narra j

Original Article

Efficacy of N-acetylcysteine and motivational enhancement therapy for nicotine addiction: A randomized clinical trial

Martina WS. Nasrun[1], Tribowo T. Ginting[2,3*], Kristiana Siste[1], Jacub Pandelaki[4], Aria Kekalih[5], Melva Louisa[6], Agus D. Susanto[7], Diah S. Utami[8], Immanuel N. Tarigan[9], Alya R. Trishna[10] and Kelvin Halim[11]

[1]Department of Psychiatry, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia; [2]Doctoral Program in Medical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia; [3]Department of Psychiatry, Persahabatan Hospital, Jakarta, Indonesia; [4]Department of Radiology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia; [5]Department of Community Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia; [6]Department of Pharmacology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia; [7]Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia; [8]Division of Rehabilitation, Indonesia National Narcotics Board, Jakarta, Indonesia; [9]Department of Insurance Claim Management, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia; [10]Persahabatan Hospital, Jakarta, Indonesia; [11]Department of Radiology, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

*Corresponding author: t_tuahta@yahoo.com

Abstract

N-acetylcysteine (NAC) is known to enhance neuroplasticity and help reduce smoking addiction by modulating brain metabolites. The use of magnetic resonance spectroscopy (MRS) in smokers receiving NAC as an adjuvant to motivational enhancement therapy (MET) represents a novel approach to understanding how this combination therapy influences brain chemistry. By utilizing MRS, the effectiveness of NAC can be quantitatively assessed by analyzing changes in smoking-affected brain metabolites. The aim of this study was to evaluate the efficacy of NAC combined with MET for nicotine addiction, using MRS to assess neurochemical alterations associated with treatment response. A stratified, randomized, parallel-group clinical trial was conducted, comparing NAC and MET combination to MET only among smokers. The study analyzed the effectiveness of NAC by evaluating glutamate-glutamine (Glx) to creatine ratio (Glx/creatine ratio) and N-acetylaspartate (NAA) to creatine ratio (NAA/creatine ratio) in the nucleus accumbens, bilateral cerebellum, medial prefrontal cortex, ventromedial prefrontal cortex, and bilateral precuneus. Our data indicated that the Glx/creatine ratios for the intervention versus control groups were as follows: nucleus accumbens (0.68 vs 0.43), bilateral cerebellum (0.68 vs 0.43), left medial prefrontal cortex (1.11 vs 0.82), ventromedial prefrontal cortex (0.32 vs 0.86), and bilateral precuneus (0.75 vs 0.58). The NAA/creatine ratios for the intervention versus control groups were as follows: nucleus accumbens (3.55 vs 8.35), bilateral cerebellum (7.82 vs 4.02), left medial prefrontal cortex (5.47 vs 5.20), ventromedial prefrontal cortex (3.55 vs 7.46), and bilateral precuneus (4.73 vs 4.00). Our analysis indicated that the Glx/creatine ratio was higher in the intervention group than in the control group in the medial prefrontal cortex (p=0.02), while the NAA/creatine ratio was higher in the intervention group than in the control group in the bilateral cerebellum (p<0.001). The reported side effects were mild to moderate discomfort and well-tolerated across both groups. These findings highlight the potential of NAC and MET combination in promoting neuroplasticity and supporting nicotine addiction treatment.

Keywords: Smoking cessation, nicotine addiction, N-acetylcysteine, glutamate-glutamine, motivational enhancement therapy

https://narraj.org/

Received: January 27, 2025 - Accepted: March 20, 2025 - Published online: March 24, 2025

Introduction

N-acetylcysteine (NAC), widely used in the management of respiratory diseases [1], has shown promise as a potential treatment for nicotine dependence. Its therapeutic potential is attributed to its ability to modulate neurotransmitter systems, particularly the dopamine and glutamate pathways. The dopamine pathway plays a crucial role in the pathophysiology of various psychiatric disorders, including addiction, schizophrenia, depression, and attention deficit hyperactivity disorder (ADHD) [2]. Dopamine release in the brain enhances the reward system, inducing pleasurable and potentially addictive sensations [3]. A pilot study demonstrated encouraging results regarding NAC's efficacy in nicotine addiction [4]. Participants who received NAC rated their first cigarette after a 3.5-day abstinence period as significantly less rewarding compared to those who received a placebo [4]. These findings suggest that NAC may alter the reinforcing effects of nicotine, highlighting its potential as an adjunctive treatment for smoking cessation.

NAC's role as a precursor to glutathione highlights its potential in mitigating the harmful effects of smoking. It provides cysteine, a critical substrate for modulating the glutamatergic system [5]. The glutamatergic system is integral to the brain's reward mechanism, and its dysregulation has been closely associated with compulsive behaviors and addiction [6]. By restoring glutamatergic homeostasis, NAC may reduce cravings and withdrawal symptoms, providing a neurochemical basis for its potential effectiveness in smoking cessation interventions [7]. Chronic smoking induces oxidative stress, leading to neuroinflammation and neuronal damage, which can reinforce addictive tendencies and contribute to cognitive decline. As an adjuvant therapy for smoking cessation, NAC has demonstrated antioxidative properties that help mitigate oxidative stress, potentially slowing the cognitive deterioration associated with long-term tobacco use [8]. In a study using rat models, NAC treatment significantly reduced tobacco-induced infarct size and improved percent fractional shortening [9]. Another animal study found that NAC effectively reduced reward-seeking behavior by targeting cystine-glutamate antiporters [10].

Complementing pharmacological intervention, motivational enhancement therapy (MET), is a psychotherapeutic approach that focuses on strengthening an individual's intrinsic motivation for behavioral change [11]. Unlike conventional cognitive-behavioral approaches, MET specifically addresses ambivalence and enhances readiness for change by fostering self-efficacy and structured goal-setting [12]. A key component of MET is personalized feedback, in which therapists provide tailored insights based on an individual's specific behaviors and circumstances. This feedback helps individuals recognize discrepancies between their current actions and personal goals, which can be instrumental in motivating change. Additionally, MET emphasizes goal setting, guiding individuals to define and commit to their aspirations for transformation [13].

