<td>1.69 (1)</td>
<td>0.21</td>
<td>0.58</td>
</tr>
<tr>
<td>Factor 2 score</td>
<td>Mean: 6.50 SD: 3.48</td>
<td>Mean: 5.90 SD: 2.47</td>
<td>0.37 (1)</td>
<td>0.55</td>
<td>0.20</td>
</tr>
<tr>
<td>MNWS</td>
<td>Mean: 14.25 SD: 7.98</td>
<td>Mean: 8.60 SD: 6.02</td>
<td>3.85 (1)</td>
<td>0.07</td>
<td>0.80</td>
</tr>
<tr>
<td>VAS reward cigarette</td>
<td>Mean: 65.58 SD: 24.70</td>
<td>Mean: 42.60 SD: 29.02</td>
<td>4.70 (1)</td>
<td>0.04</td>
<td>0.85</td>
</tr>
</tbody>
</table>

QSU: Questionnaire on Smoking Urges; MNWS: Minnesota Nicotine Withdrawal Scale; VAS: Visual Analogue Scale.

**DISCUSSION**

In the current pilot study, we examined the short-term effects of N-acetylcysteine 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 1800 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. (2009) compared four weeks of 2400 mg NAC per day (n=14) with four weeks 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 to 10 days (Blondal et al. 1999; Hays et al. 2001). Major contributors to this early relapse are withdrawal symptoms (McCarthy et al. 2006; Piasecki et al. 2003). Withdrawal symptoms emerge within the first hours after the last cigarette (Markou 2008). 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 (Baker et al. 2003a). It is found that the stimulation of group II mGluR receptors inhibits synaptic glutamate transmission and diminishes the rewarding effects of nicotine (Liechti et al. 2007). 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. (2009) in smoking and LaRowe et al. (2007) in cocaine dependence. However, whereas withdrawal symptoms increase dramatically immediate after cessation, craving is often found to be higher during ad lib smoking than after cessation (Hughes 1992; Shiffman et al. 1997). 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 (McClernon et al. 2009). Cue-induced craving can continue to occur for long periods of time after quitting (Shiffman et al. 1997) and predicts relapse (Waters et al. 2004). 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. (2007) reported that NAC had no effect on craving but 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 (Cahill et al. 2008). 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 two subjects in the NAC condition reported mild stomach ache as opposed to five subjects in the placebo condition. This corresponds to previous findings that high dosages of NAC are well tolerated in cocaine dependent subjects (LaRowe et al. 2006) and pathological gamblers (Grant et al. 2007).

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 (John et al. 2003; Vink et al. 2005). 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 expecting 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 and colleagues (2009) is suggestive for higher dosage of NAC as a promising and easily accessible medical aid for smoking cessation.