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# Does N-Acetylcysteine Supplementation Alleviate Compulsive Behavior in Adults with Impulse Control Disorders?

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# **Does N-acetylcysteine supplementation alleviate compulsive behavior in adults with impulse control disorders?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences-Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## ABSTRACT

### Objective:

The objective of this systematic review is to determine whether or not “Does N-acetylcysteine supplementation alleviate compulsive behavior in adults with impulse control disorders?”

### Study Design:

Review of three English primary studies published between 2007 and 2009.

### Data Sources:

One double-blind RCT, one open label trial followed by double-blind RCT, one case study. Studies were found using PubMed, Cochrane Systematic Reviews, OVID and Ebsco databases.

### Outcomes Measured:

Primary outcomes measured include severity of trichotillomania symptoms measured by MGH-HPS, reduction of pathological gambling symptoms measured by YBOCS-PG, and reduction of compulsive grooming urges measured by patient reports.

### Results:

In Grant, Odlaug et al.’s study, 44% of subjects assigned to NAC had a 50% or greater reduction on the MGH-HPS compared to 0% of those assigned to placebo. In Grant, Kim et al.’s study, 69.6% of subjects were responders on the PG-YBOCS at the end of the open-label NAC phase. At the end of the double-blind phase of the same trial, 83.3% of subjects assigned to NAC still met responder criteria, compared to 28.6% of subjects assigned to placebo. In Odlaug et al.’s study, 3 out of 5 subjects treated with NAC reported cessation of compulsive behaviors within 3-5 months on 1800-2400 mg/day NAC.

### Conclusions:

Evidence is inconclusive regarding the use of NAC in the treatment of impulse control disorders. Its use appears promising, but long term research in larger populations is indicated. Tailored treatment may be warranted based on the severity and type of impulse control disorder, the presence of co-morbid psychiatric disease, and individual treatment responses. Further insight into long-term effects of NAC is indicated before its widespread use in the clinical setting.

### Key Words:

N-acetylcysteine, trichotillomania, pathological gambling, glutamate, impulse control disorders



## Introduction

Impulse control disorders (ICD's) are relatively common psychiatric disorders for which the primary etiology is unknown.<sup>1</sup> They are characterized by the irresistible impulse to engage in behaviors that are harmful or destructive to oneself or others.<sup>2</sup> The DSM-IV currently recognizes the following ICD's: pathological gambling (PG), kleptomania, trichotillomania (TTM), intermittent explosive disorder, and pyromania. Pathological skin picking (PSP), compulsive sexual behavior and compulsive buying are classified as Impulse Control Disorders Not Otherwise Specified.<sup>2</sup> Consequences of ICD's include impaired social and occupational functioning, decreased quality of life, financial loss and legal consequences.<sup>3,4</sup> This review is limited to the discussion of PG, TTM, and pathological grooming disorders including PSP.

In the US, the estimated lifetime prevalence of PG and TTM is 0.4-1.6% and 0.5-3.9%, respectively.<sup>2</sup> Lifetime prevalence of PSP has been estimated to be 0.2-1.4% in the general population,<sup>2</sup> 2% of dermatology patients, and 3.8% of college students.<sup>5</sup> Costs incurred for PSP and TTM include physicians' and hospital fees, medication, psychotherapy, and cosmetic products and procedures to hide scarring and bald spots.<sup>6</sup> Total costs for PG including health care expenses are estimated to be \$5 billion annually.<sup>7</sup> Estimated total health care costs and amount of annual health care visits for ICD's are not available at this time.

ICD's are relatively common, yet their nature and treatment are poorly understood by health care providers.<sup>3</sup> At this time there are no FDA-approved drugs for treatment of ICD's.<sup>2</sup> Current methods of treatment include opioid antagonists, mood stabilizers, anti-depressants,<sup>8</sup> cognitive behavioral therapy (CBT),<sup>2</sup> and support groups such as Gamblers Anonymous<sup>1</sup> or Hair Pullers Anonymous. Individuals with TTM may benefit from topical steroids, hydroxyzine

hydrochloride or hypnosis.<sup>1</sup> Treatments being used are not effective for all patients and more options are needed to optimize patient care.<sup>3,4</sup>

Animal studies have led to the hypothesis that the pathophysiology of behavioral addictions involves glutamate and dopamine actions in the nucleus accumbens.<sup>4</sup> The reduction of compulsive behavior has been associated with restoration of extracellular glutamate concentration in the nucleus accumbens.<sup>3</sup> N-acetylcysteine (NAC) is a hepatoprotective antioxidant believed to increase extracellular glutamate levels.<sup>4</sup> In animal models, NAC has successfully penetrated the blood–brain barrier<sup>9</sup> and reduced compulsive and reward-seeking behavior in rats with cocaine addiction.<sup>4</sup> The question of whether the glutamatergic modulator NAC can have the same effect in humans has prompted various studies on the subject.