The combination of MET with pharmacological agents, such as NAC, offers a comprehensive framework for addiction therapy, targeting both the physiological and psychological aspects of nicotine dependence. One innovative approach for assessing the effectiveness of this combination therapy is magnetic resonance spectroscopy (MRS), a non-invasive neuroimaging technique that provides insights into biochemical changes occurring in the brain during addiction treatment [3]. MRS enables the quantitative assessment of brain metabolite concentrations, offering a more objective and precise evaluation compared to other neuroimaging modalities such as functional magnetic resonance imaging (MRI) or positron emission tomography (PET) scans [14]. This capability makes MRS a valuable tool for investigating the neurochemical effects of NAC and MET in smoking cessation intervention, facilitating a deeper understanding of the underlying mechanisms of addiction and recovery.

The aim of this study was to evaluate the efficacy of NAC combined with MET in facilitating smoking cessation. This approach not only advances the theoretical understanding of addiction pathology but also provides practical implications for designing interventions to meet the unique needs of individuals undergoing smoking cessation treatment. By integrating neurochemical insights with behavioral strategies, healthcare providers could optimize treatment outcomes, leading to more effective and personalized approaches to controlling nicotine addiction.

Methods

Study design and setting

A stratified, randomized, parallel-group clinical trial was conducted at the Smoking Cessation Clinic of Persahabatan Hospital, East Jakarta, Indonesia, from December 2022 to March 2023. The aim of this study was to evaluate the effectiveness of NAC administration in smoking addiction by analyzing the glutamate-glutamine (Glx) and N-acetylaspartate (NAA) to creatine ratios in the nucleus accumbens, bilateral cerebellum, medial prefrontal cortex, ventromedial prefrontal cortex, and bilateral precuneus. Glx can be used as an indicator of brain injury, while NAA is a marker for neuronal integrity [15,16]. The study was registered on clinicaltrials.gov (NCT05903014) and conducted in accordance with ethical guidelines. Informed consent was obtained from all participants prior to enrollment. The study was initiated with participant recruitment, informed consent, and baseline data collection, and lasted for a total of 12 weeks. Patients were divided into intervention and control groups, receiving NAC and placebo, respectively, in week 0, followed by MET sessions and readiness ruler measurement. Follow-ups were conducted at weeks 2, 4, 8, 10, and 12 to assess MET progress, side effects, and adherence. In addition, MRS evaluation was conducted along with Glx/creatine and NAA/creatine measurement.

Samples and criteria

This study included male and female active smokers aged at least 18 years who were willing to quit smoking by stating their intention to quit (on a scale from 1 to 10, with a score above 7 was considered willing to quit), had smoked at least ten cigarettes per day for at least six months, and were in the preparation or action stage of smoking cessation based on the University of Rhode Island Change Assessment (URICA) questionnaire [17]. Patients had to be capable of reading, understanding, and following written research instructions and procedures. Exclusion criteria included patients with systemic medical disorders or psychiatric conditions requiring acute management, electronic cigarette users, patients on oral glucocorticoids, those with acute gastrointestinal ulcers, pregnant or breastfeeding women, and those planning pregnancy within the next six months. Participants with a history of self-reported allergic reactions to NAC or its components or those currently undergoing smoking cessation therapy with bupropion, varenicline, or nicotine replacement therapy were also excluded. The criteria for participant dropout included instances where the participants were lost to follow-up, withdrew from the study, or discontinued NAC medication for a duration of ten weeks.

Sampling strategy and randomization

The sample size was determined using the mean differences from unpaired hypothesis tests. The highest calculated minimum sample size was 38 per group (with two groups in total), with an anticipated 10% dropout rate, resulting in a total required sample size of 84 participants. Participants were stratified based on age, daily cigarette consumption, and willingness to quit smoking. Stratified random sampling was employed, and participants were allocated into intervention and control groups using a parallel design with randomizer.com. Double blinding was implemented by coding medicine containers as A and B to ensure that neither researchers nor participants were aware of NAC or placebo allocation. Both NAC and placebo were administered with identical appearances and modes of administration to maintain consistency.

Intervention

The clinical trial was divided into two groups: intervention and control groups. The intervention group received a combination of NAC (pharmacological intervention) and MET, while control group received placebo and MET. The study was conducted over a 12-week period, during which side effects were monitored using self-reported control cards provided to the participants.

NAC was administered at a total dose of 3600 mg per day, divided into two doses, provided once in the morning and once at night for a period of 12 weeks. To optimize therapeutic efficacy and reduce gastrointestinal side effects, NAC was prescribed postprandially, which facilitated optimal absorption and enhanced tolerability. To prevent potential pharmacological interactions, patients were advised not to take NAC concurrently with other medications. Adherence to the

prescribed regimen was closely monitored using a daily consumption control card, which allowed both patients and healthcare providers to track compliance.

MET was delivered biweekly throughout the intervention period, with each session adapted to the individual needs and circumstances of the participants by the therapists. This adaptation was guided by standardized MET protocols (**Table 1**), ensuring a structured yet flexible approach to fostering motivation for behavioral change. The therapy sessions were conducted in person, online, or in a group format, depending on participant preference and availability. For individual sessions, online meetings were offered as an alternative, subject to mutual agreement between the participant and therapist. This flexible delivery method maximized accessibility, accommodated various schedules and comfort levels, and helped reduce potential barriers to engagement, thereby promoting consistent participation throughout the intervention.

Table 1. Motivational enhancement therapy (MET) protocol

MET sessions	Contents	Type
First session	Orientation: introductions, explanation about counseling, determining the stages of change (behavior change stages), determining the readiness ruler, and assessing motivation.	Individual session
Second session	Building motivation for patient change: reflection, establishing empathy, personal feedback, and self-statements (statements about the intention to change). Enhancing the patient's awareness to progress through the stages of change. Measuring readiness ruler.	Individual session
Third session	Requesting the patient to undertake an exercise evaluating the advantages and disadvantages of quitting smoking. Measuring readiness ruler.	Group session
Fourth session	Follow-through to assess the patient's progress by: Observing changes and symptom improvements, as well as evaluating complaints, such as nicotine withdrawal symptoms. Renewing and reinforcing motivation. Recommitting to maintaining a smoke-free status or committing to reducing the number of cigarettes smoked. Measuring readiness ruler.	Group session
Fifth session	Review and termination: Measuring readiness ruler, reviewing the patient's smoking cessation status and progress, revisiting their motivation, encouraging the patient to envision a smoke-free future, concluding the counseling session, and leaving the door open for the patient to return for future consultations.	Group session

Data collection procedures

Participants were recruited through online announcements and notice boards at primary healthcare clinics. Interested individuals contacted the research team and underwent eligibility screening at the Smoking Cessation Clinic of Persahabatan Hospital, East Jakarta, Indonesia.

