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HOT TOPIC

The Potential of N-acetyl Cysteine in Behavioral Addictions and Related Compulsive and Impulsive Behaviors and Disorders: a Scoping Review

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Abstract

Purpose of Review Behavioral addictions (also termed disorders due to addictive behaviors) contain impulsive and compulsive features and have been shown to involve glutamate dysregulation. N-acetylcysteine (NAC), a well-tolerated cysteine pro-drug and antioxidant, may reduce addictive behaviors by restoring glutamate homeostasis. The current review details and discusses the use of NAC in behavioral addictions and related impulsive and compulsive behaviors, including gambling disorder, problematic use of the internet, problematic video gaming, compulsive sexual behavior, problematic shopping/buying, problematic stealing, repetitive self-injurious behavior, and binge eating disorder.

Recent Findings Preliminary results have indicated the usefulness of NAC in gambling disorder, self-injurious behaviors, and compulsive sexual behaviors. Preclinical studies indicate that NAC is effective in improving binge eating behavior, but clinical trials are limited to a small open-label trial and case report. Studies are lacking on the efficacy of NAC in problematic use of the internet, problematic video gaming, problematic stealing, and problematic shopping/buying.

Summary NAC demonstrates potential for use in behavioral addictions and compulsive behaviors, particularly in gambling disorder and self-injury. However, more studies are needed to assess the effectiveness of NAC in other behavioral addictions and the mechanisms by which NAC improves these conditions.

Keywords N-acetylcysteine · Addictive Behaviors · Impulse Control Disorders · Impulsive Behaviors · Compulsive Behaviors · Glutamate Hypothesis

Introduction

Over the past two decades, increased attention has been dedicated to investigating non-substance-based addictive behaviors, also termed behavioral addictions or disorders due to addictive behaviors. Gambling disorder is formally recognized as a non-substance-related addictive disorder in the fifth edition of the Diagnostic and Statistical Manual (DSM-5). Other conditions such as problematic use of the internet, problematic shopping/buying, compulsive sexual behaviors, social-network-use disorder, and problematic video gaming have gained considerable attention, due to their addictive components and negative impacts on patients [1•, 2]. However, these conditions are not in the clinical section of DSM-5, although criteria for internet gaming disorder are included in section III, a location that includes research criteria [3]. The eleventh revision of the International Classification of Diseases (ICD-11) includes gambling and gaming disorders as disorders due

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to addictive behaviors, and the term "other specified disorders due to addictive behaviors" may be applied to other behavioral addictions [1•, 2]. These conditions typically involve impaired inhibition, compulsive engagement, craving, difficulty cutting back, and repetitive engagement in the behaviors despite negative consequences [1•]. Some behavioral addictions, like gambling disorder, are also characterized by craving, tolerance, and withdrawal [4]. These conditions often begin as ego-syntonic, with motivations towards positive reinforcement, such as seeking excitement or joy, and progress to become ego-dystonic with cravings, compulsions, and motivations towards negative reinforcement in later stages [5]. Researchers have also drawn similarities between certain compulsive behaviors and addictive behaviors [6, 7]. Repetitive self-injurious behavior (SIB) and binge eating disorder (BED) may have addictive features, such as craving, preoccupation and urges for the behaviors, tension relieved only by the behaviors, difficulty reducing the behaviors despite negative consequences, and a relapsing course of the behaviors [6–12]. Accordingly, several researchers have conceptualized these conditions from the lens of behavioral addictions [6–12]. As a result of the shared characteristics across addictive behaviors and these compulsive behaviors, similar treatments may be effective in these conditions.

Dysregulation of glutamatergic signaling has been implicated in a wide range of impulsive, compulsive, and addictive behaviors [13–18]. Under normal conditions, glutamate homeostasis is maintained by several proteins including: the glial-glutamate transporter-1, which transfers glutamate from the synaptic cleft to astrocytes; the cysteine-glutamate antiporter, which exchanges astrocyte glutamate for extrasynaptic cysteine; and metabotropic glutamate receptors which reduce synaptic glutamate release when activated [19•].