NAC has been used for decades in the treatment of paracetamol overdose and more recently as a mucolytic and in the treatment of HIV.<sup>9</sup> NAC has also shown some benefit in treating COPD and contrast-induced nephropathy.<sup>9</sup> NAC may be effective as a relatively cheap non-prescription treatment for individuals with ICD's. Treatment with NAC may be relevant to psychiatry based on its mechanism of action in non-specific pathways common to various psychopathologies.<sup>9</sup> Alterations of oxidative stress, dysregulation of glutamate, and inflammatory pathways have been elucidated in psychiatric disease.<sup>9</sup> NAC's potential effect on these pathways makes it a source of continued interest. Furthermore, NAC's limited adverse event profile may make it a good alternative to other pharmaceutical agents.<sup>4</sup> This paper attempts to determine the efficacy of NAC as a treatment option for individuals with ICD's.

## Objective

The objective of this systematic review is to determine whether or not “Does N-acetylcysteine supplementation alleviate compulsive behavior in adults with impulse control disorders?”

## Methods

Studies reviewed include one case study, one double-blind RCT, and one open label trial followed by a double-blind RCT. All three studies analyze the effects of N-acetylcysteine in individuals over the age of 18 with a DSM-IV diagnosis of an impulse control disorder.<sup>3,4,5</sup>

The intervention applied in each study is NAC in doses between 600-2400 mg/day.<sup>3,4,5</sup> Subjects of the Grant, Kim et al. and Grant, Odlaug et al. studies were compared to an experimental group receiving an identical placebo for 12 weeks and 6 weeks, respectively.<sup>3,4</sup> Results from these two studies were obtained from clinical questionnaires.<sup>3,4</sup> Subjects in the Odlaug et al. study were not evaluated against a comparison group and results were obtained from patient reports.<sup>5</sup> Subjects in the Odlaug et al. study were treated for several months.<sup>5</sup>

The author searched for articles using PubMed, Cochrane Systematic Reviews, OVID and Ebsco using the keywords “N-acetylcysteine,” “trichotillomania,” “pathological gambling,” “glutamate,” and “impulse control disorders.” All articles were published in English in peer-reviewed journals. The inclusion criteria were RCT’s or case studies published after 1996 of adults aged 18 or older with an ICD. Articles were selected based on validity of the clinical trials, relevance to the author’s clinical hypothesis, and the inclusion of POEM’s. Studies of individuals under the age of 18 were excluded. Grant, Odlaug et al.’s study included CER, EER, a p-value of <.001 and a 95% confidence interval(CI).<sup>3</sup> Grant, Kim et al.’s study included CER, EER, and a p-value of <.001.<sup>4</sup> Studies were further evaluated by the author for RRR, ARR, and

NNT. Odlaug et al.'s study did not include statistical values. Table 1 provides demographic information and specific characteristics of the studies included in this review.

**Table 1: Demographics and Characteristics of Included Studies**

Study	Type	#Pts	Age (yrs.)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Grant, Odlaug et al. (2009)	Double-blind RCT	50	18-59	Men and women aged 18-65 with a primary DSM-IV diagnosis of trichotillomania. Women required a negative pregnancy test result and the use of a medically acceptable contraceptive throughout the study	History of seizures, unstable medical illness, bipolar disease, dementia, schizophrenia or psychotic disorder; abnormalities on physical exam/lab tests at screening; MI within 6 mos., substance abuse/dependence within 3 mos.; Current pregnancy/lactation; Lack of contraception in women of childbearing age; Reported suicidal thoughts; Previous NAC treatment; Asthma	6	NAC 1200 mg/day x6 wks increased to 2400 mg/d for remaining 6 weeks unless clinical improvement occurred at lower dose
Grant, Kim et al. (2007)	Open Label Trial	27	21-65	Men and women aged 18-75 with a primary DSM-IV diagnosis of PG; Score of 15 or greater on PG-YBOCS; Subjects required to have gambled within a week prior to enrollment ;Women required a negative pregnancy test result and the use of medically acceptable contraceptive throughout the study	Gambling not meeting DSM-IV criteria for PG; Current pregnancy/lactation; Lack of contraception in women of childbearing age; History of seizures, unstable medical illness, bipolar disease, dementia, schizophrenia, psychotic disorder; abnormalities on physical exam at screening; MI within 6 mos., substance abuse/dependence within 3 mos.; Previous NAC treatment; Positive urine drug screen test; psychotherapy or behavior therapy initiated within 3 mos. of study	4	NAC 600 mg/d x2 wks, increased to 1200 mg/day x2 wks, increased to 1800 mg/d for remainder of study unless clinical improvement occurred at lower dose  Subjects who responded to open-label NAC randomized to dose at which they completed open-label phase or identical placebo
	Followed by Double-Blind RCT	16				3	
Odlaug et al. (2007)	Case Study	5	28-52	Adults with pathological grooming behaviors	N/A	2	N-acetylcysteine 600-2400 mg/d



### Outcomes Measured

Outcomes measured include the efficacy and tolerability of NAC in adults with TTM and in adults with PG, severity of TTM symptoms, reduction of PG symptoms, reduction of compulsive grooming behaviors, reduction of anxiety and depression, psychosocial function, and quality of life.<sup>3,4,5</sup> Each of these outcomes qualifies as patient oriented evidence that matters.

The primary outcome measured in Grant, Odlaug et al.'s study was severity of TTM symptoms, measured by the Massachusetts General Hospital Hair Pulling Scale (MGH-HPS).<sup>3</sup> This is a 7-item scale that rates hair pulling urges and the associated behaviors and emotions.<sup>3</sup> Total scores range from 0-28.<sup>3</sup> Secondary outcome measures in this study were measured by the Psychiatric Institute Trichotillomania Scale (PITS), Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), Sheehan Disability Scale (SDS), Clinical Global Impression-Improvement and Severity Scales (CGI), and Quality of Life Inventory (QOLI).<sup>3</sup> This review is limited to results from MGH-HPS.

The primary outcome measured for the subjects of the Grant, Kim et al. study was reduction of PG symptoms, measured by The Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS).<sup>4</sup> This is a reliable 10-item clinician-administered scale rating gambling symptoms from the past 7 days.<sup>4</sup> Total scores range from 0-40.<sup>4</sup> Secondary measures were assessed using the Gambling Symptom Assessment Scale (G-SAS), CGI, SDS, HAM-A, HAM-D, and QOLI.<sup>4</sup> This review is limited to results from the PG-YBOCS.

The primary outcomes measured in Odlaug et al. were the reduction of compulsive grooming behaviors and associated urges.<sup>5</sup> Specific behaviors included nail biting, hair pulling and skin picking, measured by reports from subjects.<sup>5</sup>

Results:**Table 2: Key Values from Trials Being Reviewed in This Paper**

	P value	CER	EER	RRR	ARR	NNT
Grant, Odlaug et al. (2009)	<.001	0	44%	undefined	0.44	2 patients
Grant, Kim et al. (2007)	<.001	28.6%	83.3%	1.9	0.547	2 patients
Oudlaug et al. (2007)	N/A	N/A	N/A	N/A	N/A	N/A

The Grant, Odlaug et al. study involved a 12-week double-blind, placebo-controlled trial. Fifty subjects with trichotillomania were randomized to 12 weeks of double-blind NAC or placebo. Results were presented as dichotomous data analyzed with the last observation carried forward in the intention-to-treat (ITT) population. Primary and secondary measures were examined using ANOVA. Twenty two out of 25 subjects (88%) assigned to NAC and 22 out of 25 subjects (88%) assigned to placebo completed the trial. Those who did not were either non-compliant with the medication or could not complete the study due to unrelated health reasons.<sup>3</sup>

Subjects were seen every 3 weeks for 12 weeks. For the first 6 weeks subjects were given 1200 mg/day NAC or identical placebo. NAC or placebo was increased to 2400 mg/day for the remaining 6 weeks unless clinical improvement occurred at a lower dose. MGH-HPS total scores decreased from a mean of  $17.6 \pm 4.64$  at baseline to  $10.4 \pm 5.55$  (95% CI and  $p < .001$ ).<sup>3</sup> (Table 3)

**Table 3: Results of Double-blind NAC/Placebo Therapy in 50 TTM Subjects**

Variable	Baseline Placebo Group (n=25)	Baseline NAC Group (n=25)	End Point Placebo Group (n=25)	End Point NAC Group (n=25)	P value	CI
MGH-HPS Total Score	16.7 (5.28) <sup>a</sup>	17.6 (4.64) <sup>a</sup>	16.0 (4.90) <sup>a</sup>	10.4 (5.55) <sup>a</sup>	<.001	95%

<sup>a</sup> Value, mean (SD)

Of the 25 subjects assigned to NAC, 44% (n=11) had a 50% or greater reduction on the MGH-HPS compared to 0% of those assigned to placebo (95% CI,  $p < .001$ ).<sup>3</sup> NAC therapy in

TTM subjects demonstrates an experimental event rate (EER) of 44% and a control event rate (CER) of 0. The absolute risk reduction (ARR) is calculated at 44% and the number needed to treat (NNT) a TTM patient effectively with NAC is 2. (Table 2)

Demographic features including but not limited to age, gender, age at TTM onset, and TTM severity did not cause statistically significant differences in treatment response among subjects.<sup>3</sup>

Evaluations of blood pressure, heart rate and weight were recorded at each visit. Adverse effects included nausea, diarrhea and cough, experienced only in the placebo group.<sup>3</sup> (Table 4)

**Table 4: Patients with TTM Reporting Adverse Effects**

Adverse Drug Event	Placebo Group (n=25)	NAC Group (n=25)	P value
Nausea	1 (4%)	0	>.99
Diarrhea	2 (8%)	0	0.49
Cough	1(4%)	0	>.99

In the Grant, Kim et al. study, 27 pathological gambling subjects were included in the ITT analysis. Of these, 23 (85.2%) were able to keep to the study schedule and complete the study. Data were presented as dichotomous and were analyzed with the last observation carried forward in the ITT population. The study included an open-label trial followed by a double-blind RCT.<sup>4</sup>

In the 8-week open-label component, PG subjects were seen weekly for weeks 1-4, then biweekly for weeks 4-8. Subjects were started on 600 mg/day of unblinded NAC for 2 weeks. NAC was increased to 1200 mg/day for the next 2 weeks, then to 1800 mg/day for the remainder of the study. Doses were not increased if clinical improvement was observed at a lower dose.<sup>4</sup>

PG-YBOCS scores decreased from a mean of  $20.3 \pm 4.08$  at baseline to  $11.8 \pm 9.81$  after 8 weeks [ $t(50)= 4.17$  and  $p<.001$ ].(Table 5) Responders were defined as those with a  $\geq 30\%$

decrease in PG-YBOCS total score. Considering only those who completed the study, (n=23) ,16 (69.6%) were responders on the PG-YBOCS at the end of the open-label phase.<sup>4</sup>

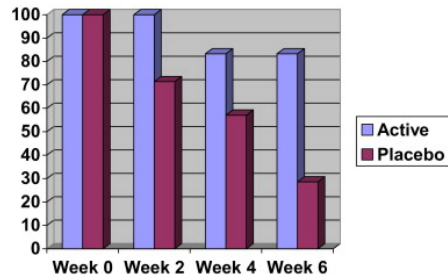
**Table 5: Results of Open-Label N-Acetylcysteine Treatment in 27 PG Subjects**

Measure	Baseline	Week 8 End Point	Paired t test	p
PG-YBOCS Total	20.3 ± 4.08 <sup>a</sup>	11.8± 9.81 <sup>a</sup>	4.17	<.001

<sup>a</sup> Value, mean (SD)

Of the 16 subjects who responded to NAC, 13 continued with the 6-week double-blind phase. Three subjects chose not to assume the risk of loss of improvement in gambling symptoms. Six of the 13 subjects were randomized to the NAC dose at which they completed the open-label phase and 7 were randomized to an identical amount of placebo. At the end of the double-blind phase, 5 out of 6 subjects (83.3%) assigned to NAC still met responder criteria, compared to 2 out of 7 subjects (28.6%) assigned to placebo.(Figure 1) NAC also maintained improvement on the primary outcome measure, the PG-YBOCS Total Score (Table 6).<sup>4</sup>

“Figure 1. Percentage of subjects meeting responder criteria each week of the double-blind discontinuation phase.”<sup>a</sup>



<sup>a</sup> This figure and its title comes directly from Grant, Kim et al.<sup>4</sup>

**Table 6: Results of 13 PG Subjects Randomized to NAC or Placebo for 6 Weeks**

Outcome Measure	Mean Rank	Z Score	p
PG-YBOCS Total Score			
Placebo	10.6	-1.67	0.095
Active	7.2		

NAC supplementation in individuals with PG demonstrates an EER of 83.3% and a CER of 28.6%.<sup>4</sup> This study demonstrates a RRR of 190% and an ARR of 54.7% for pathological gamblers taking NAC. The number needed to treat (NNT) a pathological gambler with NAC based on these results is two (Table 2). The mean effective daily dose of NAC was  $1476.9 \pm 311.3$  mg. The only adverse event was mild flatulence, reported by two subjects.<sup>4</sup>

In the case study by Odlaug et al., five subjects were enrolled and underwent structured clinical interviews.<sup>5</sup> Two of the five subjects (40%) did not respond to treatment with NAC.<sup>5</sup> Results of this study include those of the three individuals who responded.