The initial phase of the study commenced with participant recruitment, applying predefined inclusion and exclusion criteria. Informed consent was obtained through a written consent form, and demographic data were collected using structured questionnaires, including the URICA questionnaire. The recorded demographic characteristics included sex, education level, employment status, marital status, and age.

Participants were then assigned to either the intervention or control group. In week 0, NAC or placebo was administered according to group allocation, followed by the first MET session, verbal readiness ruler assessment, and distribution of written control cards. Follow-up assessments were conducted at weeks 2, 4, 8, 10, and 12, incorporating MET sessions, verbal readiness ruler measurements, side effect monitoring, and adherence tracking using the distributed control cards. The study concluded with an MRS evaluation, analyzing Glx/creatine and NAA/creatine ratios. The steps of the study procedure and data collection are presented in **Figure 1**.

Magnetic resonance spectroscopy (MRS) examination: Study endpoints

The outcomes of the study were the results of MRS examination. Patients underwent MRS examination on the day following the last consumption of 12-week NAC treatment. The MRS procedure was conducted at the Radiology and Nuclear Medicine Services Installation of Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Prior to the examination, patients were provided with detailed explanations of the procedure, confirmed they were not pregnant, and

underwent screening based on a designated screening form. The MRS examination was performed using a 3-Tesla Philips System Ingenia MRI (Philips Healthcare, Best, Netherlands) equipped with Echo Planar Imaging (EPI) sequences. We observed spectrums (ppm) of Glx and NAA relative to creatine in the nucleus accumbens, bilateral cerebellum, medial prefrontal cortex, ventromedial prefrontal cortex, and bilateral precuneus. The acquisition parameters were as follows: field of view (FoV) of 240×240×140 mm; voxel size of 0.9×0.9×10 mm; slice thickness of 0.9 mm with a 6 mm gap; repetition time (TR) of 2000 ms; echo time (TE) of 35 ms; and 25 axial slices. The total duration of the MRS scan was 10 minutes with a phase of 300. The detailed protocol is presented in **Table 2**.

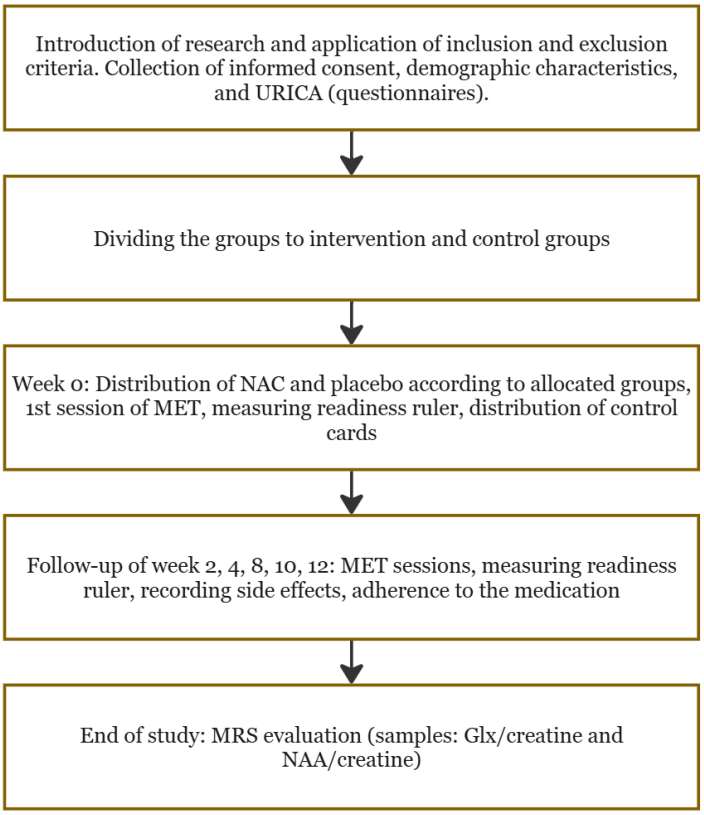

Figure 1. Main steps of the study procedure and data collection.

Table 2. Protocols of magnetic resonance spectroscopy (MRS)

	T1 3D brain	T2 3D brain	Spectroscopy	
			TE 35 (short)	TE 144 (long)
Time of repetition (ms)	Shortest	2500	2000	1500
Time of echo (ms)	Shortest	Shortest	35	144
Field of view (mm)	240×240 mm	240×240 mm	140×140 mm	240×240 mm
Voxel size (mm)	0.9×0.9 mm	0.9×0.9 mm	10×10 mm	10×10 mm
Slice thickness (mm)	0.9 mm	0.9 mm	15 mm	15 mm
Interslice gap (mm)	0	0	6 mm	6 mm
Number of slices	220	440	3	3
NEX/NSA	1	2	1	1
Scan time	07:02	05:53	02:34	02:36

NEX: number of excitations; NSA: number of signals averaged; T1: longitudinal relaxation time; T2: transverse relaxation time; TE: time of echo

Statistical analysis

The results of the univariate analysis for demographic characteristics were presented as frequencies, percentages, and medians (min-max). Bivariate tests, specifically the Chi-squared test, were used to compare the proportions of demographic characteristics between study groups. Comparison of MRS results between study groups in each region (nucleus accumbens, bilateral cerebellum, medial prefrontal cortex, ventromedial prefrontal cortex, and bilateral precuneus)

was performed using an unpaired t-test analysis, with the alternative Mann-Whitney test applied when appropriate. To conduct a more detailed analysis, Robust Poisson Regression was used to assess differences in MRS results between the control and treatment groups. The analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 20 (IBM Corp., Armonk, USA) and STATA version 17 (StataCorp LLC, College Station, USA).