Due to the presence of glutamatergic dysregulation and phenotypic similarities across impulsive, compulsive, and addictive behaviors, glutamatergic agents have been investigated for use in these conditions with some success. N-acetylcysteine (NAC) is a cysteine pro-drug, glutamatergic agent, and antioxidant that has shown promise in impulse-control disorders (like trichotillomania, skin-picking, and impulsive self-harm/irritability in autism), substance-use and addictive disorders, and obsessive–compulsive-spectrum disorders [19•, 20, 21, 22•, 23–31]. Animal models have shown that NAC reduces compulsive drug-seeking behavior by upregulating glial glutamate transporter-1 to increase astrocyte uptake of synaptic glutamate, as well as increasing xCT activity through cysteine-glutamate exchange, leading to metabotropic glutamate receptor activation and decreasing synaptic glutamate release in the nucleus accumbens [19•, 32–34]. NAC has also been shown to restore long-term potentiation and depression of synapses and reduce oxidative stress [19•]. Through these mechanisms, NAC may reduce compulsive and addictive behaviors [19•].

While several reviews have explored the use of NAC in some of the substance-use behaviors, obsessive–compulsive-spectrum disorders, and impulsive disorders mentioned above, none has fully discussed behavioral addictions and related impulsive/compulsive behaviors [15, 20, 22•, 24, 25, 35, 36]. As such, the current review details and discusses the use of NAC in non-substance-based behavioral addictions and impulsive/compulsive behaviors that have been described as having addictive features (including repetitive SIB and BED). The addictive, impulsive, and compulsive behaviors reviewed here include gambling disorder, problematic use of the internet, problematic video gaming, compulsive sexual behaviors, problematic shopping/buying, problematic stealing, repetitive SIB, and BED.

Methods

Articles were selected by reviewing the PubMed, Web of Science, and Cochrane Central Registry of Controlled Trials databases, using the following search in "All Fields" (including author, title, abstract, and keywords): ((N-acetyl cysteine) OR (N-acetylcysteine)) AND ((behavioral addiction) OR (problem* video gaming) OR (internet gaming disorder) OR (gaming addiction) OR (problem* internet use) OR (internet addiction) OR (problematic use of the internet) OR (compulsive sexual behavior) OR (pornography addiction) OR (pathologic gambling) OR (gambling disorder) OR (gambling addiction) OR (problem* gambling) OR (self injurious behavior) OR (self harm) OR (self-injury) OR (binge eating) OR (bulimia) OR (eating addiction) OR (eating disorder) OR (problematic stealing) OR (kleptomania) OR (compulsive buying) OR (compulsive shopping) OR (problem* shopping) OR (shopping addiction)). A review of ClinicalTrials.gov was performed to assess ongoing clinical trials using the same search strategy. The searches were performed in September 2022.

A PRISMA diagram of the search process, including exclusion criteria, is displayed in Fig. 1 (original figure). Additionally, Supplemental Spreadsheet 1 contains a full list of the articles that resulted from the search and whether they were included in the final review or not. Additionally, for clinical trials on ClinicalTrials.gov that had results or methods published in another article, the article was included in place of the data posted on ClinicalTrials.gov. Eleven studies were included in the final review, and information about these studies is summarized in Table 1 (original table).

