A Randomized, Placebo-Controlled Trial of *N*-Acetylcysteine Plus Imaginal Desensitization for Nicotine-Dependent Pathological Gamblers

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ABSTRACT

Objective: Pathological gambling is associated with elevated proportions of nicotine dependence, and tobacco smoking in pathological gamblers has been associated with increased problem-gambling severity. This study examined the addition of *N*-acetylcysteine to imaginal desensitization in adults with co-occurring nicotine dependence and pathological gambling.

Method: Twenty-eight individuals with co-occurring *DSM-IV* nicotine dependence and pathological gambling who were receiving behavioral therapy were recruited from December 2009 to February 2012 and randomized to augmentation with *N*-acetylcysteine or placebo in an 12-week, double-blind trial. Subjects were assessed with measures of nicotine and gambling severity and followed for 3 months after treatment. The primary outcomes were the Fagerström Test for Nicotine Dependence and the pathological gambling adaptation of the Yale-Brown Obsessive-Compulsive Scale.

Results: During the first 6 weeks, there was a significant benefit of *N*-acetylcysteine treatment versus placebo on Fagerström Test for Nicotine Dependence total scores ($t = -2.224$; $P = .031$). After the initial 6 weeks, all subjects significantly ($P < .001$) benefited from imaginal desensitization. During the 3-month follow-up, there was a significant additional benefit for *N*-acetylcysteine versus placebo on measures of problem-gambling severity ($t = 2.069$; $P = .043$).

Conclusions: *N*-acetylcysteine treatment during therapy facilitates long-term application of behavioral therapy techniques once patients are in the community after therapy has been completed.

Trial Registration: ClinicalTrials.gov identifier: NCT00967005

J Clin Psychiatry 2014;75(1):39–45

Submitted: *February 6, 2013; accepted May 21, 2013.*
Online ahead of print: *November 26, 2013 (doi:10.4088/JCP.13m08411).*
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There are an estimated 1.3 billion smokers worldwide, and recent global estimates place the mortality burden from tobacco use at over 6 million annually.[1] Among US adults, 12.8% report nicotine dependence, and nicotine dependence is highly associated with a variety of psychiatric disorders.[2,3] Pathological gambling represents a serious public health problem, with detrimental effects on individuals and families and an estimated yearly cost to society of $5 billion US dollars due to lost jobs, debt, bankruptcy, and incarcerations.[4] Pathological gambling is associated with elevated proportions of nicotine dependence (> 60%),[3,5] and tobacco smoking in clinical samples of pathological gamblers has been associated with increased problem-gambling severity and more frequent psychiatric problems.[6] In addition, some research suggests that continued tobacco use is associated with greater rates of relapse among pathological gamblers who received behavioral therapy[7] (for contrary findings, see Odlaug et al[8]). Despite increased awareness of the relationship between nicotine dependence and pathological gambling and the possible effects of nicotine dependence on problem-gambling severity, there is a paucity of clinical trials exploring effects of treatment on concomitant nicotine dependence and pathological gambling.

Behavioral therapy using imaginal desensitization and motivational interviewing has shown promise in reducing the severity of pathological gambling.[7,9–11] Despite the efficacy of treatments for pathological gambling and nicotine dependence, relapse is common among individuals with nicotine dependence and pathological gambling. Preclinical studies have suggested that levels of glutamate within the nucleus accumbens mediate reward-seeking behavior and may underlie relapse seen in addictions.[12–14] *N*-acetylcysteine, a dietary supplement, amino acid, and cysteine prodrug, appears to modulate glutamate within the nucleus accumbens and has shown benefit in reducing the reward-seeking behavior in individuals with a range of addictive behaviors, including nicotine dependence and pathological gambling.[15–18] Using proton magnetic resonance spectroscopy, higher dorsal anterior cingulate cortex (dACC) glutamate levels were shown to be associated with greater levels of questionnaire-rated impulsivity in healthy controls and in people with cocaine dependence.[19] Furthermore, *N*-acetylcysteine treatment selectively normalized excess dACC glutamate levels in cocaine-dependent individuals, suggesting that this medication modulates a key neural region involved in impulse control, with potential implications for relapse prevention across multiple addictive behaviors.