Results

Characteristics of the patients

A total of 90 patients were enrolled, with 46 participants in the intervention group and 44 in the control group. Ten patients (11.11%) withdrew during the study, with reasons including relocation and concerns over potential side effects. Of those who withdrew, seven were in the intervention group and three in the control group, indicating a slightly higher dropout rate in the intervention group (**Figure 2**).

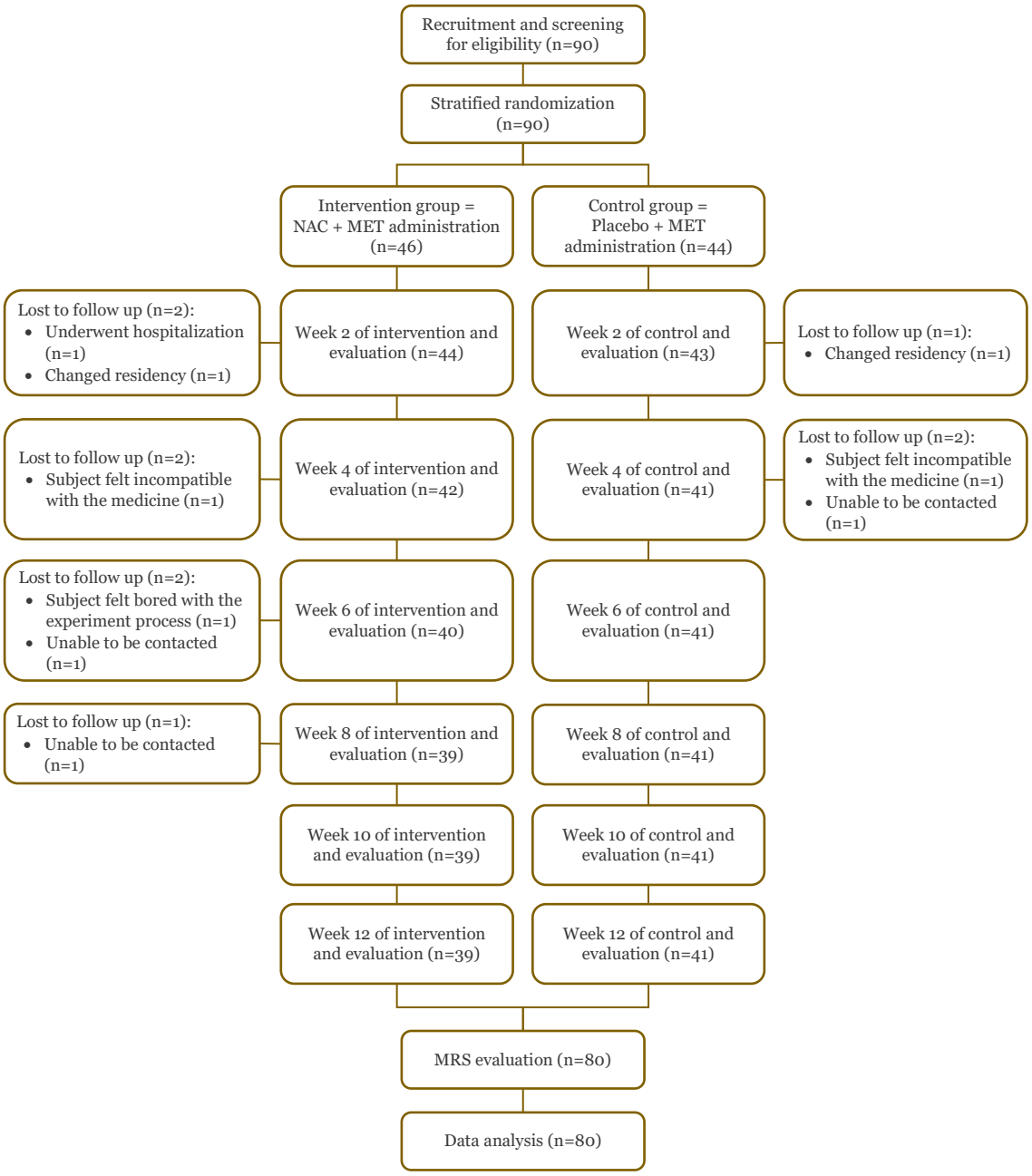

Figure 2. CONSORT diagram of the study.

The demographic characteristics of the included patients are presented in **Table 3**. Out of the total participants, the mean age was 36.23 years, and the majority had completed basic education (61.5% in intervention group and 53.6% in control group). In both groups, vast majority were employed (97.4% in intervention and 97.5% in control), and were married (71.8% in intervention and 78.1% in control). Our statistical analysis indicated there was no significant difference in participant characteristics between the two groups (**Table 3**).

Table 3. Characteristics of active smoker participants included in the study (n=80)

Characteristics	Intervention group (n=39)	Control group (n=41)	*p*-value
	n (%)	n (%)	
Sex			1.000[a]
Male	38 (97.4)	40 (97.5)	
Female	1 (2.56)	1 (2.4)	
Level of education			0.476[a]
Basic education	24 (3.3)	22 (53.6)	
Advanced education	15 (38.5)	19 (46.3)	
Employment status			0.518[a]
Employed	38 (97.4)	40 (97.5)	
Not employed	1 (2.56)	32 (78.0)	
Marital status			0.518[a]
Not married	11 (28.2)	9 (21.9)	
Married	28 (71.8)	32 (78.0)	
Age (average ± standard deviation)	36.38±10.99	37.22±9.33	0.715[b]

[a]Analyzed using Chi-squared test
[b]Analyzed using unpaired Student t-test

Magnetic resonance spectroscopy (MRS) examination

Differences in the ratios of Glx and NAA relative to creatine (Glx/creatine and NAA/creatine) were analyzed across five specific brain regions of interest: the nucleus accumbens, bilateral cerebellum, left medial prefrontal cortex, ventromedial prefrontal cortex, and bilateral precuneus. The example of metabolite levels observed by MRS is presented in **Figure 3**. These regions were selected due to their critical involvement in the neurobiological mechanisms underlying addiction and cognitive processes. Detailed of MRS results are presented in **Underlying data**.