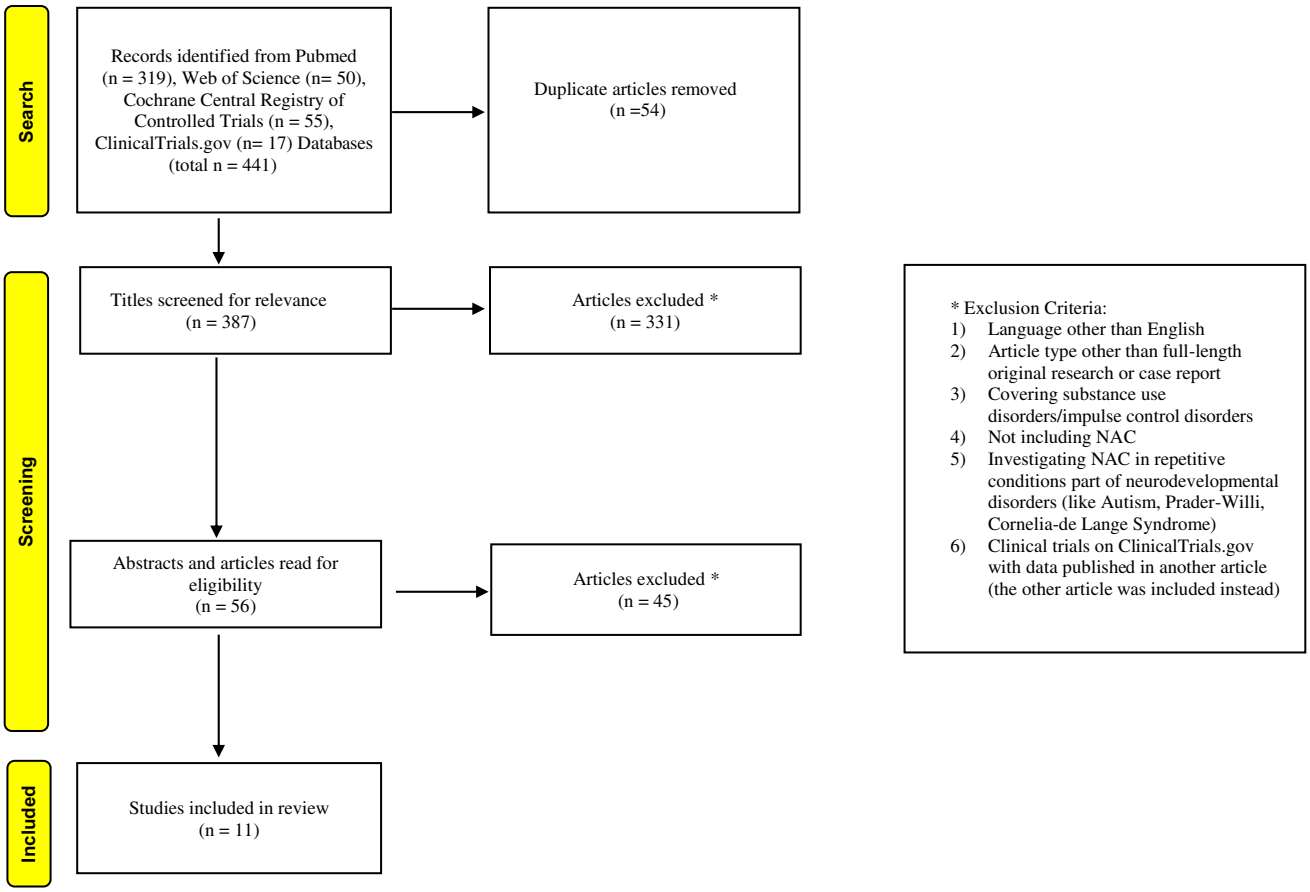

Fig. 1 PRISMA diagram of search results

Pathological Gambling/Gambling Disorder

Initially included as pathological gambling in DSM-III and renamed (to reduce potential stigma) and reclassified (as a non-substance-related addictive disorder instead of an impulse-control disorder based on gathered data), gambling disorder is defined as "persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress" [37]. In the USA, the prevalence of gambling disorder among adults has been reported as high as 1.1%, with an additional 1–2% meeting criteria for problem gambling [38]. Despite negative correlates with quality of life, interpersonal relationships, and financial well-being, gambling disorder often goes unrecognized in primary care, psychiatric, and other clinical settings, and there remains no current FDA-approved medication with an indication for the disorder [39, 40].

Similar to substance-use disorders, glutamatergic signaling has been implicated in gambling disorder. Researchers have found that cerebrospinal fluid in people with versus without gambling disorder contains higher concentrations of glutamate [41]. Additionally, several glutamatergic agents have been examined in gambling disorder including memantine, amantadine, modafinil, gabapentin, pregabalin, and topiramate with mixed results [42–47]. Together, these studies suggest that glutamate dysregulation may contribute to gambling disorder, suggesting that NAC holds potential in treating this condition.

Two studies have investigated the efficacy of NAC in gambling disorder. In one study, 27 participants with gambling disorder were enrolled in an 8-week, open-label trial with double-blind discontinuation with NAC dosed at 1200–1800 mg/day. At the end of the open-label phase, responders, defined as showing a $\geq$30% reduction in scores on the Yale-Brown Obsessive Compulsive Scale: Pathological Gambling Modification (PG-YBOCS), were randomized to an additional 6 weeks of NAC vs. placebo, double-blind. Over 59% of the original cohort qualified as responders under this criterion, and over 83% of the enrolled responders responded again at the end of the double-blind phase, and this contrasted with the 28.6% who maintained response on placebo [48].

