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Effectiveness of N-acetylcysteine in Treating Clinical Symptoms of Substance Abuse and Dependence: A Meta-analysis of Randomized Controlled Trials

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Objective: Treatment with N-acetylcysteine (NAC) is believed to reduce the clinical symptoms among individuals with substance abuse or dependence. We conducted a meta-analysis of randomized controlled trials to evaluate the effectiveness of NAC in treating substance abuse and dependence.
Methods: PubMed, EMBASE, ClinicalTrials.gov registry, and the Cochrane Library were searched for trials published before June 2020.
Results: A total of 16 trials were analyzed. The treatment effectiveness domains assessed in this study were craving and depressive symptoms, withdrawal syndrome, adverse events, and smoking frequency. Standardized mean difference (SMD), weighted mean difference (WMD), and odds ratio (OR) were used for evaluation where appropriate. A significant decrease in craving symptoms was observed in the NAC treatment group compared with the control group (SMD, −0.67; 95% confidence interval [CI], −1.21 to 0.21). When withdrawal and depressive symptoms were considered as a single domain, the NAC treatment group demonstrated a significantly higher overall improvement than the control group (SMD, −0.35; 95% CI, −0.64 to −0.06). No between-group differences in term of the OR of adverse events (OR, 1.18; 95% CI, 0.68 to 2.06) and a non-significant trend toward reduction in smoking frequency was observed in the NAC treatment group compared with the control group (WMD, −3.09; 95% CI, −6.50 to 0.32).
Conclusion: NAC provides certain noticeable benefits in attenuating substance craving and might help alleviate depressive symptoms and withdrawal syndrome. Precautious measures should be considered when using NAC although no difference in adverse effects was found between NAC treatment and control group.

KEY WORDS: Acetylcysteine; Addiction; Substance; Craving; Depression; Withdrawal.

INTRODUCTION

According to the 2015 National Survey on Drug Use and Health conducted in the United States, 27.1 million people aged 12 or older had used illicit drugs within the preceding 30 days. Moreover, an estimated 52 million people were current cigarette smokers and 138.3 million were current alcohol users, and approximately 20.8 million people had substance use disorders (i.e., substance abuse and substance dependence) related to their use of alcohol or illicit drugs within the preceding year [1]. The Global Burden of Disease Study 2010 also indicated that substance use disorders accounted for 14.7% of dis-

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ability-adjusted life years, computed as the sum of the number of years living with disability and that of years lost to premature mortality. A large proportion of patients choose to discontinue treatment for various reasons such as experiencing severe withdrawal symptoms and psychological problems, and ultimately, the disorders relapse [2]. Therefore, developing a more effective treatment strategy for substance abstinence and the alleviation of accompanying adverse effects is imperative.

Synaptic transmission within the central nervous system is mainly mediated by glutamate and extracellular glutamate is maintained by the exchange of extracellular cysteine for intracellular glutamate [3]. An imbalance between synaptic and non-synaptic glutamate may be linked to the development of addictive behaviors in different substance use disorders [4-9]. N-acetylcysteine (NAC), a common mucolytic agent, breaks the disulfide bridges of glycoprotein and converts to glutathione [10] to act as a physiological reservoir of neuronal glutamate [11]. The balance of glutamate level and between neural cells influences synaptic excitability [12]. Several animal studies have showed that NAC may have the ability to normalize glutamate levels in abnormally excited synapses. Baker *et al.* [13] demonstrated that repeated cocaine administration reduced the basal extracellular glutamate levels in the nucleus accumbens and the cysteine-glutamate exchange rate in cocaine treated rats. Importantly, infusion of NAC has been shown to increase the extracellular glutamate levels of the cocaine-withdrawn rats and inhibited the cocaine-primed reinstatement of drug seeking behavior. Also, Ducret *et al.* [14] showed that cocaine-addicted rats under NAC treatment are more sensitive to punishment compared to the placebo group. These findings suggest that managing glutamate levels through NAC administration may be a promising and low-cost strategy for treating substance addiction and preventing relapse.

The effectiveness of NAC in treating substance use disorders has recently been investigated in several randomized controlled trials (RCTs). Several systematic reviews have described the effects of NAC on other addiction management [15-17]. Although a recent meta-analysis of RCTs examined the effectiveness of NAC in treating substance use disorders, the analysis focused only on the presentation of craving among the patients [18]. Thus, we conducted a meta-analysis on RCTs that have been available to this date to investigate the general effectiveness of NAC in alleviating the common clinical symptoms of substance abuse and dependence.

METHODS

Inclusion and Exclusion Criteria

Trials evaluating the effectiveness of NAC for treating substance use disorders among participants who abused or were dependent on nicotine, alcohol, cocaine, amphetamine, or cannabis were included. We selected RCTs that clearly reported the inclusion and exclusion criteria; drug dosage; and craving, depression, and withdrawal status of the participants. We excluded the trials that met at least one of the following criteria: (1) participants were of severe psychiatric disorders other than substance abuse or dependence, or were of physical disorders, (2) effects of NAC confounded, (3) cohorts were reported in duplicate.

Searching Strategy and Study Selection

Relevant published trials published before August 2020 searched and identified from the PubMed, Cochrane Library Database, and EMBASE. The following Medical Subject Headings terms were used: *addiction* OR *abstinence* OR *cessation* OR *craving* OR *dependence* OR *substance use disorder* OR *depression* OR *withdrawal* OR *addictive disorder* AND *N-acetylcysteine* OR *glutamate level*. The "related articles" option in PubMed was used to broaden the search scope and all retrieved abstracts, studies, and citations were reviewed. In addition, trials were searched in the reference sections of relevant papers and through correspondence with field experts. Finally, unpublished studies were collected from the ClinicalTrials.gov registry (http://clinicaltrials.gov/). No language restrictions were applied. The proposal of our systematic review and meta-analysis was reviewed and accepted by PROSPERO (registration number: CRD42017072830).