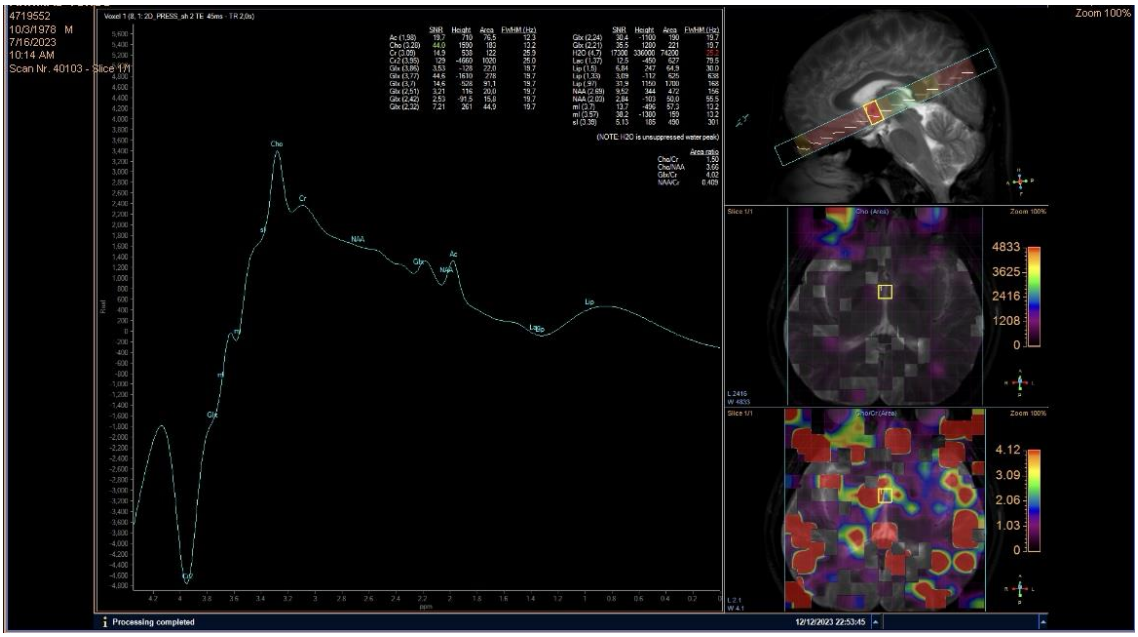

Figure 3. Example of metabolite levels observed by magnetic resonance spectroscopy (MRS) in nucleus accumbens.

Glutamate-glutamine (Glx) to creatine

The Glx/creatine ratio in various brain regions of interest between groups is presented in **Table 4**. The Glx/creatine ratio showed no statistically significant differences between the intervention and control groups across all brain regions analyzed (p>0.05). In the nucleus accumbens, bilateral cerebellum, and ventromedial prefrontal cortex, the intervention group had lower median values, while the opposite was observed in the left medial prefrontal cortex and bilateral precuneus. However, none of these differences reached statistical significance.

Table 4. Comparison of glutamate-glutamine to creatine ratio (Glx/creatine ratio) in specific regions of the brain between groups

Brain region	Glutamate-glutamine to creatine ratio		p-value[a]
	Median (min-max)		
	Intervention (n=39)	Control (n=41)	
Nucleus accumbens	3.55 (0.12–244.00)	8.35 (0.24–355.00)	0.445
Bilateral cerebellum	7.82 (0.41–264.00)	4.02 (0.05–847.00)	0.194
Left medial prefrontal cortex	5.47 (0.34–150.00)	5.20 (0.15–148.00)	0.889
Ventromedial prefrontal cortex	3.55 (0.16–379.00)	7.46 (0.23–430.00)	0.134
Bilateral precuneus	4.73 (0.17–209.00)	4.00 (0.29–183.00)	0.459

[a]Analyzed using Mann-Whitney test

N-acetylaspartate (NAA) to creatine ratio

The NAA/creatine ratio in various brain regions is presented in **Table 5**. In the nucleus accumbens, the intervention group had a ratio of 3.55, compared to 8.35 in the control group (p=0.445). In the bilateral cerebellum, the ratios were 7.82 and 4.02 for the intervention and control groups, respectively (p=0.194). The left medial prefrontal cortex also showed similar ratios between groups (5.47 vs 5.20, p=0.889). In the ventromedial prefrontal cortex, the intervention group had a ratio of 3.55, while the control group had 7.46 (p=0.134). In the bilateral precuneus, the ratios were 4.73 and 4.00 for the intervention and control groups, respectively (p=0.459). These data indicated that the NAA/creatine ratio had no statistically significant differences between the intervention and control groups across all brain regions analyzed.

Table 5. Comparison of N-acetylaspartate to creatine ratio (NAA/creatine ratio) in specific regions of the brain between groups

Region of interest	N-acetyl-aspartate to creatine ratio		p-value[a]
	Median (min-max)		
	Intervention (n=39)	Control (n=41)	
Nucleus accumbens	3.55 (0.12–244.00)	8.35 (0.24–355.00)	0.445
Bilateral cerebellum	7.82 (0.41–264.00)	4.02 (0.05–847.00)	0.194
Left medial prefrontal cortex	5.47 (0.34–150.00)	5.20 (0.15–148.00)	0.889
Ventromedial prefrontal cortex	3.55 (0.16–379.00)	7.46 (0.23–430.00)	0.134
Bilateral precuneus	4.73 (0.17–209.00)	4.00 (0.29–183.00)	0.459

[a]Analyzed using Mann-Whitney test

Ratio comparison of glutamate-glutamine to creatine and NAA to creatine between intervention and control group

The comparisons of the ratios of Glx/creatine and NAA/creatine across different brain regions of interest between treatment and control groups are presented in **Table 6**. The analysis was conducted using Robust Poisson Regression, with the incidence rate ratios (IRR), 95% confidence intervals (CI), and corresponding p-values reported for each region. For the nucleus accumbens, the IRR for the Glx/creatine ratio was 1.0002 (95%CI: 0.9963–1.0041; p=0.912), while the NAA/creatine ratio had an IRR of 0.9978 (95%CI: 0.9782–1.0179; p=0.836), with neither showing statistical significance. Similarly, in the bilateral precuneus, the IRR for Glx/creatine was 0.9928 (95%CI: 0.9190–1.0063; p=0.853), and for NAA/creatine, it was 0.9935 (95%CI: 0.9445–1.0359; p=0.777), indicating no significant differences. In the ventromedial prefrontal cortex, neither the Glx/creatine ratio nor the NAA/creatine ratio had significant differences. The left medial prefrontal cortex showed a statistically significant IRR of 1.0187 (95%CI: 1.0002–1.0345; p=0.020) for the Glx/creatine ratio, while the NAA/creatine ratio was not significant. In the bilateral cerebellum, the NAA/creatine ratio showed statistical significance with an IRR of

1.0016 (95%CI: 1.0010–1.0020; $p<0.001$), whereas the Glx/creatine ratio was also not statistically significant (**Table 6**).