In another study, 28 participants with both gambling disorder and tobacco use disorder (TUD) were randomized to

Table 1 Original table detailing the studies reviewed

Condition	Author, year	Study type	Participants	Dose, duration, (admin route)	Adjunctive therapy	Modality and endpoint	Primary findings
Gambling disorder (GD)	Grant et al., 2007 [48]	Open-label	27 GD participants	1200–1800 mg/day, 8 weeks (PO)	None	Percentage of participants who had > 30% reduction PG-YBOCS	59% of patients had > 30% reduction in PG-YBOCS
	Grant et al., 2014 [49]	RCT	28 GD participants	1200–1300 mg/day, 12 weeks (PO)	Imaginal desensitization behavioral therapy	Reduction in PG-YBOCS	Statistically significant reduction in PG-YBOCS at post-treatment follow-up relative to placebo
Repetitive SIB	Pittenger et al., 2005 [59]	Case study	2 female participants with BPD	1200 mg/day, 6 months (PO)	100 mg/day riluzole	Craving for SIB, SIB frequency	Significant reduction in craving at 2–4 weeks in both patients; no SIB for 6 months
	Cullen et al., 2018; Cullen et al., 2020 [60••, 61••]	Open-label	35 female adolescents	1200 mg/day for 2 weeks; 2400 mg/day for 2 weeks; 3600 mg/day for 4 weeks (PO)	None	SIB frequency	Significant reduction in SIB frequency; reduction in depression scores; increased amygdala-frontal resting state connectivity
	Sahasrabudhe et al., 2021 [62]	Open-label	Actively recruiting	3600–5400 mg/day, 4 weeks (PO)	None	SIB frequency and change in glutamate and glutathione concentration on ^{1}H-MRS	Study ongoing
Binge eating disorder/ bulimia nervosa	Hurley et al., 2016 [63••]	Preclinical	Rats	90 mg/kg/day, 14 days (IV)	None	Self-administration of high-carbohydrate, high-fat food vs. standard chow	Significant reduction in high-carbohydrate/high-fat intake and compensatory increase in standard chow
	Sketriene et al., 2021 [64]	Preclinical	Obese vs. non-obese rats	100 mg/kg/day, 14 days (IP)	None	Self-administration of high-carb high-fat food	NAC reduced lever presses in obese rats to levels of lean rats
	Guerdjikova et al., 2013 [65]	Open-label	8 participants with bulimia nervosa	600–2400 mg/day, 12 weeks (PO)	None	Number of binge/purge episodes	No significant reduction
	Zhao et al., 2021 [67]	Case study	1 patient with BED and Trichotillomania	1800 mg/day, 14 weeks (PO)	Fluvoxamine 150 mg/day, Bupropion 300 mg/day	Number of binge episodes	Rapid and sustained (for 14 weeks) improvement in binge episodes and trichotillomania

Table 1 (continued)

Condition	Author, year	Study type	Participants	Dose, duration, (admin route)	Adjunctive therapy	Modality and endpoint	Primary findings
Compulsive sexual behaviors	Blum and Grant, 2022 [69•]	Case series	8 male patients with compulsive sexual behaviors	2400–3600 mg/day	Bupropion, escitalopram, fluoxetine, naltrexone, phenelzine, CBT, or none (see main text)	CSB-Y-BOCS score	5/8 of the participants had significant improvement (> 35%) in CSB-Y-BOCS score after NAC treatment compared to before. The remaining 3 participants had minimal (< 15%) to no improvement

IP, intraperitoneal; *IV*, intravenous; *PO*, oral; *NAC*, N-acetylcysteine; *GD*, gambling disorder; *BPD*, borderline personality disorder; *BED*, binge eating disorder; *SIB*, self-injurious behaviors; *^{1}H-MRS*, proton magnetic resonance spectroscopy; *CBT*, cognitive behavioral therapy; *PG-Y-BOCS*, pathological gambling Yale-Brown Obsessive Compulsive Scale; *CSB-Y-BOCS*, Compulsive Sexual Behaviors Yale-Brown Obsessive Compulsive Scale