The first subject reported cessation of urges to engage in nail biting and hair pulling for 3 months on 1800 mg/day of NAC. The only side effect reported was mild flatulence during the first 2 weeks. The second subject achieved abstinence from TTM symptoms after 5 months of 2400 mg/day NAC. She reported the cessation of hair pulling and associated urges and was able to stop wearing her wig. She reported no side effects. The third subject reported 4 months of abstinence from skin picking with only occasional mild urges on 1800 mg/day. Reports of her side effects were not included in the study.<sup>5</sup> (Table 7)

**Table 7: Results of NAC in Individuals with Pathological Grooming Disorders**

Subject	Diagnosis	Symptoms	Intervention	Result	Adverse effects
28 y.o. white male	Nail biting x 22 yrs and TTM x 16 yrs	Daily biting 2-3 hrs/d; Hair pulling 30 min/d; Significant social impairment	NAC 600 mg/d x 2 wks increased to 1200 mg/d, then to 1800 mg/d	Cessation of urges/thoughts to engage in compulsive behavior x 3 mos.	Mild flatulence x 2 weeks
40 y.o. white female	TTM x 36 years	Daily hair pulling from head and pubic area; intense shame + embarrassment	NAC 600 mg/d increased to 1200 mg/d, then to 1800 mg/d, finally to 2400 mg/d	Cessation of pulling + urges; Ability to stop wearing wig; Abstinence at 5 mos.	None

Subject	Diagnosis	Symptoms	Intervention	Result	Adverse effects
52 y.o. African American female	Skin picking x 37 years	Daily uncontrollable picking of skin on arms + legs; Frequent infections	NAC 600 mg/d increased to 1200 mg/d, then to 1800 mg/d	Absence of picking behavior w/ only occasional mild urges x 4 mos.	Not reported

### Discussion:

Grant, Odlaug et al.'s study shows improvement on the primary outcome measure in the experimental group with effects seen within 9 weeks of treatment initiation.<sup>3</sup>

Grant, Kim et al.'s study shows improvement of PG symptoms in the majority of subjects taking NAC. This study, however, has some limitations. Findings were based on a small population and only NAC responders were included in the second trial phase, possibly leading to exaggeration of NAC's effects relative to placebo.<sup>4</sup> Also, subjects with depression were taking medications in addition to the NAC, possibly affecting its efficacy.<sup>4</sup> An interesting finding in this study was that the few subjects taking psychotropic medications did not respond to NAC.<sup>4</sup>

Odlaug et al.'s study, while informative, consisted of a particularly small population size and only studied those who saw improvement with NAC. Controlled studies to investigate the same interventions applied in this study are needed to confirm the findings.

The above trials were limited by the fact that the optimal effective dose of NAC has yet to be established.<sup>9</sup> Subjects in the above trials who did not respond to NAC or who responded minimally may have had better outcomes with higher doses. Overdose of NAC, however, can lead to seizures and vigilance with its administration necessary<sup>9</sup>. Secondly, the long-term effects of NAC can not be assessed from these studies, which designed brief treatment periods in a population of subjects with a chronic, often lifelong disorder.<sup>4</sup> Longer term treatment may have shown higher levels of response. Lastly, these studies did not examine NAC treatment in

conjunction with CBT, which has proven to be beneficial in the treatment of ICD's.<sup>3</sup> The potential synergistic effects of CBT with NAC supplementation has yet to be investigated.

Conclusion:

The studies reviewed provide inconclusive evidence regarding the use of NAC in the treatment of impulse control disorders. NAC appears to be a promising alternative, but given the small population sizes and short-term use in the studies reviewed, further research is required. ICD's may require more individualized treatment approaches based on the severity and type of ICD, presence of co-morbid psychiatric disease, and individual treatment response. Future studies focused on NAC treatment in conjunction with other treatments and in tailored amounts would provide more insight. NAC is generally well-tolerated with minimal adverse effects, but there is currently no evidence for adverse outcomes with long-term use.<sup>9</sup> Long-term effects must be understood before NAC can be used in the clinical setting.

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