These data indicated that the IRRs for the Glx/creatine and NAA/creatine ratios showed no statistically significant differences across most brain regions, except for the left medial prefrontal cortex, where the Glx/creatine ratio was significant, and the bilateral cerebellum, where the NAA/creatine ratio reached statistical significance.

Table 6. Ratio comparison of N-acetylaspartate (NAA) per creatine and glutamate-glutamine (Glxx) per creatine between intervention and control group

Region of interest	Spectroscopy ratio	Incidence rate ratio	95% confidence interval	*p*-value[a]
Nucleus	Glx/creatine	1.0002	0.9962–1.0041	0.912
	NAA/creatine	0.9978	0.9782–1.0179	0.836
Bilateral precuneus	Glx/creatine	0.9992	0.9916–1.0069	0.853
	NAA/creatine	0.9934	0.9494–1.0395	0.777
Ventromedial cortex	Glx/creatine	1.0017	0.9966–1.0068	0.502
	NAA/creatine	0.9837	0.9539–1.0143	0.294
Left medial prefrontal cortex	Glx/creatine	1.0018	1.0002–1.0034	0.020*
	NAA/creatine	1.0138	0.9901–1.0382	0.255
Bilateral cerebellum	Glx/creatine	1.0011	0.9998–1.0023	0.077
	NAA/creatine	1.0015	1.0010–1.0020	<0.001*

[a]Analyzed with Robust Poisson Regression
*Statistically significant at $p<0.05$

Adverse effects

Regarding side effects, 25 patients in the intervention group and 26 in the control group self-reported adverse reactions. The side effects were verbally reported during MET sessions and written in control cards given. Commonly reported symptoms included gastrointestinal issues (nausea, vomiting, mild abdominal pain, bloating, diarrhea, and constipation), along with headaches and dry mouth (**Table 7**). Importantly, none of these side effects necessitated medical intervention or discontinuation of the treatment, beyond the voluntary withdrawals. These findings suggest that while the treatment was associated with mild to moderate discomfort, it was generally well-tolerated across both groups.

Table 7. Comparisons of adverse effects between intervention and control groups

Adverse effects	Intervention (n=39)	Control (n=40)	*p*-value
	n (%)	n (%)	
Subjects experiencing adverse effects	25 (64.1)	26 (63.1)	0.949[a]
Nausea and vomiting	8 (20.5)	5 (12.2)	0.313[a]
Abdominal pain	6 (15.3)	4 (8.7)	0.513[b]
Bloating	10 (25.6)	8 (19.5)	0.512[a]
Diarrhea	12 (30.7)	10 (24.3)	0.523[a]
Constipation	1 (2.5)	2 (4.8)	1.000[b]
Headache	6 (15.3)	7 (17.1)	0.838[a]
Dry mouth	7 (17.9)	5 (12.2)	0.471[a]

[a]Analyzed using Chi-squared test
[b]Analyzed using Fisher Exact test

Discussion

NAC, an adjuvant therapy for smoking cessation, has demonstrated antioxidative properties that help slow cognitive decline [18]. It is a derivative of the natural amino acid l-cysteine, which rapidly oxidized to cystine and serves as a substrate for the cystine/glutamate antiporter. Cystine is transported into cells and exchanged with glutamate, regulating extracellular glutamate levels [19]. Inside cells, cystine is reduced to cysteine, a key component in the synthesis of glutathione (GSH), the body's primary antioxidant. Increasing evidence suggests that NAC indirectly regulates dopamine release through glutamatergic neurotransmission, acting via presynaptic mGlu2/3 receptors located primarily on neuronal terminals [20]. The dopamine system is implicated in various disorders, including addiction, schizophrenia, depression, and ADHD [2]. NAC also plays a crucial role in modulating the dopaminergic system in individuals with

psychiatric conditions [21]. Additionally, dopamine and its oxidized metabolites can have cytotoxic and neurotoxic effects under oxidative stress, while NAC, as an antioxidant and GSH precursor, could counteract dopamine level fluctuations [22]. In vitro and in vivo studies indicated that NAC directly influenced the dopamine system by increasing dopamine transporter (DAT) binding [23]. Rodent models further demonstrate NAC's protective effects on the dopaminergic pathway, of which under oral administration, NAC has been shown to prevent damage to dopaminergic terminals associated with excessive α-synuclein expression [24]. In rodents overexpressing α-synuclein, NAC treatment increased the density of striatal tyrosine hydroxylase-positive terminals, whereas no such increase was observed in those on a controlled diet [24].

A pilot study demonstrated the effectiveness of NAC combined with psychotherapy for smoking addiction over three months [25]. The combination therapy significantly reduced tobacco consumption in the NAC group and carbon monoxide exhalation (COEXH) levels in patients with therapy-resistant smoking addiction. However, reductions in tobacco consumption have yet to be evaluated using radioimaging. MRS offers a non-invasive method to quantitatively assess connectivity disruptions in aerobic metabolism in the brain [26]. Glx levels reportedly increase when patients are in a state of nicotine satisfaction compared to abstinence [27]. A previous study [28] found that smokers had lower levels of NAA, glutamate, creatine, and myo-inositol in the anterior cingulate cortex and dorsolateral prefrontal cortex compared to non-smokers. NAC administration has been linked to changes in metabolite ratios of Glx and NAA, which serve as key indicators of neuronal function and transmission [16,29]. Glutamate, the brain's most abundant neurotransmitter, and NAA, a marker of neuronal density and integrity, both play essential roles in neuroplasticity [30].