12 weeks of NAC (1200–1300 mg/day) or placebo, in addition to imaginal desensitization behavioral therapy for gambling disorder and a smoking cessation behavioral therapy. Compared to placebo, NAC significantly improved measures of TUD at earlier points in time within treatment and significantly improved measures of gambling disorder on the PG-YBOCS at treatment follow-up, suggesting NAC may improve the persistence of treatment effects [49]. Together, these results implicate a role both for NAC as a standalone pharmacological intervention and in facilitating long-term behavioral therapy for gambling disorder. While encouraging, more research is needed to evaluate the efficacy of NAC in the treatment of gambling disorder. There are currently no active studies for NAC on gambling disorder registered on clinicaltrials.gov. Given increasing access to forms of gambling (e.g., sports and internet-based gambling), further investigation into this promising treatment is warranted [50]. Additionally, neuroimaging studies may be helpful to investigate whether NAC efficacy may relate to the restoration of brain glutamate homeostasis. Researchers have used proton magnetic resonance spectroscopy (^{1}H-MRS) to measure glutamate and glutamine levels in various brain regions and have shown that NAC changes baseline alterations on glutamate levels in individuals with cocaine use disorder [51, 52••]. This technology could be helpful in determining whether NAC has a similar effect in gambling disorder, and future studies should consider directly comparing gambling disorder and other SUDs like cocaine use disorder given similarities and differences in the neurobiological correlates of these conditions [53–56].

Self-injurious Behaviors

Repetitive self-injurious behavior (SIB) has been conceptualized by some researchers as a behavioral addiction, in part due to its impulsive and compulsive features and its association with other behavioral addictions [57, 58]. Due to these features, one case study investigated the role of 1200 mg/day NAC and 100 mg/day riluzole, another glutamatergic agent, in two patients with borderline personality disorder and repetitive SIB. In both patients, the two medications reduced cravings for SIB and SIB frequency, although one should cautiously interpret these findings given the open-label nature of the report and the small sample [59].

Following up on these initial results, two studies investigated the use of NAC in repetitive SIB. In an open-label study of thirty-five female adolescents with SIB, treatment with 1200 mg/day of NAC for 2 weeks, followed by 2 weeks of 2400 mg/day and then 4 weeks of 3600 mg/day, was associated with a significant decrease in SIB frequency from baseline, at weeks 6 and 8 of the trial [60••]. NAC was also associated with a decrease in depression scores after week 8, compared to baseline [60••]. Within the same study group,

improvements in SIB and depression scores after NAC treatment were associated with increased amygdala-frontal resting-state functional connectivity (rsFC), compared to before NAC treatment [61••]. Additionally, improvement in SIB and depression scores correlated with a decrease in positive connectivity between the amygdala and supplementary motor area (SMA) [61••]. These findings suggest that NAC may strengthen amygdala-frontal and limbic-SMA circuits to decrease SIB. To better understand the potential mechanisms of action of NAC, a clinical trial is currently underway. The trial is using ^{1}H-MRS at 7 T to investigate the correlates of clinical improvement in SIB after NAC treatment. Specifically, ^{1}H-MRS is being employed to examine potential changes in glutathione and glutamate in the brain [62]. The use of ultrahigh-field imaging at 7 T with ^{1}H-MRS permits distinguishing of glutamine and glutamate levels and quantification of levels of cortical glutathione to assess potential oxidative stress [62]. This study will help assess whether NAC improves repetitive SIB in adolescents by modulating glutamate signaling and/or reducing oxidative stress.