Data Extraction

Baseline and outcome data were independently abstracted by two reviewers (C.T.C. and P.J.H.). Trial characteristics (study design, demographics, inclusion criteria, and intervention) and data on craving, depression, urine tests, and smoking patterns were extracted. The reviewers' individually recorded decisions were compared (C.T.C. and C.H.L.) and disagreements were resolved by consult-

ing the third and fourth reviewers (K.W.T. and E.W.L.). Authors of the analyzed trials were contacted for additional information when necessary.

Methodological Quality Appraisal

Two reviewers (C.T.C. and P.J.H.) independently assessed the methodological quality of each trial based on the revised Cochrane risk of bias tool for randomized trials [19] and disagreements were resolved by consulting the third and fourth reviewers (K.W.T. and E.W.L.). The assessed domains were selection, performance, detection, attrition, and reporting biases.

Outcomes

The primary outcomes were craving, depressive symptoms, and withdrawal syndrome. Thus, trials with at least one of the above outcomes meeting the inclusion criteria and survived the excluded criteria were used in this study. The secondary outcomes were adverse events and smoking frequency. Adverse events are generally reported when evaluating the effectiveness of a target drug. Smoking frequency was included in our study because smoking generally occurs alongside substance abuse or dependence.

Statistical Analyses

Data were entered and analyzed using Review Manager Version 5.3 (Cochrane Collaboration, Oxford, UK) and the meta-analysis was performed in accordance with the PRISMA guidelines [20]. When not reported, standard deviations were estimated based on the provided confidence interval (CI) limits and standard errors. Because different craving and depression scales were used in the included trials, the standardized mean difference (SMD), an effect measure which has been proved feasible when pooling results of different scales and units [21], was used for the current analysis. The weighted mean difference (WMD) was used to evaluate the smoking frequency, and odds ratio (OR) were used to compare the incidence of any adverse event between patients treated with NAC and controls. The precision of each effect size was reported as a 95% CI. The pooled estimate was computed using the random-effects model [22]. Cochran's Q test was conducted and I^2 statistics were calculated to evaluate statistical heterogeneity and inconsistency between treatment effects across the trials. Statistical significance was set at $p < 0.1$ for Cochran's Q test. Statistical heterogeneity across studies was assessed using the I^2 test, which quantifies the proportion of total outcome variability across trials. For the ease of reporting, we tentatively assigned low, moderate, and high to I^2 values of 0−25%, 25−50%, and 50−75% [23]. For I^2 values higher than 75%, we assigned them to very high.

RESULTS

Trial Characteristics

Figure 1 illustrates the screening and selection procedures of the trials. The initial search yielded 1,035 citations, from which 258 duplicates were removed. The remaining 775 citations were retained for further evaluation. Among these, 673 were ineligible because they were not related to our research topic or uncompleted trials without sufficient data. The contents of the remaining 102 citations were fully assessed. Sixty-five of them were excluded because they were trials of other disorders and another 14 studies were excluded for being wrong article type. Another 7 articles were further excluded for meeting

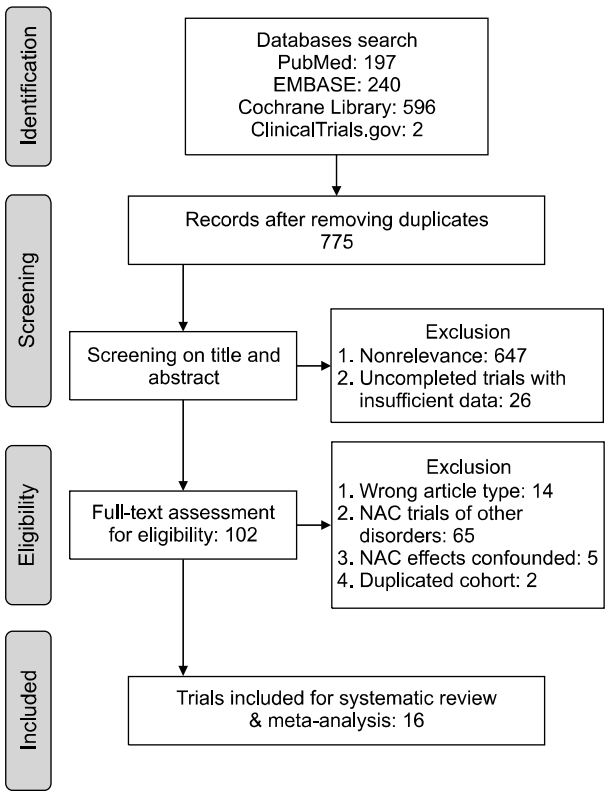

Fig. 1. Flowchart of trials selection.
NAC, N-acetylcysteine.

the exclusion criteria, including 5 trials with NAC effect confounded and another 2 trials that used a duplicated cohort. Although Roten *et al.* [24] used the same patient cohort as that used by Gray *et al.* [25], the results of both trials were analyzed in our study because they evaluated different domains of interest. Finally, 16 trials were eligi-