Our data indicated that the Glx and NAA metabolite ratios relative to creatine across various brain regions had differences between the intervention and control groups, although not statistically significant. The Glx/creatine ratio was generally lower in the intervention group compared to the control group in the nucleus accumbens and ventromedial prefrontal cortex. Conversely, the NAA/creatine ratio was higher in the intervention group in the nucleus accumbens, left medial prefrontal cortex, and bilateral precuneus. Further analysis using Robust Poisson Regression revealed significant differences in the Glx/creatine ratio in the left medial prefrontal cortex (p=0.020) and the NAA/creatine ratio in the bilateral cerebellum (p<0.001). These findings suggested glutamate regulation in the left medial prefrontal cortex (a key cognitive region) and an increase in the NAA/creatine ratio in the bilateral cerebellum (a reward-related area). Higher NAA levels are associated with better neurocognitive functioning, while elevated glutamate is often linked to neuronal damage, as seen in conditions such as traumatic brain injury, encephalopathy, and hyperammonemia [28]. A study demonstrated significant decrease in Glx/creatine levels with NAC administration in cocaine-dependent patients [31]. Another study used fMRI to assess NAC's effects on nicotine addiction, showing increased connectivity in the nucleus accumbens, medial and ventromedial prefrontal cortex, bilateral cerebellum, and precuneus compared to the placebo group [32]. These areas, linked to reward processing, decision-making, and craving, are critical in addiction. A study evaluated NAC's neuroprotective effects in spinal cord injury patients and found that NAC treatment reduced the expression of the pro-apoptotic protein Bcl-2 associated X-protein (BAX) in cervical spinal cord tissue, suggesting its potential role in neural plasticity recovery [33].

This study demonstrates that NAC has a statistically significant impact on glutamate metabolism, a key component of the Glx cycle. This metabolic pathway is believed to possess antioxidant and anti-inflammatory properties, which are essential for maintaining homeostasis in the central nervous system. By influencing glutamate metabolism, NAC has the potential to modulate the function of the glutamatergic system, which is closely associated with addiction mechanisms and reward-seeking behaviors. The potential glutamate-modulating effects of NAC are thought to arise from its ability to correct neurotransmitter imbalances often observed in individuals struggling with addiction. These imbalances can perpetuate compulsive behaviors and disrupt brain's reward system, both of which are critical in nicotine dependence.

In addition to its effects on neurotransmitter regulation, NAC may also play a neuroprotective role by preserving neuronal health and supporting the maintenance of healthy

levels of NAA, which serves as a marker of neuronal integrity and function. Through this neuroprotective action, NAC is thought to enhance neuroplasticity, the brain's ability to adapt and reorganize itself in response to changes or injury. This promotion of neuroplasticity is particularly relevant in the context of nicotine addiction, as it may aid in the recovery and restoration of brain functions impaired by prolonged exposure to nicotine. Collectively, these findings suggest that NAC not only addresses the neurochemical aspects of addiction but also supports overall brain health, making it a promising therapeutic agent in smoking cessation and addiction treatment strategies.

This study has limitations, including a single-time-point MRS evaluation and the absence of long-term follow-up radiological assessments. Future research should incorporate baseline MRS assessments, including non-smokers and various types of smokers, explore other addiction populations, and conduct subgroup analyses with different modalities and biomarkers. These steps would provide a more comprehensive understanding of NAC's effects and the potential of MRS in nicotine addiction management.

Conclusion

This clinical trial indicated that NAC and MET combination therapy influenced brain metabolite levels. The Glx/creatine ratio was higher in the left medial prefrontal cortex, while the NAA/creatine ratio was higher in the bilateral cerebellum in the intervention group compared to the control group. These findings suggest differences in neuroplasticity among smokers receiving NAC and MET combination therapy compared to those receiving MET alone. Nevertheless, although the combination of NAC and MET shows promise, larger-scale studies are needed to validate and generalize these findings.

Ethics approval

Ethical approval for this study was granted by two reputable institutions: the Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia (Approval Number: KET-727/UN2.F1/ETIK/PPM.00.02/2022) and the Ethics Committee of Persahabatan Hospital (Approval Number: 71/KEPK-RSUPP/08/2022). The study adhered to rigorous ethical standards, protecting the rights, welfare, and confidentiality of all participants involved. The informed consent was obtained from each participant prior to their inclusion in the study. The process included providing detailed explanations about the study's objectives, procedures, potential risks, and benefits, ensuring that all participants understood and voluntarily agreed to participate.

Acknowledgments

We would like to extend our deepest gratitude to all the participants who generously volunteered their time, effort, and valuable insights to make this research possible. Their willingness to engage in the study and share their experiences was critical to the success of this project, and their contributions have provided meaningful data that we hope will lead to impactful advancements in the field. We sincerely appreciate their dedication and cooperation, which were essential to achieving our research objectives. Furthermore, we wish to express heartfelt thanks to our families and friends for their unwavering support, patience, and encouragement throughout the course of this endeavor. Their belief in our work and their understanding of the challenges we faced played an invaluable role in helping us stay focused and motivated. Whether through emotional support, practical advice, or simply being a source of inspiration, their contributions have been an integral part of this journey. Without their encouragement and steadfast presence, this research would not have been possible, and for that, we are profoundly grateful.

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

This work was supported by Universitas Indonesia (Grant Number 345).

Underlying data

Detailed of MRS results are available at https://data.mendeley.com/datasets/8rsnzt3529/2.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

How to cite

Nasrun MWS, Ginting TT, Siste K, *et al.* Efficacy of N-acetylcysteine and motivational enhancement therapy for nicotine addiction: A randomized clinical trial. Narra J 2025; 5 (1): e2178 - http://doi.org/10.52225/narra.v5i1.2178.