We hypothesized that, among individuals receiving imaginal desensitization and motivational interviewing for pathological gambling and behavioral therapy for nicotine dependence, *N*-acetylcysteine (versus placebo) would result in greater reduction in features/severity of both nicotine dependence and pathological gambling during the acute treatment phase and would enhance long-term abstinence following cue-exposure therapy. If shown to be effective, *N*-acetylcysteine could serve as a viable, low-cost, and easily available treatment augmentation for nicotine-dependent pathological gamblers who receive behavioral therapy.

METHOD

Subjects

Male and female adults aged 18–75 years, with nicotine dependence and pathological gambling, were entered into the study after providing written informed consent and fulfilling inclusion criteria. Subjects were seeking treatment for both nicotine dependence and pathological gambling. Nicotine dependence was defined as a Fagerström Test for Nicotine Dependence score of ≥ 4,[20] and pathological gambling was diagnosed based on the Structured Clinical Interview for Pathological Gambling (SCI-PG).[21] Subjects needed to meet criteria for nicotine dependence and pathological gambling for at least 6 months prior to study entry. Other inclusion criteria comprised subjects who (1) were not currently receiving psychosocial treatment, pharmacologic treatment, or both for nicotine dependence or pathological gambling; (2) if on psychotropic medications for other disorders, had been on a stable dose for at least 3 months prior to entry; and (3) had completed a complete blood count, urinalysis, liver function tests, thyroid function tests, and pregnancy test, with no evidence of significant laboratory abnormalities. Exclusion criteria were (1) subjects who had started attending Gamblers Anonymous within the 3 months prior to study initiation; (2) subjects who had an unstable and significant medical illness; (3) current clinically significant suicidality (determined by a score of 3 or 4 on item 3 of the Hamilton Depression Rating Scale [HDRS][22] or the clinical judgment of the study physician) or any other disorder requiring immediate intervention; (4) lifetime history of bipolar I or II disorder, dementia, or psychotic disorder; (5) current (past 12 months) *DSM-IV* substance abuse or dependence (except nicotine dependence); (6) positive urine drug screen at screening; (7) asthma (given possible worsening of asthma due to *N*-acetylcysteine); (8) cognitive impairment interfering with capacity to understand and self-administer medication or to provide written informed consent; (9) current pregnancy or lactation, or inadequate contraception in women of childbearing potential; and (10) previous treatment with *N*-acetylcysteine. The subjects were recruited from December 2009 to February 2012. The institutional review board of the University of Minnesota approved the study and the consent statement. All study procedures were carried out in accordance with the Declaration of Helsinki[23] and standards of Good Clinical Practice.[24] The study was registered on ClinicalTrials.gov (identifier: NCT00967005).

Overall Design

Subjects were randomized to 12-week treatment with *N*-acetylcysteine (1,200 mg/d titrating to 3,000 mg/d based on clinical judgment) or placebo, in a double-blind design. This dose was higher than that used in a previous study of pathological gambling.[18] Subjects took *N*-acetylcysteine or placebo for the entire 12-week period. In addition, all subjects received smoking cessation treatment based on Ask-Advise-Refer therapy[25–27] for nicotine dependence (weeks 0–6). Ask-Advise-Refer therapy is a telephone-based tobacco cessation service that is accessed through a toll-free number and provides callers with educational materials, referral to formal cessation programs, and individualized telephone counseling.[27] The initial 6 weeks was followed by 6 sessions of imaginal desensitization plus motivational interviewing for pathological gambling (weeks 6–12).[9,28,29] Homework was assigned daily as part of the imaginal desensitization and motivational interviewing therapy. In addition, imaginal exposures were performed 4 times a day every day starting at the third treatment session. At week 12, both pharmacologic and psychological treatments ended, and subjects were subsequently reassessed 3 months later. Subjects were asked at follow-up assessment about nicotine and gambling behavior. Frequency of use of exposure tapes or behavioral modification techniques was not quantified.