Eating Disorders

Binge eating disorder (BED) and bulimia nervosa (BN) are both characterized by compulsive binge eating episodes, during which patients consume excessively large quantities of food without an unmet homeostatic need [63••]. Due to the seemingly compulsive and potentially addictive nature of these two disorders, researchers have explored the potential use of NAC, with mixed results. NAC has been proposed to decrease the frequency of binge-eating episodes and investigated in a rodent model [63••]. In an established preclinical model for binge eating, rodents were given constant access to standard chow, with the addition of limited daily access to high carbohydrate, high-fat food to promote and simulate binge-eating episodes [63••]. Rodents administered intravenous NAC demonstrated significant reductions in binge eating, with a decrease in overall consumption of the high-carbohydrate, high-fat food, compared to untreated rodents, and a compensatory increase in standard chow consumption. Importantly, no difference was found in daily caloric intake between NAC-treated and untreated rodents, suggesting that NAC selectively alters the binge eating of highly palatable food in rodents, without altering overall caloric homeostasis [63••]. In a similar study, the potential of NAC to diminish addictive-like eating behaviors was investigated in obese rats [64]. After 8 weeks of exposure to high-fat, high-sugar food, rats in the upper third of weight gain (diet-induced obesity-prone, or DIO rats) were compared to the lower third (diet-induced obesity-resistant, or DR rats). Both groups were then subjected to operant conditioning, during which they could press a lever for high-fat high-sugar pellets, and then periods of lever pressing without pellet rewards. DIO versus DR rats demonstrated more lever presses and ate more pellets during the operant phase. The DIO rats also had more lever presses without pellets during the next phase, compared to DR rats. Daily intraperitoneal injections with 100 mg/kg of NAC reduced lever pressing during both phases in the DIO rats to the levels of the DR rats [64]. These results suggest that NAC ameliorates addiction-like binge eating in obese rats.

A 12-week, open-label clinical trial was conducted with 8 patients with BN [65]. While preclinical studies suggest the usefulness of NAC in binge eating, a significant decrease in binge-purge episode frequency or improvement in clinical severity was not observed with NAC treatment. The study also showed a high rate of discontinuation among study participants, either due to lack of improvement from treatment or experiencing of adverse effects, including rash, edema, and pruritis. The study had several limitations, including the small sample size of eight patients and the open-label design. Additionally, only three of eight participants received a total daily dose of 2400 mg of NAC, while the others received between 600 and 1200 mg daily. Prior studies of NAC use in substance-use disorders or behavioral addictions have used dosages of 2400 to 3600 mg/day which may explain in part why no difference was observed in the current study [52••, 65, 66]. In contrast, in one case report, a patient with trichotillomania and binge eating disorder was given 1800 mg/day of NAC, on top of prior ineffective treatment with fluvoxamine 150 mg/day and bupropion 300 mg/day. The addition of NAC resulted in rapid improvement in both her hair plucking and BED, with sustained improvement during a 14-week follow-up [67]. This report resonates with a larger study indicating NAC's efficacy and tolerability in treating people with trichotillomania [21] and excoriation (skin-picking) disorder [68]. Future studies should investigate whether combinations of NAC with other treatments are more effective than monotherapy and the efficacy and tolerability of NAC in larger samples of people with BED.

Compulsive Sexual Behaviors

Compulsive sexual behaviors are characterized by preoccupation, urges, and repetitive engagement in sexual behaviors that result in psychosocial impairment [69•]. Some have referred to the condition as "sexual addiction," due to the addictive features of the behaviors [70]. Glutamatergic afferents have been implicated in sexual behaviors [71]. Due to the phenotypic similarities between compulsive sexual behaviors and formal behavioral addictions, a recently published case series investigated the role of NAC in the treatment of the condition [69•]. The patients involved in the study were eight males with compulsive sexual behaviors who were stable on other psychiatric medications (phenelzine, fluoxetine, escitalopram, naltrexone,

or bupropion) for at least 3 months or on no other psychiatric therapies. Participants were started on 2400–3600 mg/day of NAC for 2–6 months, and Yale-Brown Obsessive Compulsive Scale: Compulsive Sexual Behavior Modification (CSB-YBOCS) measures were obtained before and after NAC therapy. Five of the eight participants demonstrated significant reduction (> 35%) in their CSB-YBOCS score, suggesting a significant effect of NAC in some patients [69•]. Given these encouraging preliminary findings, the similarities between compulsive sexual behaviors and formal behavioral addictions, and the role of glutamate in rewarding and sexual behaviors, larger studies should be performed evaluating NAC in compulsive sexual behaviors [72].

Other Behavioral Addictions

A comprehensive review of the literature for problematic internet use, problematic video gaming, repetitive stealing or kleptomania, and problematic shopping/buying revealed that NAC has not been investigated in these conditions. Similar addictive features in these conditions, analogous to gambling disorder and substance-use disorders, as well as impulsive and compulsive features, suggest that NAC holds promise. Additionally, glutamate dysregulation has been implicated in several of these conditions. For example, memantine, an N-methyl-D-aspartate receptor antagonist, reduces glutamate excitability, and preliminary results have demonstrated its efficacy in problematic shopping/buying [73]. This finding suggests that glutamate dysregulation may contribute to problematic shopping/buying. In a study of participants with internet gaming disorder, serum levels of glutamate have been found to be lower relative to individuals without the disorder [74]. While the precise neurobiological significance of this finding is still uncertain, it suggests that altered glutamatergic neurotransmission may contribute to internet gaming disorder [74]. Furthermore, in a neuroimaging study of participants with problematic use of the internet or "smartphone addiction," participants were found to have higher g-aminobutyric acid (GABA)-to-creatine ratios in the anterior cingulate cortex, relative to individuals without the condition [75]. This suggests that disrupted GABA and glutamate balance may impact synaptic glutamate excitability and contribute to problematic use of the internet or smartphones [75]. Glutamatergic differences in problematic use of the internet and smartphones, problematic video gaming, and problematic shopping/buying suggest that NAC warrants direct examination in clinical trials.

Discussion

In the current manuscript, we reviewed the existing literature on NAC's use in several behavioral addictions and related compulsive behaviors with addictive features, namely problematic gambling, problematic use of the internet, problematic video gaming, compulsive sexual behaviors, problematic shopping/buying, problematic stealing, repetitive SIB, and BED. The choice to include these disparate conditions in one review was due to the phenotypic similarities between many behaviors that are classified as addictive, compulsive, and impulsive disorders [6–12]. For several impulsive and compulsive behaviors, there exists significant debate about whether they fit better under a framework of addiction or ones related to impulse control or compulsivity. For example, compulsive sexual behavior was included in the ICD-11 as an impulse-control disorder, though significant research has indicated that poorly controlled and interfering patterns of pornography viewing may best be understood as addictive, given its behavioral and neuroimaging similarities to substance-use and gambling disorders [2]. Brand et al. argued that a similar classification would fit for problematic shopping/buying and social-network-use disorder [2]. Conversely, some behaviors under the umbrella of problematic use of the internet, which many have argued would be best conceptualized as addictive, have also been considered to have phenotypic similarities to impulse-control disorders (such as online shopping), or obsessive–compulsive spectrum disorders (such as repeatedly checking e-mails/social media, cyberhoarding, or repeated online searching of health-related information known as "cyberchondria") [76]. Due to the significant debate about how best to characterize these potentially addictive, compulsive, and impulsive behaviors and the shared presence of difficulties with impulse control and compulsiveness in all these behaviors, we reviewed the use of NAC in these conditions. Behaviors that have been largely considered impulse-control disorders (such as trichotillomania, excoriation disorder, or onychophagia) or obsessive–compulsive disorder have been reviewed previously and were therefore not included in the current review [15, 20, 22•, 24, 25, 35, 36].

While NAC has been studied extensively in substance-use disorders, impulse-control disorders, and obsessive–compulsive-spectrum disorders, only a few studies have been performed on behavioral addictions and related compulsive disorders and behaviors. Although it is sometimes difficult to model these conditions in preclinical studies, this has been accomplished with some of them, such as BED, facilitating the translational exploration of NAC's effects [63••]. In clinical research settings, current and future studies should further explore neurobiological correlates of NAC's actions using neuroimaging tools such as proton-magnetic resonance spectroscopy (^{1}H-MRS). ^{1}H-MRS is a tool that has been used in the exploration of NAC effects of cocaine use disorder and, similar to studies on cocaine, it may be used to explore glutamatergic effects of NAC on these behavioral addictions and related conditions, as well as explore potential antioxidant effects through measurement of glutathione

[77, 78]. Despite negative findings in the open-label trial of NAC in BED, the success of NAC in preclinical BED trials, the small size of the clinical BED trial and the low dose of NAC in that trial suggest that NAC warrants more investigation in this condition. In the studies reviewed here, the range of NAC doses used was between 600 and 3600 mg/day. