Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria

Braz J Psychiatry. 2020 Sep-Oct;42(5):519-526
doi:10.1590/1516-4446-2019-0753
Brazilian Psychiatric Association

ORIGINAL ARTICLE

N-acetylcysteine as an adjunctive treatment for smoking cessation: a randomized clinical trial

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Objective: This randomized controlled trial examined the efficacy and safety of *N*-acetylcysteine as an adjunctive treatment for smoking cessation.
Methods: Heavy smokers were recruited from smoking cessation treatment for this 12- week randomized controlled trial. Eligible tobacco use disorder outpatients (n=34) were randomized to *N*-acetylcysteine or placebo plus first-line treatment. Abstinence was verified by exhaled carbon monoxide (CO_{exh}). The assessment scales included the Fagerström Test for Nicotine Dependence, the Hamilton Depression Rating Scale, the Hamilton Anxiety Rating Scale, the Minnesota Nicotine Withdrawal Scale, and the Medication Adherence Rating Scale. We also assessed anthropometrics, blood pressure, lipid profile, and soluble tumor necrosis factor receptor (sTNF-R) levels 1 and 2.
Results: First-line treatment for smoking cessation plus adjunctive *N*-acetylcysteine or placebo significantly reduced CO_{exh} ($p < 0.01$). In the *N*-acetylcysteine group, no significant changes were found in nicotine withdrawal symptoms, depressive and anxiety symptoms, anthropometric measures, blood pressure, or glucose compared to placebo. However, there was a significant reduction in sTNF-R2 levels between baseline and week 12 in the *N*-acetylcysteine group.
Conclusions: These findings highlight the need to associate *N*-acetylcysteine with first-line treatment for smoking cessation, since combined treatment may affect inflammation and metabolism components.
Clinical trial registration: NCT02420418

Keywords: *N*-acetylcysteine; inflammation; metabolism; tobacco use; smoking cessation

Introduction

Tobacco use disorder (TUD) is the leading cause of preventable morbidity, disability, and premature deaths from smoking-related diseases, including several types of cancer, type 2 diabetes mellitus, heart disease, and chronic obstructive pulmonary disease.[1] Quitting smoking reduces the risk of developing tobacco-related diseases.[2] Strategies to reduce smoking prevalence in the community remain a key public health priority. Available therapies have limited efficacy: quit rates are low and relapse rates are high in clinical practice, which indicates an urgent need for more effective smoking cessation treatment and reductions in tobacco-related diseases.

The first-line pharmacotherapeutic interventions for smoking cessation are nicotine replacement therapy, alpha4beta2 nicotinic acetylcholine receptor partial agonist (varenicline) therapy, and norepinephrine-dopamine reuptake inhibitor (bupropion).[3] After 12 weeks of smoking cessation treatment, varenicline was found more effective than placebo (44 vs. 17.7%) and bupropion (29.5%).[4]

N-acetylcysteine (NAC), a safe and well-tolerated glutamatergic agent, is promising as a potential pharmacotherapy for treating substance use disorders by inhibiting drug seeking.[5] Given its role as a precursor to the antioxidant glutathione, NAC may be efficacious in TUD treatment. NAC restores glutathione levels and modulates glutamatergic transmission, neurotrophins, and inflammatory pathways. NAC's effects on craving and reward in substance-related disorders are in part due to glutamate modulation; it restores prefrontal-nucleus accumbens glutamate transmission, which protects against relapses.[6-8] Reduced firing rates of glutamate projection neurons from the prefrontal cortex to the

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Submitted Jul 25 2019, accepted Feb 21 2020, Epub Jul 27 2020.

How to cite this article: Machado RCBR, Vargas HO, Baracat MM, Urbano MR, Verri WA Jr, Porcu M, et al. *N*-acetylcysteine as an adjunctive treatment for smoking cessation: a randomized clinical trial. Braz J Psychiatry. 2020;42:519-526. http://dx.doi.org/10.1590/1516-4446-2019-0753

nucleus accumbens is related to drug seeking, the recurring desire to take drugs, and decreased ability to control craving.[8] In individuals with nicotine dependence due to NAC-modulated glutamatergic pathways, NAC has been proven efficient for reducing craving and the number of cigarettes smoked per day.[2,9-11] These studies did not assess anthropometric measures, blood pressure (BP), lipid profiles, or soluble receptor levels of tumor necrosis factor (sTNF-R) -1 and -2.

Furthermore, NAC has antioxidant and anti-inflammatory properties: it increases intracellular glutathione, which leads to detoxification, and acts directly as a free radical scavenger. Moreover, NAC may reduce inflammatory cytokines[12] and reduces hepatic lipid accumulation by lowering triglyceride and cholesterol levels in the liver.[13]

Thus, our 12-week randomized controlled trial was designed to investigate the effect of NAC as an adjunctive treatment for smoking cessation. The primary outcome measure was whether adjunctive treatment with NAC would be superior to placebo regarding exhaled carbon monoxide (CO_{exh}). The secondary outcome measures were whether adjunctive treatment with NAC would lead to changes in craving and withdrawal symptoms, depressive and anxiety symptoms, vital signs, anthropometric measures, glucose levels, lipid profiles, Castelli risk indexes I and II, and leptin, and sTNF-R1 and sTNF-R2 levels.

Methods

Study population

This was a 12-week double-blind randomized placebo-controlled trial. Current smokers (n=129) were recruited from among outpatients at the Smoking Treatment Reference Center (Centro de Referência de Abordagem e Tratamento do Tabagismo [CRATT]), a smoking cessation program at Universidade Estadual de Londrina, state of Paraná, Brazil. The treatment consisted of cognitive therapy and pharmacological agents (bupropion and nicotine replacement therapy) and was used in accordance with Brazilian Ministry of Health guidelines.[14-16]

The CRATT treatment program is usually delivered in a group format of 10-15 participants, with sessions lasting approximately 1½ hours. After an individualized assessment by a physician, the patient attends four weekly group sessions followed by 2 biweekly sessions until week 6. After 6 weeks of treatment, patients are followed monthly for 52 weeks. Parallel to the group sessions, patients also receive pharmacological intervention and monitoring through individual visits if needed. The smoking cessation treatment consists of a cognitive therapy program and pharmacological agents (bupropion and nicotine replacement therapy).[17] The combined program of non-pharmacological treatment and pharmacological agents is effective for both genders, as well as for depressed and non-depressed smokers.[18] After 4 weeks of conventional treatment in the CRATT program, participants who did not stop smoking or reduce their daily number of cigarettes (according to self-reporting and CO_{exh} measures) were invited to participate in the NAC study. After eligibility assessment, patients were randomly allocated into the NAC or placebo group. NAC (1,800 mg/day) and placebo were provided twice daily as identical-looking capsules. A fixed-dose regimen of 1.8 g/day of NAC was prescribed.[19]

Study design

A total of 129 TUD patients from the CRATT program were invited to participate in this study, of whom only 76 agreed. However, 42 of these were found ineligible due to not meeting the inclusion criteria. Thus, 34 TUD outpatients were randomized to the NAC (1,800 mg) or placebo group plus first-line treatment and completed 12 weeks of treatment in an intention-to-treat trial.

Group allocation was performed in a 1:1 ratio. During block randomization, two age-matched groups based on 5-year intervals were selected out of two boxes for assignment to NAC or placebo treatment in a double-blind study.

Except for the pharmacist, all patients and clinicians were blinded to group allocation. All participants were assessed at baseline and at 12 weeks of follow-up with a questionnaire, scales, anthropometric and vital sign measurements, laboratory results, and self-reporting, as well as CO_{exh} levels, which were considered a marker of smoking cessation. This study was registered at ClinicalTrials.gov (registration no. NCT02420418).

All observed or self-reported adverse events were documented. Patients initially returned to CRATT for 2 biweekly treatment sessions, followed by monthly sessions until week 12. Adherence was monitored by pill count at each visit.

Inclusion criteria

Participants aged 18-65 years were accepted for this study, regardless of sex or ethnicity.

Exclusion criteria

The following individuals were excluded: anyone with 1) abnormal blood values in laboratory tests (hemogram, aspartate transaminase, alanine transaminase, urea, and creatinine); 2) cognitive disorders that would compromise understanding of the terms and conditions of the study; 3) pregnant women; 4) a medical illness (including human immunodeficiency virus, hepatitis B and C, auto-/immune disorders, and diabetes type 1); or 5) anyone using immune modulatory drugs, (e.g., glucocorticoids or antioxidants).

Clinical assessment

Questionnaire

A structured questionnaire was used to obtain information on sociodemographic characteristics, such as age, gender, marital status, and educational background. The collected clinical data involved smoking behavior, family history of smoking, prior treatment, and maternal smoking during pregnancy.

Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence (FTND),[20] which has been translated and adapted to Portuguese,[21] was used to determine the nicotine dependence level of all participants. Total FTND scores range from 0 to 10, with nicotine dependence with withdrawal defined as a score $\geqslant$ 6.[22-25]

Lifetime cigarette consumption (pack-years)

The number of pack-years was calculated as the number of cigarettes smoked per day divided by 20 (one pack = 20 cigarettes) multiplied by number of years of exposure.

Heavy smokers

In this study, heavy smoking was defined as smoking at least 20 cigarettes daily, scoring at least FTND $\geqslant$ 6 points and having at least 25 pack-years.

Structured clinical interview

The diagnostic criteria for TUD were assessed by trained psychiatrists according to the Structured Clinical Interview for DSM-IV – Clinical Version, which has been translated and validated for Portuguese,[26] and the ICD-10.[27]

Family history of smoking

Reported smoking in first-degree relatives (siblings, parents, and children) was considered a family history of smoking.

Smoking cessation status according to exhaled carbon monoxide

Smoking status was evaluated using CO_{exh}, which was measured using a Micro CO Meter (Micro Medical Ltd, Rochester, UK) with an electrochemical sensor. All participants were instructed to breathe deeply and hold their breath for 20 seconds, after which they exhaled slowly and completely through a mouthpiece. Smoking cessation was determined according to the CO_{exh} cut-off point: less than 10 parts per million (ppm) was interpreted as likely evidence of smoking cessation.

Hamilton Depression Rating Scale

Depression severity was assessed using the 17-item Hamilton Depression Rating Scale (HDRS-17), which has been translated and adapted for use in Brazil.[28]

Hamilton Anxiety Rating Scale

Developed in 1959, the Hamilton Anxiety Rating Scale (HAM-A)[29] measures the severity of anxiety symptoms. Each item is scored on a scale of 0 (not present) to 4 (severe), with total scores ranging from 0-56.

Minnesota Nicotine Withdrawal Scale

The Minnesota Nicotine Withdrawal Scale (MNWS) is a 5-point scale (scored from 0 to 4: none, slight, mild, moderate, severe), to measure withdrawal symptoms (i.e., craving, irritability, anxiety, difficulty concentrating, restlessness, increased appetite or weight gain, depression, and insomnia). Heart rate (beats per minute) and weight (kg) are also measured.[30] The MNWS was administered at baseline and week 12.

Medication Adherence Rating Scale

Treatment adherence and adverse effects were determined by the 10-item Medication Adherence Rating Scale. The patients answered the statements in the questionnaire by circling the answer that best described their behavior or attitude towards their medication during the past week.[31] The Medication Adherence Rating Scale has been translated and validated for Portuguese.[32]

Anthropometrics and vital measurements

Body mass index (BMI) was calculated as weight (Kg) divided by height squared (m^2). Waist circumference was measured during expiration at the midline between the lower costal margins and the iliac crest parallel to the floor while the participant stood in a relaxed position.

Systolic and diastolic blood pressure

After 10 minutes of rest and in a sitting position, the participant's systolic and diastolic BP were measured with a mercury sphygmomanometer on the right arm. The mean of two measurements, taken 5 minutes apart, was used in the analysis.

Laboratory measurements

Peripheral blood samples were collected from all participants after overnight fasting (12 to 14 hours). All samples were centrifuged at 1,950 *g* for 15 minutes, and plasma or serum aliquots were stored at -80 °C until assayed. The interassay and intra-assay coefficient of variability were $<$ 10% for all assays of human serum. Total cholesterol, low-density lipoprotein cholesterol (LDL-c) (mg/dL), high-density lipoprotein cholesterol (HDL-c) (mg/dL), triglycerides (mg/dL), and glucose (mg/dL) levels were determined by an automated method: Dimension® RXL (Siemens Healthcare Diagnostics Inc, Newark, NJ, USA). HDL-c levels were measured directly, without sample pretreatment or specialized centrifugation steps. LDL-c was calculated by the Friedewald equation. The Friedewald equation is typically used to calculate LDL-c concentration when a lipid panel is performed. Serum triglycerides were measured using an enzymatic procedure employing combinations of enzymes.

Total/HDL cholesterol and LDL-c/HDL-c ratios were calculated. The total/HDL cholesterol ratio is a vascular risk indicator known as the atherogenic or Castelli index. Castelli risk index I and II are computed as total cholesterol/HDL-c and LDL-c/HDL-c, respectively. The LDL-c/HDL-c ratio is also an indicator of vascular risk, the predictive value of which is greater than the isolated parameters.[33] Plasma insulin levels were determined by microparticle enzyme immunoassay (AxSYM, Abbott® Laboratory, Wiesbaden, Germany). A MAGPIX® system

assay (Luminex, Austin, TX, USA) was used to evaluate sTNF-R1, and sTNFR-2, biomarkers of serum leptin levels.

Statistical analysis

The statistical analysis examined the relationship between sociodemographic, clinical, and laboratory data. To compare the NAC and placebo groups at baseline, Student's *t*-test was used for normally-distributed quantitative data; for non-normally distributed data, the Wilcoxon signed rank test was used. The chi-square test or Fisher's exact test were used for qualitative variables. The significance level was set at 0.05. To compare normally distributed data from the NAC and placebo groups at baseline and week 12, a paired Student's *t*-test was used; for non-normally distributed data, the Wilcoxon signed rank test for paired data was used.[34]

Ethics statement

All participants provided written informed consent prior to participating in the study. The study was approved by the Universidade Estadual de Londrina research ethics committee (CAAE 34935814.2.0000.5231).

Results

The baseline, pre-treatment, and clinical characteristics are presented in Table 1. In this 12-week randomized controlled trial, no significant differences were found at baseline regarding heavy smoking (25 pack-years or more), nicotine dependence (FTND $\geqslant$ 6), or cigarettes/day ($\geqslant$ 20) between the NAC and placebo groups. There were no significant differences between two groups at baseline regarding gender, age, years of education, age at onset, years of smoking, family history of smoking, smoking during pregnancy, number of smoking cessation treatments, or the use of nicotine replacement/ bupropion.

The sample's clinical characteristics at baseline and week 12 are summarized in Table 2. P-value 1 compares placebo from baseline to week 12 with placebo treatment; p-value 2 compares NAC from baseline to week 12 with NAC treatment; p-value 3 compares NAC at baseline and placebo at baseline; and p-value 4 compares NAC at week 12 and placebo at week 12.

There were no significant intergroup differences for depression severity (HDRS-17 scale), anxiety severity (HAM-A scale), or nicotine withdrawal symptoms (MNWS) at baseline and week 12. At week 12, there was a significant difference in CO_{exh} between the NAC and placebo groups, although, according to the CO_{exh} data at week 12, the abstinence rates of both groups were significant.

No significant differences were found in clinical measures between baseline and week 12 in either group. No clinically relevant changes occurred over time, and no intergroup differences were found in BMI, BP, or anthropometric measures between baseline and week 12.

Table 3 summarizes the laboratory data at baseline and week 12. No significant intergroup differences were found in glucose and insulin levels at week 12. In the NAC group, significant differences were found between baseline and week 12 in LDL, total cholesterol, leptin, and Castelli risk indexes I and II, as well as a statistically significant reduction in sTNF-R2 levels (p = 0.01). No significant reduction in sTNF-R1 or leptin levels were found in either group at week 12.

Table 4 summarizes the Medication Adherence Rating Scale results at baseline and week 12. No significant intergroup differences were found at week 12 regarding treatment compliance in nine questions, although there

Table 1 Smokers receiving NAC or placebo: baseline sociodemographic characteristics, smoking status, maternal smoking during pregnancy, previous treatment

Variables	Placebo (n=17)	NAC (n=17)	p-value*
Age (years)	46.88 (13.07)	47.06 (9.13)	0.96
Year of education	8.82 (4.89)	9.59 (4.77)	0.65
Gender			0.47
Female	70.60	58.80	
Male	29.40	41.20	
Pack-years	28.20 (15.80)	35.32 (30.78)	0.90
Age at onset (years)	13.71 (2.66)	15.00 (3.08)	0.21
Years of smoking	33.18 (13.00)	32.31 (8.42)	0.21
Cigarettes day $\geqslant$ 20	70.60	52.90	0.29
FTND $\geqslant$ 6	47.10	52.90	0.73
Family history of smoking	76.50	87.50	0.41
Maternal smoking in pregnancy	23.50	30.80	0.66
Nicotine replacement therapy			
Patch	29.40	47.10	0.29
Bupropion	23.50	52.90	0.08

Data presented as mean (standard deviation) or %.
FTND = Fagerström Test for Nicotine Dependence; NAC = *N*-acetylcysteine.
* p-value obtained by Student's *t*-test or the Wilcoxon signed rank test (for quantitative variables) or by the chi-square test or Fisher's exact test (for qualitative variables).

Table 2 Clinical characteristics at baseline and week 12 in a placebo-controlled trial of NAC

Variables	Placebo		p-value 1*	NAC		p-value 2†	p-value 3‡	p-value 4§
	Baseline (n=17)	12 weeks (n=17)		Baseline (n=17)	12 weeks (n=17)			
HDRS-17	8.59 (7.57)	7.00 (6.87)	0.17	6.12 (5.73)	7.06 (7.08)	0.60	0.62	0.67
HAM-A	10.47 (10.97)	7.29 (8.49)	0.20	11.77 (10.83)	11.18 (11.37)	0.81	0.58	0.22
Waist circumference	94.88 (13.55)	94.31 (12.33)	0.63	94.67 (13.56)	99.12 (11.97)	0.07	0.97	0.27
Systolic BP	120.00 (15.06)	119.38 (14.82)	0.83	126.00 (19.57)	124.71 (13.28)	0.99	0.35	0.28
Diastolic BP	78.44 (8.11)	77.19 (9.99)	0.83	77.33 (14.86)	80.88 (13.60)	0.06	0.42	0.51
CO_{exh}	6.50 (5.07)	0.81 (1.28)	< 0.01	10.54 (6.84)	2.88 (3.06)	< 0.01	0.08	0.02
$CO_{exh\ \%}$	7.43 (23.70)	0.13 (0.20)	< 0.01	6.56 (17.29)	0.47 (0.49)	< 0.01	0.24	0.06
MNWS	20.07 (13.35)	10.08 (11.07)	0.08	22.69 (9.84)	19.50 (14.28)	0.33	0.57	0.06
BMI	27.57 (5.08)	27.41 (4.38)	0.99	26.72 (4.66)	26.85 (4.52)	0.57	0.62	0.73

Data presented as mean (standard deviation).
BMI = body mass index; BP = blood pressure; CO_{exh} = exhaled carbon monoxide; HAM-A = Hamilton Anxiety Rating Scale; HDRS-17 = 17-item Hamilton Depression Rating Scale; MNWS = Minnesota Nicotine Withdrawal Scale; NAC = *N*-acetylcysteine.
* p-value 1 obtained for placebo data at baseline and week 12 using Student's *t*-test or the Wilcoxon signed rank test (paired data).
† p-value 2 obtained for NAC data at baseline and week 12 using Student's *t*-test or the Wilcoxon signed rank test (paired data).
‡ p-value 3 obtained for placebo and NAC data at baseline using Student's *t*-test or the Wilcoxon signed rank test (independent data).
§ p-value 4 obtained for placebo and NAC data at week 12 using Student's *t*-test or the Wilcoxon signed rank test (independent data).

Table 3 Laboratory measurements at baseline and week 12 in a placebo-controlled trial of NAC

Biomarkers	Placebo		p-value 1*	NAC		p-value 2†	p-value 3‡	p-value 4§
	Baseline (n=17)	12 weeks (n=17)		Baseline (n=17)	12 weeks (n=17)			
Glucose (mg/dL)	96.06 (14.91)	96.93 (12.93)	0.72	102.41 (39.84)	104.80 (51.10)	0.85	0.99	0.6
Insulin (mU/mL)	9.53 (7.28)	9.75 (5.81)	0.64	7.33 (2.85)	8.94 (6.11)	0.29	0.86	0.69
Lipids (mg/dL)								
TC	200.41 (36.28)	191.42 (29.53)	0.34	203.29 (37.71)	182.13 (27.39)	< 0.01	0.82	0.38
LDL	124.13 (34.42)	113.60 (26.55)	0.58	129.88 (38.36)	105.13 (28.14)	0.02	0.66	0.40
HDL	50.06 (13.07)	51.20 (15.61)	0.29	41.53 (14.00)	42.53 (12.23)	0.98	0.08	0.10
Triglycerides	128.71 (95.81)	132.67 (78.96)	0.85	168.59 (140.25)	167.40 (105.41)	0.82	0.26	0.32
Castelli I	4.28 (1.43)	4.03 (1.11)	0.16	5.44 (2.20)	4.67 (1.69)	0.02	0.09	0.23
Castelli II	2.58 (0.89)	2.40 (0.80)	0.24	3.50 (1.95)	2.75 (1.37)	0.01	0.34	0.40
Leptin (pg/ml)	2,991.40 (3,018.73)	5,368.16 (3,100.73)	< 0.01	1,745.84 (2,479.72)	3,948.53 (3,150.51)	< 0.01	0.14	0.23
sTNF-R1 (pg/ml)	466.43 (496.36)	1,074.35 (493.96)	< 0.01	408.27 (337.49)	1,047.98 (395.68)	< 0.01	0.99	0.88
sTNF-R2 (pg/ml)	6,544.42 (3,961.29)	4,032.89 (1,289.70)	0.13	6,969.85 (4,086.44)	4,083.03 (1,270.21)	0.01	0.87	0.92

Data presented as mean (standard deviation).
HDL = high-density lipoprotein; LDL = low-density lipoprotein; NAC = *N*-acetylcysteine; sTNF-R = soluble tumor necrosis factor; TC = total cholesterol.
* p-value 1 obtained for placebo data at baseline and week 12 using Student's *t*-test or the Wilcoxon signed rank test (paired data).
† p-value 2 obtained for NAC data at baseline and week 12 using Student's *t*-test or the Wilcoxon signed rank test (paired data).
‡ p-value 3 obtained for placebo and NAC data at baseline using Student's *t*-test or the Wilcoxon signed rank test (independent data).
§ p-value 4 obtained for placebo and NAC data at week 12 using Student's *t*-test or the Wilcoxon signed rank test (independent data).

Table 4 Medication Adherence Rating Scale in smokers receiving *N*-acetylcysteine or placebo at week 12

	N-acetylcysteine		Placebo		
Medication Adherence Rating Scale questionnaire	Compliance	Non-compliance	Compliance	Non-compliance	p-value*
Do you ever forget to take your medication?	58.80	41.20	56.20	43.80	0.88
Are you careless at times about taking your medication?	76.50	23.50	68.80	31.20	0.62
When you feel better, do you sometimes stop taking your medication?	100.00	0.00	68.80	31.20	0.01
Sometimes if you feel worse when you take the medication, do you stop taking it?	88.20	11.80	87.50	12.50	0.95
I take my medication only when I am sick.	100.00	0.00	75.00	25.00	0.03
It is unnatural for my mind and body to be controlled by medication.	88.20	11.80	68.80	31.20	0.17
My thoughts are clearer on medication.	35.30	64.70	68.80	31.20	0.06
By staying on medication, I can prevent getting sick.	47.10	52.90	56.20	43.80	0.60
I feel weird, like a zombie on medication.	94.10	5.90	100.00	0.00	0.33
Medication makes me feel tired and sluggish.	76.50	23.50	62.50	37.50	0.38

Data presented as %, unless otherwise specified.
Compliance = no to questions 1-6, 9 and 10, and yes to questions 7 and 8.
* p-value obtained by the chi-square test or Fisher's exact test for qualitative variables.

was significant intergroup difference for the question "When you feel better, do you sometimes stop taking your medication?."

No differences were found in either group regarding adverse events during the treatment period. No participants were withdrawn from the study due to adverse events.

Discussion

In a sample of current heavy smokers, after 12 weeks of first-line treatment that followed clinical practice guidelines, we found improvement in smoking cessation. It has been shown that an association of pharmacotherapy and counseling can substantially improve smoking cessation rates and can significantly increase long-term abstinence rates.[35] Our CO_{exh} level findings at week 12 corroborated this, since an association of first-line treatment for smoking cessation and NAC affected smoking cessation. Nevertheless, both the NAC and placebo groups had significant reductions in CO_{exh} at week 12.

It has been reported that NAC has a potential role in substance use disorder due to its involvement in glutamate signaling and drug seeking behavior.[5,36] NAC reduces cravings via a glutamate pathway[8] and restores extracellular glutamate concentrations, which blocks behaviors associated with nicotine reward.[37] Other studies have found that NAC was superior to placebo in reducing the number of cigarettes smoked daily.[9-11] On the other hand, these studies found no reduction in CO_{exh} of continuous abstinence from smoking.

This 12-week randomized controlled trial showed that treatment with NAC led to significantly greater reductions in sTNF-R2 levels between baseline and week 12. NAC reduces inflammatory cytokines.[12] Conversely, the higher leptin and sTNF-R1 levels should be considered a negative result of NAC and placebo treatment.

NAC is efficacious for neuropsychiatric disorders when the pathophysiology includes glutamatergic transmission, the antioxidant glutathione, neurotrophins, apoptosis, mitochondrial function, and inflammatory pathways.[6] TUD is highly comorbid with depressive disorders, which increase the risk of inflammation. Higher levels of tumor necrosis factor-alpha, interleukin-6, and C-reactive protein were found in depressed-smokers than non-depressed smokers.[38] These findings may contribute to a better understanding of the effects of NAC, an antioxidant, on inflammation.[39] Reducing inflammation may help prevent or treat tobacco-related diseases in heavy smokers with at least 25 pack-years of smoking exposure. Smoking intensity, i.e. the number of packs smoked divided by the number of years of exposure, was the main predictor of increased inflammatory pathway activation.[39]

The NAC group had significant reductions in Castelli risk indexes I and II, as well as other components of metabolism, such as total cholesterol and LDL between baseline and week 12. Due to its antioxidant and anti-inflammatory properties, NAC reduced plasma and liver triglyceride levels.[18] One study reported that male smokers had significantly higher BMI, HDL levels, plasma glucose, and triglycerides than female smokers.[39] Data not shown revealed statistically significant differences in BMI and waist circumference measurement in both groups at 12-week NAC vs. placebo treatment. Several studies have found an association between smoking cessation and weight gain.[40-42] Nicotine-induced weight loss is a result of reduced appetite signaling. Conversely, both active and passive smoking increase the risk of type 2 diabetes mellitus and abdominal fat accumulation.[43]

As expected, we observed no changes in treatment adherence or adverse effects. No changes were found in BP or HDL within or between groups. Smoking cessation treatment with NAC appears to be safe.

These findings should be interpreted in the context of several limitations. Only one NAC dosing regimen was investigated in early remission for 12 weeks, and this was a single-center study with a relatively small sample of current smokers. Future studies are needed to replicate these findings in other settings and explore the efficacy of varying doses of NAC in larger samples of specific populations (including adolescents and older smokers) in sustained remission (12 months or longer). Additional research is needed to establish the effectiveness and safety of NAC in pregnant smokers.

In conclusion, the results of this randomized controlled trial suggest that although NAC and placebo both effectively lowered CO_{exh} levels, NAC significantly decreased sTNF-R2 levels and Castelli risk indices I and II. NAC treatment was not associated with any changes in BP, anthropometrics, withdrawal symptoms, or severity of depression and anxiety. No participants withdrew from the study due to adverse events. Since NAC was a well-tolerated treatment with no considerable side effects, it appears to be safe.

Associating NAC with first-line smoking cessation treatment may affect inflammation and metabolism components, which should reduce tobacco-related diseases and help heavy smokers quit.

Acknowledgements

This study was supported by the Programa de Pós-Graduação em Ciências da Saúde, Universidade Estadual de Londrina (RCBRM's and MP's PhD projects, supervised by SOVN). SOVN has received grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; 470344/2013-0) and is a senior professor at Fundação Araucária, Curitiba, PR, Brazil.

The authors wish to thank the Centro de Referência de Abordagem e Tratamento do Tabagismo, Unidade de Psiquiatria as well as the clinical and research laboratories at Universidade Estadual de Londrina, Londrina, PR, Brazil.

Disclosure

The authors report no conflicts of interest.

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