Table 1. Characteristics of the selected randomized controlled trials

Trial	Inclusion criteria	N (% male)	Age	Substance	Intervention
Back *et al.* 2016 [36]	DSM-IV current substance use disorder, and PTSD or subthreshold PTSD MMSE > 21	I: 14 (100) C: 13 (92.3)	R: 18−65 I: 49.9 ± 8.1 C: 48.0 ± 8.6	Poly-drug	I: NAC 2,400 mg/day × 8 weeks C: Placebo
Froeliger *et al.* 2015 [27]	FTND > 3, ≥ 10 cigarettes/day and nicotine delivering > 0.05 mg for at least 2 years	I: 8 (75) C: 8 (62)	I: 35.0 ± 14.4 C: 38.0 ± 9.6	Tobacco	I: NAC 2,400 mg/day × 4 days C: Placebo
Grant *et al.* 2014 [26]	DSM-IV nicotine dependence and pathological gambling, FTND ≥ 4	I: 13 (NA) C: 15 (NA)	R: 25−70 47.6 ± 10.9	Tobacco	I: NAC 1,200−3,000 mg/day × 12 weeks C: Placebo
Gray *et al.* 2012 [25] & Roten *et al.* 2013 [24]	DSM-IV cannabis dependence	I: 58 (68.4) C: 58 (77.6)	I: 18.9 ± 1.5 C: 18.8 ± 1.5	Cannabis	I: NAC 2,400 mg/day × 8 weeks C: Placebo
Gray *et al.* 2017 [31]	DSM-IV-TR cannabis dependence with positive urine cannabinoid test	I: 153 (76.5) C: 149 (66.4)	R: 18−50 I: 29.8 ± 8.7 C: 30.8 ± 9.3	Cannabis	I: NAC 2,400 mg/day × 12 weeks C: Placebo
Knackstedt *et al.* 2009 [28]	≥ 10 cigarettes/day for at least 1 year	I: 14 (NA) C: 15 (NA)	I: 48.6 ± 10.5 C: 51.3 ± 10.1	Tobacco	I: NAC 2,400 mg/day × 8 weeks C: Placebo
LaRowe *et al.* 2006 [33]	DSM-IV cocaine dependence with positive urine drug screen	I: 6 (46.2) C: 7 (53.8)	R: 23−45 M: 37.1	Cocaine	I: NAC 2,400 mg/day × 3 days C: Placebo
LaRowe *et al.* 2013 [32]	DSM-IV cocaine dependence	I: 40 (75) C: 33 (76)	I: 43.5 ± 10.1 C: 43.3 ± 8.9	Cocaine	I: NAC 2,400 mg/day × 8 weeks C: Placebo
Mousavi *et al.* 2015 [39]	DSM-IV-TR methamphetamine dependence	I: 11 (81.8) C: 12 (83.3)	R: 22−40 I: 29.9 ± 4.7 C: 28.5 ± 5.1	Amphetamine	I: NAC 600 mg/day × 0−2 weeks and 1,200 mg/day × 2−4 weeks C: Placebo
McClure *et al.* 2014 [37]	Cannabis dependence (> 3 days/week)	I: 34 (NA) C: 34 (NA)	R: 15−21 M: 18.8	Tobacco and cannabis	I: NAC 2,400 mg/day × 8 weeks C: Placebo
Prado *et al.* 2015 [2]	DSM-IV Tobacco use disorder	I: 17 (41) C: 14 (14)	R: 18−65 I: 51.9 ± 7.0 C: 50.7 ± 11.8	Tobacco	I: NAC 3,000 mg/day × 14 months C: Placebo
Schmaal *et al.* 2011 [29]	Undergraduate students, ≥ 15 cigarettes/day	I: 10 (40) C: 12 (42)	I: 21.4 ± 2.1 C: 20.3 ± 1.1	Tobacco	I: NAC 3,600 mg/day × 3.5 days C: Placebo
Schulte *et al.* 2017 [30]	Smokers, ≥ 15 cigarettes/day, FTND ≥ 3	I: 19 (100) C: 20 (100)	R: 15−55 I: 37.0 ≥ 9.9 C: 33.1 ≥ 9.6	Tobacco	I: NAC 2,400 mg/day × 14 days C: Placebo
Yoon 2013 [34]	DSM-IV alcohol dependence	I: 22 (90.9) C: 24 (91.7)	I: 50.1 ± 11.3 C: 56.5 ± 7.0	Alcohol	I: NAC 900 mg/day × 1 week, NAC 1,800 mg/day × 1 week, NAC 2,700 mg/day × 1 week, NAC 3,600 mg/day × 5 weeks C: Placebo
Yoon 2017 [35]	DSM-IV alcohol dependence	I: 31 (93.5) C: 33 (84.8)	R: 18−64	Alcohol	I: NAC plus high-dose Naltrexone (150 mg) × 12 weeks C: High-dose Naltrexone (150 mg)

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; PTSD, posttraumatic stress disorder; MMSE, Mini-Mental State Examination; FTND, Fagerström Test for Nicotine Dependence; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision; N, exact number of participants used in statistical analysis; I, intervention; C, control; R, range; M, mean; NAC, N-acetylcysteine.
LaRowe *et al.* [32] used two intervention groups- one with NAC 1,200 mg/day × 8 weeks and one with NAC 2,400 mg/day × 8 weeks. We chose the intervention group treated with NAC 2,400 mg/day × 8 weeks. Yoon [35] reported data of three intervention groups. The first group was treated with NAC plus high-dose Naltrexone (150 mg) × 12 week, the second group was treated with high-dose Naltrexone (150 mg) alone, and third group was treated with low-dose Naltrexone (50 mg) alone. We chose the first two groups for meta-analysis. Gray *et al.* 2012 [25] and Roten *et al.* 2012 [24] were considered as one single trial. Only the information of the selected groups is presented in the table.

ble for our study. Their characteristics are presented in Table 1.

The aforementioned trials were published between 2006 and 2018 and had sample sizes ranging from 13 to 302 with a total of 897 participants. Six trials were related to smoking in which 1 recruited participants who met the criteria for tobacco use disorder [2], 1 recruited participants who met the criteria for nicotine dependence [26], 2 recruited participants who smoked more than 10 cigarettes per day [27,28], and 2 recruited participants who smoked more than 15 cigarettes per day [29,30]; 2 recruited participants who met the criteria for cannabis abuse [25,31]; 1 recruited participants with methamphetamine dependence [30]; 2 recruited participants with cocaine dependence [32,33]; 2 recruited participants with alcohol dependence [34,35], and 2 recruited participants who abused multiple substances [36,37]. All trials compared NAC with a placebo except Yoon [35] in which NAC plus Naltrexone was compare with Naltrexone.

The methodological quality of the analyzed trials is summarized in Table 2. Regarding the overall bias, 12 trials contained some concerns, 1 was low risk, and 2 were high risk. The major sources of overall bias came from selection, performance and detection bias, all of which were judged according to the availability of descriptions of allocation and concealment methods, and management strategy; however, randomization was claimed. Seven trials had a low risk of attrition bias (loss of follow-up $< 20\%$), while 6 trials contained some concerns ($20\% \leq$ loss of follow-up $< 30\%$) and 2 trials had a high risk (loss of follow-up $\geq 30\%$) in this domain. For detection bias, 9 trials contained some concerns and 6 trials had a low risk. We found no obvious signs of reporting bias and thus all included trials were graded with low risk.

Baseline

All baseline data of the following outcomes were reported in the included trials except LaRowe *et al.* [32]. No differences in baseline were observed between the comparison groups for those which reported the baseline data.

Craving Symptoms

For meta-analysis of craving symptoms, we used the included trials in which the participants were treated for at least 4 weeks and craving symptoms assessed after 4 weeks treatment or more because anti-craving effect of a drug is not clinically meaningful at the treatment initiation days. Seven included trials met these criteria. Among these trials, 6 reported the endpoint results and one reported average result. Among the 6 trials that reported the endpoint results, craving symptoms were measured by using the Visual Analogue Scale [36], Questionnaire for Smoking Urges-Brief [38], Cocaine Craving Questionnaire-Brief [39], Marijuana Craving Questionnaire [24], and Penn Alcohol Craving Scale [34,35] at baseline and after 4 weeks [38,39], 8 weeks [24,34,36], and 12 weeks [35]. For LaRowe *et al.* [32] who reported no information on baseline, the overall result of Brief Substance Craving

Table 2. Risk of bias

Trial	Selection	Performance	Attrition	Detection	Reporting	Overall
Back *et al.* 2016 [36]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Froeliger *et al.* 2015 [27]	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Grant *et al.* 2014 [26]	Some concerns	Some concerns	Some concerns	Some concerns	Low risk	Some concerns
Gray *et al.* 2012 [25] and Roten *et al.* 2013 [24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Gray *et al.* 2017 [31]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Knackstedt *et al.* 2009 [28]	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Some concerns
LaRowe *et al.* 2006 [33]	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns
LaRowe *et al.* 2013 [32]	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Mousavi *et al.* 2015 [39]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
McClure *et al.* 2014 [37]	Some concerns	Some concerns	Some concerns	Some concerns	Low risk	Some concerns
Prado *et al.* 2015 [2]	Some concerns	Some concerns	High risk	Some concerns	Low risk	High risk
Schmaal *et al.* 2011 [29]	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Schulte *et al.* 2017 [30]	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Yoon 2013 [34]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Yoon 2017 [35]	Some concerns	Low risk	High risk	Low risk	Low risk	High risk