Clinical Points

- Nicotine dependence is common among individuals with pathological gambling and can be addressed simultaneously with the gambling problem.
- *N*-acetylcysteine used during psychotherapy treatment may facilitate long-term application of behavioral therapy techniques.

Assessments

All assessments (except the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Patient Edition [SCID-I/P][30]) were performed at study entry, at 6 weeks, at 12 weeks, and then at 3 months after all treatment had been stopped.

Nicotine dependence and severity were examined using the Fagerström Test for Nicotine Dependence.[20] Pathological gambling was diagnosed using the Structured Clinical Interview for Pathological Gambling (SCI-PG),[21] and problem-gambling severity was assessed with the pathological gambling adaptation of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS).[31] Co-occurring psychiatric disorders were examined with the SCID-I/P.[30] Depression and anxiety were assessed using the HDRS (17-item)[22] and Hamilton Anxiety Rating Scale (HARS),[32] respectively.

Data Analysis

Primary outcome measures comprised PG-YBOCS total and subscale scores, Fagerström Test for Nicotine Dependence total scores, HDRS total scores, and HARS total scores. Changes over time on these outcome measures across the whole sample were first explored using a mixed model (MIXED procedure; SAS Institute Inc, Cary, North Carolina) for repeated measures on each of the 6 dependent variables. There was no recoding of missing data. The between-subjects factor was the experimental group (placebo or *N*-acetylcysteine). The within-subjects repeated measure was data collection point (week) coded as 0, 1, 2, or 3. For the within-subjects repeated measure of week with 3 degrees of freedom, 3 contrasts were examined in which each week was

compared to baseline. After conducting the MIXED model, we also undertook a secondary analysis using generalized linear mixed model with a last-observation-carried-forward (LOCF) approach to ensure the primary results were robust (results from the generalized linear model available from the authors on request).

Statistical significance was defined as $P < .05$, 2-tailed throughout.

RESULTS

Twenty-eight subjects met inclusion criteria and completed at least 1 nonbaseline assessment. Demographic characteristics of the sample are provided in Table 1. At entry, the mean PG-YBOCS total score was 21.8 (SD = 5.8), consistent with moderate to high problem-gambling severity. The Fagerström Test for Nicotine Dependence mean score was 6.6 (2.0), with a cotinine range of 23–471 ng/mL, results that are consistent with presence of nicotine dependence. The number of subjects assigned to placebo and *N*-acetylcysteine were 15 and 13, respectively; there were no statistically significant differences between these subgroups in terms of baseline characteristics (all *P* values > .10). Figure 1 shows the subject disposition throughout the study.

As anticipated, across the whole sample, there were significant improvements across most primary outcome measures between study entry and all subsequent time points ($P < .05$; Table 2). Outcome measures over time as a function of pill randomization are summarized in Table 2, and results of the MIXED model are indicated in Table 3. It can be seen that there was a significant benefit of *N*-acetylcysteine plus Ask-Advise-Refer therapy versus placebo plus Ask-Advise-Refer therapy on Fagerström Test for Nicotine Dependence total scores, as measured at week 6. This significant differential benefit of *N*-acetylcysteine, however, was no longer evident following subsequent 6-week treatment with pill plus imaginal desensitization and motivational interviewing, nor at follow-up. In terms of gambling symptoms, it can be seen that, although no significant differential benefit of *N*-acetylcysteine versus placebo was observed following 6 weeks of pill plus Ask-Advise-Refer therapy or subsequent 6 weeks of pill plus imaginal desensitization and motivational interviewing, a significant benefit was seen at follow-up (ie, 3 months after treatment had ended).