References

1. Tenório MC dos S, Graciliano NG, Moura FA, *et al.* N-acetylcysteine (NAC): Impacts on human health. Antioxidants 2021;10(6):967.
2. Smaga I, Frankowska M, Filip M. N-acetylcysteine as a new prominent approach for treating psychiatric disorders. Br J Pharmacol 2021;178(13):2569-2594.
3. Benowitz NL. Neurobiology of nicotine addiction: Implications for smoking cessation treatment. Am J Med 2008;121(4):S3-S10.
4. Schmaal L, Berk L, Hulstijn KP, *et al.* Efficacy of N-acetylcysteine in the treatment of nicotine dependence: A double-blind placebo-controlled pilot study. Eur Addict Res 2011;17(4):211-216.
5. Mokhtari V, Afsharian P, Shahhoseini M, *et al.* A review on various uses of N-acetylcysteine. Cell J 2017;19(1):11-17.
6. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat Neurosci 2010;13(5):635-641.
7. Sansone RA, Sansone LA. Getting a knack for NAC: N-Acetyl-cysteine. Innov Clin Neurosci 2011;8(1):10-14.
8. Harlivasari AD, Susanto AD, Taufik FF, Ginting TT. The role of twice-daily N-acetylcysteine (NAC) 2400 mg in smoking cessation: A randomized, placebo-controlled trial in Indonesia. Cureus 2024;16(2):e54322.
9. Khanna AK, Xu J, Mehra MR. Antioxidant N-acetylcysteine reverses cigarette smoke-induced myocardial infarction by inhibiting inflammation and oxidative stress in a rat model. Lab Invest 2012;92(2):224-235.
10. Baker DA, McFarland K, Lake RW, *et al. N*-acetycysteine-induced blockade of cocaine-induced reinstatement. Ann N Y Acad Sci 2003;1003(1):349-351.
11. Dunn EC, Neighbors C, Larimer ME. Motivational enhancement therapy and self-help treatment for binge eaters. Psychol Addict Behav 2006;20(1):44-52.
12. Kumar S, Srivastava M, Srivastava M, *et al.* Effect of motivational enhancement therapy (MET) on the self efficacy of individuals of alcohol dependence. J Family Med Prim Care 2021;10(1):367-372.
13. Asmita A, Patil PS, Sahu N. Evaluating the impact of motivational enhancement therapy on tobacco cessation in schizophrenia: A comprehensive review. Cureus 2024;16(9):e70046.
14. Egerton A. The potential of ^{1}H-MRS in CNS drug development. Psychopharmacology 2021;238(5):1241-1254.
15. Shutter L, Tong KA, Holshouser BA. Proton MRS in acute traumatic brain injury: Role for glutamate/glutamine and choline for outcome prediction. J Neurotrauma 2004;21(12):1693-1705.
16. Ward P, Moss HG, Brown TR, *et al.* N-acetylcysteine mitigates acute opioid withdrawal behaviors and CNS oxidative stress in neonatal rats. Pediatr Res 2020;88(1):77-84.
17. DiClemente CC, Schlundt D, Gemmell L. Readiness and stages of change in addiction treatment. Am J Addict 2004;13(2):103-119.
18. Raghu G, Berk M, Campochiaro PA, *et al.* The multifaceted therapeutic role of N-acetylcysteine (NAC) in disorders characterized by oxidative stress. Curr Neuropharmacol 2021;19(8):1202-1224.
19. Piani D, Fontana A. Involvement of the cystine transport system xc- in the macrophage-induced glutamate-dependent cytotoxicity to neurons. J Immunol 1994;152(7):3578-3585.
20. Baker DA, Madayag A, Kristiansen LV, *et al.* Contribution of cystine–glutamate antiporters to the psychotomimetic effects of phencyclidine. Neuropsychopharmacology 2008;33(7):1760-1772.
21. Minarini A, Ferrari S, Galletti M, *et al.* N-acetylcysteine in the treatment of psychiatric disorders: Current status and future prospects. Expert Opin Drug Metab Toxicol 2017;13(3):279-292.

22. Möller M, Du Preez JL, Viljoen FP, *et al.* N-acetylcysteine reverses social isolation rearing induced changes in cortico-striatal monoamines in rats. Metab Brain Dis 2013;28(4):687-696.
23. Monti DA, Zabrecky G, Kremens D, *et al.* N-acetyl cysteine is associated with dopaminergic improvement in Parkinson's disease. Clin Pharmacol Ther 2019;106(4):884-890.
24. Clark J, Clore EL, Zheng K, *et al.* Oral N-acetyl-cysteine attenuates loss of dopaminergic terminals in α-synuclein overexpressing mice. PLoS One 2010;5(8):e12333.
25. Prado E, Maes M, Piccoli LG, *et al.* N-acetylcysteine for therapy-resistant tobacco use disorder: A pilot study. Redox Rep 2015;20(5):215-222.
26. Elshal FIS, Elshehaby WA, Dawoud MA, *et al.* Magnetic resonance imaging and spectroscopy in evaluation of hypoxic ischemic encephalopathy in pediatric age group. Egypt J Radiol Nucl Med 2021;52(1):198.
27. Sumithrarachchi SR, Jayasinghe R, Warnakulasuriya S. Betel quid addiction: A review of its addiction mechanisms and pharmacological management as an emerging modality for habit cessation. Subst Use Misuse 2021;56(13):2017-2025.
28. Durazzo TC, Gazdzinski S, Banys P, *et al.* Cigarette smoking exacerbates chronic alcohol-induced brain damage: A preliminary metabolite imaging study. Alcohol Clin Exp Res 2004;28(12):1849-1860.
29. McQueen G, Lally J, Collier T, *et al.* Effects of N-acetylcysteine on brain glutamate levels and resting perfusion in schizophrenia. Psychopharmacology 2018;235(10):3045-3054.
30. Hellem T, Shi X, Latendresse G, *et al.* The utility of magnetic resonance spectroscopy for understanding substance use disorders. J Am Psychiatr Nurses Assoc 2015;21(4):244-275.
31. Schmaal L, Veltman DJ, Nederveen A, *et al.* N-acetylcysteine normalizes glutamate levels in cocaine-dependent patients: A randomized crossover magnetic resonance spectroscopy study. Neuropsychopharmacology 2012;37(9):2143-2152.
32. Froeliger B, McConnell PA, Stankeviciute N, *et al.* The effects of N-acetylcysteine on frontostriatal resting-state functional connectivity, withdrawal symptoms and smoking abstinence: A double-blind, placebo-controlled fMRI pilot study. Drug Alcohol Depend 2015;156:234-242.
33. Karalija A, Novikova LN, Kingham PJ, *et al.* The effects of N-acetyl-cysteine and acetyl-L-carnitine on neural survival, neuroinflammation and regeneration following spinal cord injury. Neuroscience 2014;269:143-151.