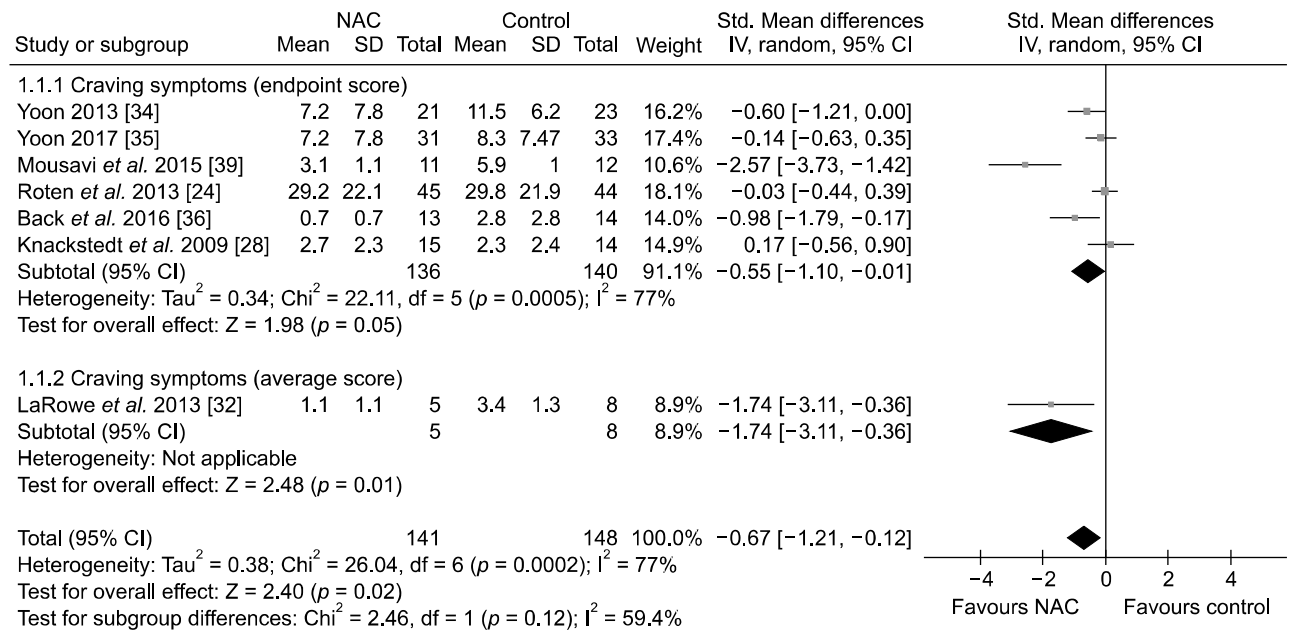

Fig. 2. Forest plot of comparison: N-acetylcysteine (NAC) versus control; outcome: craving symptoms. SD, standard deviation; Std, standardized; 95% CI, 95% confidence interval; IV, inverse variance.

Scale from weeks 1 through 7 was presented. A meta-analysis of the 6 trials with endpoint results significantly favored the NAC treatment group over the control group (SMD, −0.55; 95% CI, −1.10 to −0.01), and significant heterogeneity was observed across trials (I^2 = 77%, p = 0.0005; Fig. 2). Adding change score results of LaRowe *et al.* [32] enhanced the statistical strength slightly (SMD, −0.67; 95% CI, −1.21 to −0.12) (I^2 = 77%, p = 0.0002; Fig. 2).

Withdrawal Syndrome and Depressive Symptoms

Depression is classically considered one of the many components of withdrawal syndrome [37]. Thus, we conducted subgroup analysis of these two clinical features and examined their overall effects. We did not restrict the meta-analysis to trials with longer length of treatment or time of measurement for withdrawal and depression symptoms because these two features are clinical meaningful at the treatment initiation days or later. Five trials measured withdrawal symptoms. These trials evaluated withdrawal syndromes by using the Shiffman−Jarvik Withdrawal Questionnaire [27] and Minnesota Nicotine Withdrawal Scale [29,30,33,38] at baseline and followed up at 62 hours [33] and on the 4th day [27,29], 2nd week [30]and 4th week [38]. Four trials reported the endpoint scores [27,29,30,38] while LaRowe *et al.* [33] reported the change score. Meta-analysis of the four trials reported endpoint results found no significant differences between groups (SMD, −0.17; 95% CI, −0.56 to 0.21) and no heterogeneity across trials (I^2 = 0%, p = 0.50; Fig. 3). Merging the change score with the endpoint results did not reveal significance between groups (SMD, −0.53; 95% CI, −1.20 to 0.14) and heterogeneity was observed across trials (I^2 = 70%, p = 0.010; Fig. 3).

Four trials measured participants' depressive symptoms. Of these, one measured depression status at baseline by using the Center for Epidemiological Studies Depression Scale [27]; however, no follow-up information was provided, and thus this trial was excluded from our analysis. The remaining three trials measured depressive symptoms by using the Beck Depressive Inventory and Hamilton Depression Rating Scale [2,25,36] and the symptoms were measured at baseline and on the 8th week [36], 12th week [25], and 24th week [2]. Analysis of these three trials revealed a nonsignificant trend toward significance in favor of the NAC treatment group over the control group (SMD, −0.40; 95% CI, −0.83 to 0.03). No significant heterogeneity was observed across trials (I^2 = 0%, p = 0.52; Fig. 4).

When withdrawal and depressive symptoms were considered as a single domain, the NAC treatment group demonstrated a significantly higher overall improvement than the placebo group (SMD, −0.35; 95% CI, −0.64 to