Table 1. Baseline Characteristics of 28 Nicotine-Dependent Pathological Gamblers

Variable	Subjects (n = 28)
Age, mean (SD) [range], y	47.6 (10.9) [25–70]
Female, n (%)	5 (17.9)
Caucasian, n (%)	23 (82.1)
Marital status, n (%)	
Single	13 (46.4)
Married	6 (21.4)
Widowed/separated/divorced	9 (32.2)
Education, n (%)	
High school graduate or less	8 (28.6)
Some college/vocational school	14 (50.0)
College graduate or postcollege	6 (21.4)
PG-YBOCS, mean (SD) [range]	
Total score	21.8 (5.8) [9–36]
Urges/thought subscale score	10.3 (3.8) [2–18]
Behavior subscale score	11.5 (3.2) [6–18]
Gambling losses per wk, mean (SD), $	352.60 (322.40)
Gambling frequency per wk, mean (SD), d	2.9 (1.8)
Primary form of gambling, n (%)	
Nonstrategic	23 (82.1)
Fagerström Test for Nicotine Dependence total score, mean (SD) [range]	6.6 (2.0) [4–11]
Serum cotinine, mean (SD) [range], ng/mL	248.7 (109.8) [23–471]
Cigarettes per day, mean (SD) [range]	24.0 (8.9) [13–40]
HDRS total score, mean (SD) [range]	8.7 (5.2) [0–24]
HARS total score, mean (SD) [range]	10.3 (8.6) [0–44]
Comorbid lifetime disorders, n (%)	
Any depressive disorder	6 (21.4)
Any anxiety disorder	2 (7.1)
Any substance use disorder (other than nicotine dependence)	12 (42.9)

Abbreviations: HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, PG-YBOCS = pathological gambling adaptation of the Yale-Brown Obsessive-Compulsive Scale

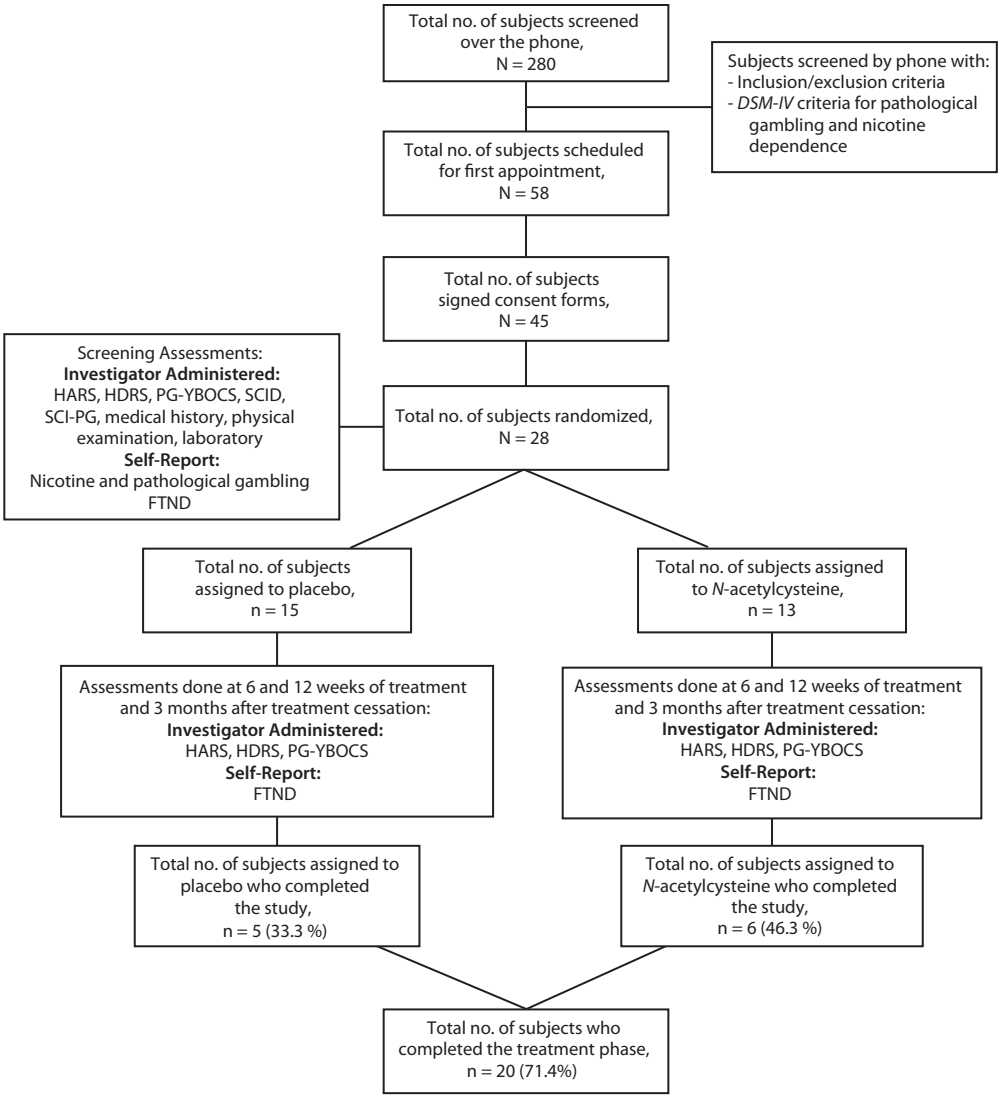
DISCUSSION

In this study, we present the first results pertaining to *N*-acetylcysteine augmentation of behavioral therapy for co-occurring nicotine dependence and pathological gambling. The first phase of behavioral therapy comprised 6 weeks of Ask-Advise-Refer therapy for nicotine dependence. The second phase of behavioral therapy, conducted between weeks 6 and 12, comprised 6 weeks of imaginal desensitization and motivational interviewing for pathological gambling. *N*-acetylcysteine seemed to augment the initial response to Ask-Advise-Refer therapy and the long-term response to imaginal desensitization and motivational interviewing. Implications are discussed below.

In terms of nicotine dependence severity (defined according to Fagerström Test for Nicotine Dependence scores), augmentation of 6-week Ask-Advise-Refer therapy with *N*-acetylcysteine was associated with significantly greater reductions in severity as compared to augmentation with placebo pill. This differential benefit, however, did not persist with subsequent treatment with imaginal desensitization and motivational interviewing (weeks 6–12), nor was it observed at follow-up (3 months after pharmacologic and psychological treatment had ended). These results are not inconsistent with a previous study[17] of *N*-acetylcysteine for nicotine dependence. Knackstedt and colleagues[17] examined *N*-acetylcysteine for nicotine dependence in a 4-week study. *N*-acetylcysteine reduced the number of cigarettes smoked but failed to demonstrate reduction in carbon monoxide levels. The study concluded by suggesting that *N*-acetylcysteine may assist smokers to resist the urge to seek nicotine but may not reduce nicotine consumption once smoking has begun. Taken together with our findings, the data suggest that the clinical benefits of *N*-acetylcysteine for nicotine dependence may be limited to those who have abstinence from nicotine prior to starting *N*-acetylcysteine or to those who also employ Ask-Advise-Refer therapy, and/or *N*-acetylcysteine has some acute, not ultimately short-lived, benefit for nicotine dependence.

Importantly, although *N*-acetylcysteine augmentation did not discriminate from placebo augmentation in terms

Figure 1. CONSORT Diagram: *N*-Acetylcysteine Plus Imaginal Desensitization for Nicotine-Dependent Pathological Gamblers



Abbreviations: FTND = Fagerström Test for Nicotine Dependence, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, PG-YBOCS = pathological gambling adaptation of the Yale-Brown Obsessive-Compulsive Scale, SCID = Structured Clinical Interview for *DSM-IV*, SCI-PG = Structured Clinical Interview for Pathological Gambling.

of effects on problem-gambling severity over the behavioral therapy treatment phases, there was a significant benefit at follow-up (3 months after the medication and therapy were discontinued). This finding may suggest that *N*-acetylcysteine treatment during therapy facilitates long-term application of behavioral therapy techniques once patients are in the community after therapy has been completed. Preclinical data suggest that learning and memory impairment may be due to impaired glutamate uptake, as glutamate neurotransmission has been known to be involved in learning and memory.[33] *N*-acetylcysteine appears to reverse this cognitive impairment in animal studies.[33] Although not examined in the current study, *N*-acetylcysteine's ability to solidify long-term benefit of behavioral therapy may be due to improved learning and memory. Clinically, this is a highly relevant finding. Some pathological gambling patients respond well and quickly to behavioral therapies, such as imaginal desensitization and motivational interviewing, and there would be no need to augment the therapy with pharmacologic treatment.[3] In contrast, some patients who might be more likely to relapse after behavioral therapy is discontinued may benefit from pharmacologic augmentation. *N*-acetylcysteine could be a potentially useful augmentation of behavioral therapy in this regard.

Our results are particularly clinically relevant in the context of viewing pathological gambling as an addiction as reflected in the *DSM-5*. The current recommended treatment strategy in Europe for substance addiction without requirement for detoxification, for example, advises the use of psychosocial intervention with pharmacotherapeutic intervention as necessary for individuals who fail to receive adequate benefit with psychosocial intervention alone.[34] As indicated in Table 3, we found that individuals taking *N*-acetylcysteine during psychological treatment experienced a greater improvement

Table 2. Summary of Raw Mean (SD) Data on Clinical Measures at Each Time Point (n = 28)

	Week 0[a]		Week 6[b]		Week 12[c]		Week 24[d]	
Measure	Placebo	*N*-acetylcysteine	Placebo	*N*-acetylcysteine	Placebo	*N*-acetylcysteine	Placebo	*N*-acetylcysteine
PG-YBOCS total score	20.4 (5.0)	23.5 (6.4)	16.3 (7.4)	17.4 (9.1)	5.5 (5.9)	7.5 (4.6)	6.4 (6.2)	1.0 (1.3)
PG-YBOCS urges/thought subscale score	9.0 (3.4)	11.8 (3.7)	7.9 (3.8)	8.9 (4.2)	2.7 (2.1)	5.5 (2.3)	3.6 (3.6)	0.8 (1.2)
PG-YBOCS behavior subscale score	11.4 (2.8)	11.7 (3.7)	8.3 (4.9)	8.5 (5.7)	2.8 (4.5)	2.0 (3.1)	2.8 (4.1)	0.2 (0.4)
Fagerström Test for Nicotine Dependence total score	6.7 (2.1)	6.5 (2.0)	5.9 (2.4)	4.0 (1.9)	5.0 (1.5)	5.3 (2.9)	5.3 (1.2)	4.6 (1.3)
HDRS total score	7.9 (4.8)	9.7 (5.7)	5.5 (3.8)	7.5 (4.7)	3.7 (3.2)	7.0 (4.9)	3.5 (1.7)	2.8 (2.1)
HARS total score	9.7 (6.6)	11.1 (10.8)	6.2 (4.0)	7.5 (4.3)	4.2 (3.2)	7.4 (3.2)	6.5 (5.2)	5.0 (3.6)

[a]Week 0 corresponds to baseline.
[b]Week 6 corresponds to end of *N*-acetylcysteine plus Ask-Advise-Refer therapy versus placebo plus Ask-Advise-Refer therapy.
[c]Week 12 corresponds to the end of 6 sessions of *N*-acetylcysteine plus imaginal desensitization and motivational interviewing versus placebo plus imaginal desensitization and motivational interviewing.
[d]Week 24 represents the 3-month follow-up period (ie, corresponds to being off *N*-acetylcysteine or placebo and done with imaginal desensitization and motivational interviewing for 12 weeks).

Table 3. Results of the MIXED Analysis for Outcome Measures of Interest (n = 28)

	PG-YBOCS Total Score			PG-YBOCS Urges/ Thought Subscale Score			PG-YBOCS Behavior Subscale Score		
Variable	Statistic	*df*	*P*	Statistic	*df*	*P*	Statistic	*df*	*P*
Between-subjects									
Group, placebo vs *N*-acetylcysteine	$F = 0.000$	(1,26.506)	.986	$F = 1.537$	(1,22.779)	.228	$F = 0.529$	(1,27.052)	.473
Within-subjects									
Week	$F = 38.551$	(3,57.824)	< .001	$F = 23.186$	(3,60.149)	< .001	$F = 33.127$	(3,56.983)	< .001
Week-by-group interaction	$F = 1.476$	(3,57.824)	.230	$F = 2.081$	(3,60.149)	.112	$F = 0.567$	(3,56.983)	.639
Within-subjects contrasts, week vs baseline									
Week 6[a]	$t = 2.633$	52.250	.011	$t = 2.153$	51.750	.036	$t = 2.285$	52.245	.026
Week 12[b]	$t = 6.500$	56.105	< .001	$t = 4.420$	56.534	< .001	$t = 6.468$	55.701	< .001
Week 24[c]	$t = 7.505$	61.105	< .001	$t = 6.583$	65.549	< .001	$t = 6.178$	59.685	< .001
Within-subjects contrasts by group interaction, (week vs baseline) by group									
Week 6[a]	$t = 0.616$	52.250	.540	$t = 0.985$	51.750	.329	$t = 0.050$	52.245	.960
Week 12[b]	$t = 0.358$	57.094	.722	$t = -0.018$	57.795	.986	$t = 0.581$	56.589	.564
Week 24[c]	$t = 2.069$	62.663	.043	$t = 2.295$	68.014	.025	$t = 1.189$	60.979	.239
	Fagerström Total Score			HDRS Total Score			HARS Total Score		
Between-subjects									
Group, placebo vs *N*-acetylcysteine	$F = 0.481$	(1,29.644)	.494	$F = 1.559$	(1,28.388)	.222	$F = 0.206$	(1,29.318)	.654
Within-subjects									
Week	$F = 8.520$	(3,48.626)	< .001	$F = 7.416$	(3,54.229)	< .001	$F = 4.202$	(3,54.599)	.010
Week-by-group interaction	$F = 2.891$	(3,48.626)	.045	$F = 0.706$	(3,54.229)	.552	$F = 0.410$	(3,54.599)	.747
Within-subjects contrasts, week vs baseline									
Week 6[a]	$t = 4.745$	46.168	< .001	$t = 1.726$	51.338	.090	$t = 1.843$	50.617	.071
Week 12[b]	$t = 2.131$	47.460	.038	$t = 2.134$	53.585	.037	$t = 2.008$	53.323	.050
Week 24[c]	$t = 1.952$	48.690	.057	$t = 3.523$	55.533	.001	$t = 2.261$	56.010	.028
Within-subjects contrasts by group interaction, (week vs baseline) by group									
Week 6[a]	$t = -2.224$	46.605	.031	$t = 0.058$	51.338	.954	$t = -0.045$	51.233	.965
Week 12[b]	$t = 0.799$	48.635	.428	$t = 0.863$	54.145	.392	$t = 0.367$	54.741	.715
Week 24[c]	$t = 0.036$	50.101	.971	$t = -0.807$	56.599	.423	$t = -0.862$	57.703	.392

[a]Week 6 corresponds to end of *N*-acetylcysteine plus Ask-Advise-Refer therapy versus placebo plus Ask-Advise-Refer therapy.
[b]Week 12 corresponds to the end of 6 sessions of *N*-acetylcysteine plus imaginal desensitization and motivational interviewing versus placebo plus imaginal desensitization and motivational interviewing.
[c]Week 24 represents the 3-month follow-up period (ie, corresponds to being off *N*-acetylcysteine or placebo and done with imaginal desensitization and motivational interviewing for 12 weeks).

compared to placebo in problem-gambling severity over the long term, as quantified by 3 months' posttreatment. The additional benefits received from *N*-acetylcysteine may aid those seeking treatment for pathological gambling and nicotine dependence to experience greater clinical improvement and underscore the benefits of introducing multimodal components of treatment in both substance and behavioral addictions.

Given that an array of medications have shown therapeutic effects in pathological gambling (for example, opiate antagonists, mood stabilizers, glutamate modulators)[35] and given the heterogeneity of pathological gambling, the question remains as to *N*-acetylcysteine's role in patient-treatment matching. *N*-acetylcysteine's ability to reduce cue-triggered cravings may suggest that it would be most appropriate for patients who report cravings to gamble and for those who are also undergoing an exposure-based psychosocial intervention. In addition, as the only nonpharmaceutical "medication" option for pathological gambling, *N*-acetylcysteine may be particularly attractive to

patients who prefer a "natural" approach to addressing their gambling problem. An evidence-based treatment algorithm addressing the heterogeneity of pathological gambling, however, awaits further research.

The optimal dose of *N*-acetylcysteine for pathological gambling, however, remains unknown. The dose used here (up to 3,000 mg/d) was notably higher than that used in the previous study of pathological gambling (1,800 mg/d).[18] The previous study, however, did not involve behavioral therapy, so it is difficult to compare across the 2 research projects. Given this limitation, preclinical data in male Sprague-Dawley rats suggest that lower concentrations of *N*-acetylcysteine inhibit glutamate transmission in the nucleus accumbens core while higher concentrations countermand this effect.[36] Therefore, whether lower doses of *N*-acetylcysteine would produce greater effects for both nicotine use and gambling remains a valid question.

Several noteworthy limitations exist in this clinical trial. First, there was no *N*-acetylcysteine only or *N*-acetylcysteine plus behavioral intervention wait-list control condition, so it is impossible to distinguish the effects of *N*-acetylcysteine monotherapy from *N*-acetylcysteine interactions with the other interventions. Second, the small sample size may have allowed for findings with large effects only. A larger, well-powered study may allow for greater examination of whether *N*-acetylcysteine augmentation provides any additional benefit to imaginal desensitization and motivational interviewing in the acute phase as well. Third, cotinine levels at follow-up visits would have provided more reliable data regarding the affects of therapy and *N*-acetylcysteine on smoking behavior. Fourth, longer term follow-up (eg, at 1 year) could help to better understand whether *N*-acetylcysteine augmentation of imaginal desensitization and motivational interviewing would persist or further increase past 3 months in a manner similar to the sleeper effect observed for cognitive-behavioral therapies in drug addictions.[37,38] Fifth, the current study did not investigate the mechanism of action underlying treatment. Given *N*-acetylcysteine's glutamatergic properties and glutamate's role in learning and memory in addictive processes,[39] it is tempting to speculate that *N*-acetylcysteine's glutamatergic properties may help reconfigure reward-based learning relevant to imaginal desensitization and motivational interviewing in pathological gambling, and this hypothesis warrants additional investigation. Finally, the study was neither designed nor powered to explore temporal associations between changes in tobacco dependence and gambling severity. It is possible that gambling outcomes could be directly influenced by changes in tobacco use, or vice versa. However, the temporal discordance between benefits of *N*-acetylcysteine on tobacco dependence and gambling severity seen here militate against this as a likely explanation for the current findings.

This study, the first to examine *N*-acetylcysteine augmentation of behavioral therapy for pathological gambling with a co-occurring addiction, indicates that *N*-acetylcysteine may be a promising augmentation to maintain the effects of behavioral therapy for pathological gambling symptoms. It also serves to encourage future research in the use of medication augmentation of behavioral therapy for dual addictions.

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Potential conflicts of interest: **Dr Grant** receives yearly compensation from Springer Publishing for acting as Editor-in-Chief of the Journal of Gambling Studies; has received research grants from the National Center for Responsible Gaming (NCRG), Transcept, Forest, and Psyadon; and has received royalties from Oxford University Press, American Psychiatric Publishing, Norton Press, and McGraw Hill. **Dr Chamberlain** has consulted for Cambridge Cognition and P1Vital. **Dr Potenza** has received honoraria from academic lectures in grand rounds, continuing medical education events and other clinical or scientific venues; has received research support from Mohegan Sun Casino and NCRG; and has provided expert testimony on legal cases involving gambling. **Dr Donahue** has received honoraria from Oxford University Press. **Mr Odlaug** has received research grants from the Trichotillomania Learning Center, has consulted for Lundbeck, and has received honoraria and royalties from Oxford University Press. **Dr Kim** and **Ms Schreiber** report no conflicts of interest.
Funding/support: National Institute on Drug Abuse grant RC1 DA028279-01 to Dr Grant and NCRG Centers of Excellence in Gambling Research grants to Drs Grant and Potenza.
Role of the sponsor: The funding agencies did not contribute to the content of this article.

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