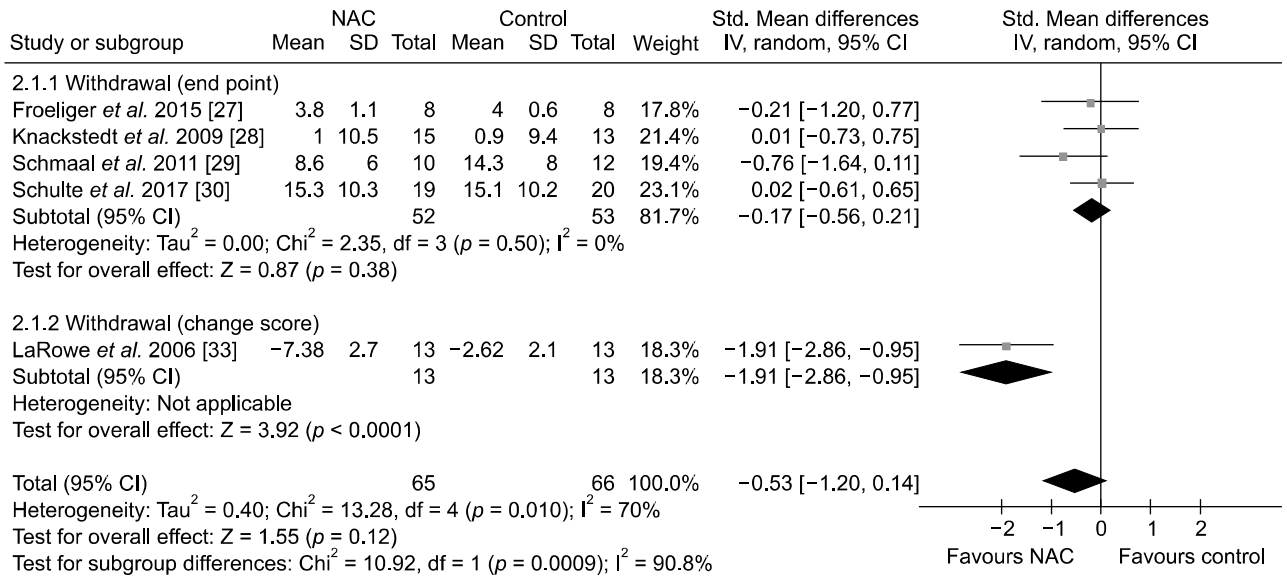

Fig. 3. Forest plot of comparison: N-acetylcysteine (NAC) versus control; outcomes: withdrawal syndrome.
SD, standard deviation; Std, standardized; 95% CI, 95% confidence interval; IV, inverse variance.

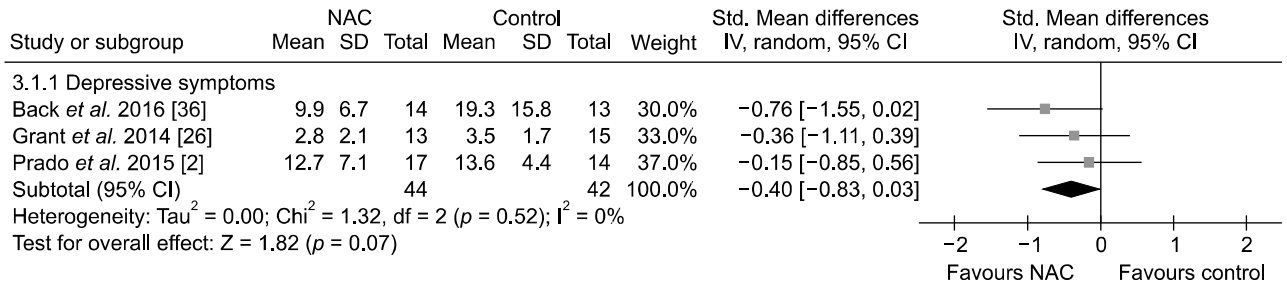

Fig. 4. Forest plot of comparison: N-acetylcysteine (NAC) versus control; outcome: depressive symptoms.
SD, standard deviation; Std, standardized; 95% CI, 95% confidence interval; IV, inverse variance.

−0.06); no heterogeneity was observed across trials (I^2 = 0%, p = 0.70; data not shown).

Adverse Events

Among all analyzed trials, 11 reported participants experiencing adverse events during the trials. Among these trials, 6 reported the occurrence of any adverse event between NAC treatment group and control group [29,30,32, 34-36,40], whereas the other 5 reported the number of various adverse events [2,24,30,33,39]. Among the 6 trials that detailed frequencies of adverse events, 1 reported no adverse events at all [30]. The remained 5 informative trials were used in the meta-analysis and the results revealed no significant difference between the groups (OR, 1.18; 95% CI, 0.68 to 2.06) or heterogeneity across trials (I^2 = 0%, p = 0.66; Fig. 5). The most common adverse events were nausea and headache.

Smoking Frequency

Like craving symptoms, the reduction of smoking frequency is clinically meaningful after a period of planned treatment. For this reason, we concerned the included trials in which the participants were treated for at least 4 weeks and smoking frequency summed up after 4 weeks treatment or more. Three trials measured changes in smoking frequency met these criteria [2,37,38]. The number of cigarettes smoked per day was recorded at baseline and 4 weeks [38], 8 weeks [37], and 12 weeks [2]. A non-significant trend toward reduction in smoking frequency was observed in the NAC treatment group compared with the control group (WMD, −3.09; 95% CI, −6.50 to 0.32) and a significant heterogeneity was ob-

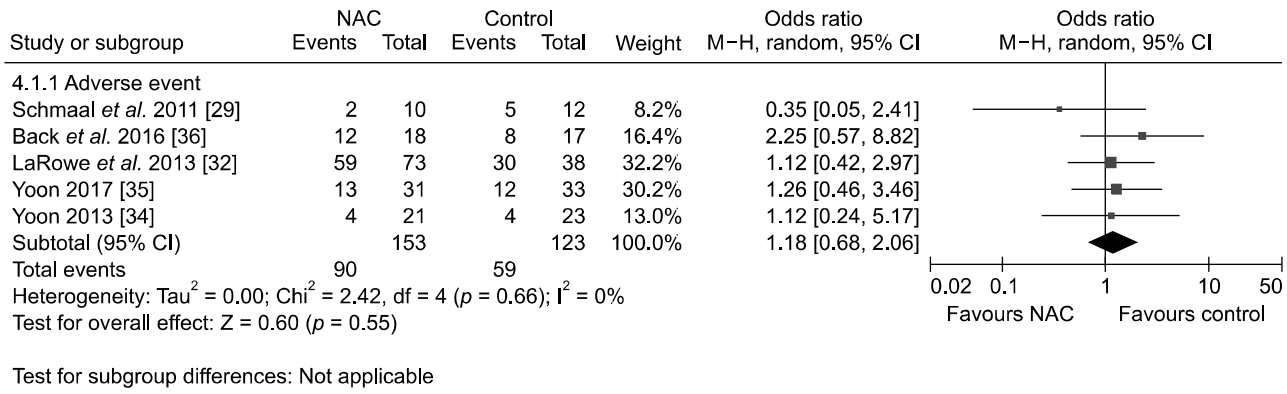

Fig. 5. Forest plot of comparison: N-acetylcysteine (NAC) versus control; outcome: any adverse event. 95% CI, 95% confidence interval; M-H, Mantel-Haenszel.

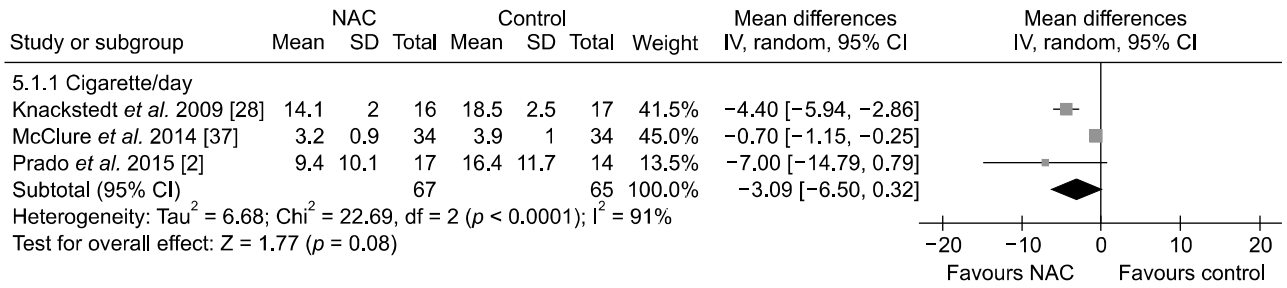

Fig. 6. Forest plot of comparison: N-acetylcysteine (NAC) versus control; outcome: smoking frequency. SD, standard deviation; 95% CI, 95% confidence interval; IV, inverse variance.

served across trials (I^2 = 91%, $p < 0.0001$; Fig. 6).

Other Symptoms

Anxiety symptoms were examined in Grant *et al.* [25] and the trial results indicated a significant reduction of anxiety symptoms in the NAC treatment group compared with the control group at all follow-up time points. Other solitary results provided additional information regarding the effectiveness of NAC treatment. Two trials examining cannabis use and dependence measured percentage changes in the results of negative cannabinoid urine tests conducted during NAC treatment and 1 demonstrated significantly higher odds in the NAC treatment groups compared with the control groups [24], while the other reported no difference of odds between groups [30]. Regarding cocaine dependence, 1 trial measured cocaine metabolite concentrations in the urine samples and found that the mean level in the NAC treatment group significantly decreased compared with that of the control group [32].

Effects of NAC in Craving, Withdrawal, and Depression in Specific Substances

To clarify the effects of NAC on clinical symptoms in specific substances, we conducted subgroup analyses on alcohol and tobacco related trials included in our study (Fig. 7). For alcohol related trials, the pooled results appeared to favor the NAC treatment group over the control group in reducing craving symptoms without a statistical significance (SMD, −2.56; 95% CI, −5.68 to 0.57) and no heterogeneity was found across trials (I^2 = 20%, p = 0.26). For tobacco related trials, the pooled results showed no difference in the reduction of withdrawal symptoms between the NAC group and the control group (SMD, −0.26; 95% CI, −1.11 to 0.59), and no heterogeneity was observed across trials (I^2 = 0%, p = 0.54). Similarly, there was no statistical difference to support a difference between the two groups in the reduction of depression symptoms (SMD, −0.72; 95% CI, −2.07 to 0.63) and no heterogeneity was observed across trials (I^2 = 0%, p = 0.93).

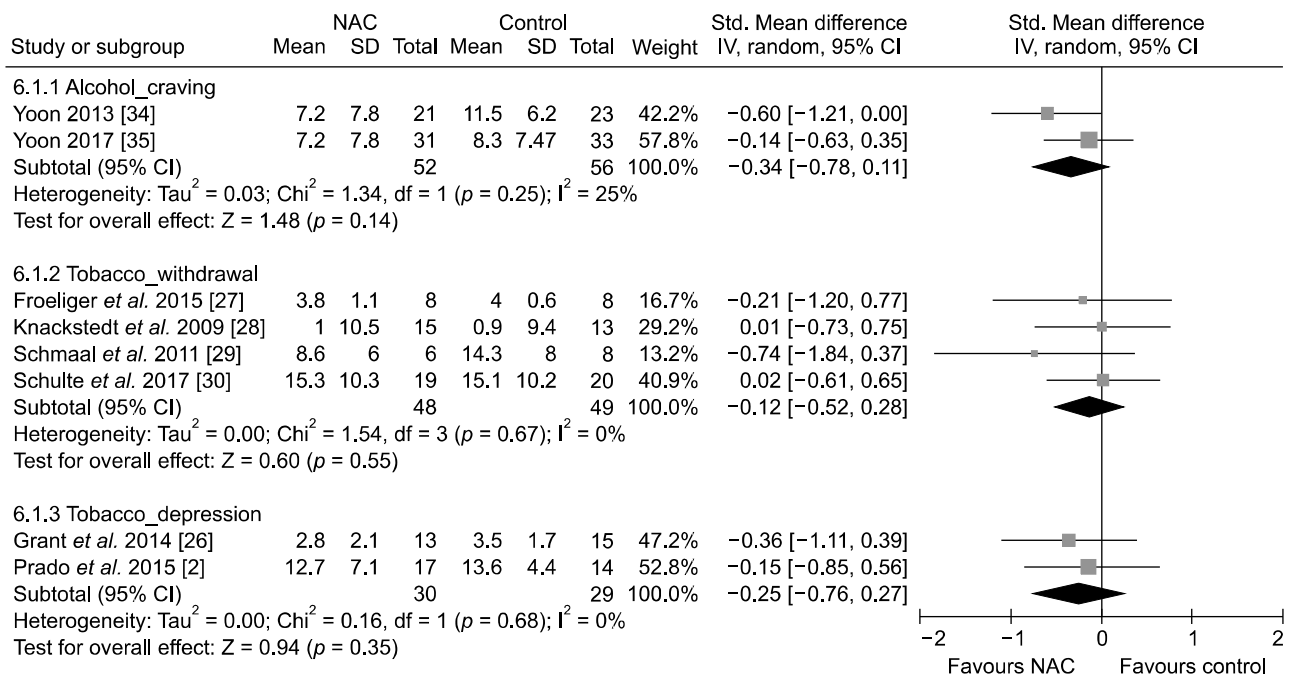

Fig. 7. Forest plot of comparison: N-acetylcysteine (NAC) versus control; outcomes of specific substances: (1) alcohol craving, (2) tobacco withdrawal, and (3) depression among smokers.
SD, standard deviation; Std, standardized; 95% CI, 95% confidence interval; IV, inverse variance.

DISCUSSION

Our study revealed some weak evidence that NAC is effective for reducing craving symptoms in participants with substance abuse or dependence. In addition, NAC might be effective for treating withdrawal and depressive symptoms in a broader sense, and in reducing smoking frequency. However, subgroup analyses of alcohol and tobacco related trials did not show an effect of NAC in reducing craving, withdrawal, and depressive symptoms. The current evidence did not reveal an effect of NAC in increasing the risk of adverse events.

Despite the availability of therapeutics and behavioral therapies and the promotion of abstinence programs, substance use disorders cause serious public health and social problems, mostly because of the severe withdrawal symptoms and depression commonly experienced during abstinence. The inability to tolerate these aspects has been proposed as the main cause of many failed attempts to abstain from using certain substances [41]. Evidence from NAC clinical trials and animal studies on addiction suggests an alternative option for treating substance addiction. Although NAC is a potential candidate drug for treating substance addiction, it is not free of side effects. Common side effects of NAC include nausea, vomiting, and sometimes allergies [42]. However, allergies induced by NAC are rare compared with those induced by other routinely used detox agents such as methadone.

The complexity of the effectiveness of adopting NAC to treat substance addiction is affected by the use of other substances (e.g., cannabis versus tobacco), as demonstrated in cannabis cessation studies assisted by using [30] and not using [37,43] NAC. However, other researchers have found no evidence that cigarette smoking influences the efficacy of NAC treatment for cannabis cessation [42]. Similarly, an NAC trial to investigate adolescent cannabis cessation found that lower cannabis use was associated with lower alcohol consumption during NAC intervention [44]. This seems to be the result of an interaction between the chemical nature of the substance, genetic nature of users, and environmental factors. The future publication of Achieving Cannabis Cessation-Evaluating N-acetylcysteine Treatment, through a multisite, randomized controlled trial in the National Institute on Drug Abuse Clinical Trials Network, a study that investigated approximately 300 treatment-seeking cannabis-dependent adults [37], may provide further insight into this concern.

Considerable heterogeneity was observed across the

trials included in our analysis. First, the age range of participants differed between trials; some trials recruited participants from all age groups, whereas others targeted adolescents. Second, the dosage of the administered NAC was not consistent across the analyzed trials; therefore, the effect of dose response cannot be ruled out. Third, a variety of scales for measuring craving, withdrawal, and depression were used in the included trials. Although theoretically, the trends of different scales in the same domain should incline in the same direction and use of SMD had restricted the difference between trials, the specific targets, purposes, and designs of scales inevitably cause variations. Fourth, trial duration varied across trials. Some trials demonstrated between-group differences within the research period, but the treatment effects did not sustain at the research endpoint. Rather than indicating ineffectiveness of the intervention, such findings more likely indicate a common fluctuating phenomenon of long-term treatment. In addition, a time and dose effect might be exerted. Fifth, although specific substances were named in the titles of the analyzed studies, single substance users are rare. Finally, some trials included contingency management interventions and brief cessation counseling as part of the treatment during NAC interventions [24], and this might have affected the overall outcomes.

Our study had several limitations. First, because trials with no restriction on specific substances were analyzed in our study, specific effects of NAC on particular substances remain unclear. Second, the longest follow-up period among the included trials was 24 weeks [2,25]. The long-term effects of NAC on substance use disorders are yet to be determined.

Large efforts have been investigated in finding new effective pharmaceutical interventions for treating addiction behaviors, and little has been achieved in the past decades. NAC provides noticeable benefits for individuals with substance abuse or substance dependence; it attenuates the craving for the substance in question and might alleviate depressive symptoms and withdrawal syndrome. However, it should be reminded that this is concluded from the pooled results of different substances. Although our study showed no difference between NAC treatment and control group in adverse effects, unveiled side effects may exist in the included trials. Besides, types of substance used may contribute to different side effects. Additional studies on dosage, frequency, and method of administration with larger sample sizes are warranted.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Chung-Ting Chang, Pei-Ju Hsieh, El-Wui Loh. Data acquisition: Chung-Ting Chang, Pei-Ju Hsieh, Chun-Hong Lo. Formal analysis: Chung-Ting Chang and Pei-Ju Hsieh. Clinical consultation: Hsin-Chien Lee, Ka-Wai Tam. Writing−original draft: Chung-Ting Chang, Pei-Ju Hsieh. Writing−review & editing: El-Wui Loh. Supervision: El-Wui Loh.

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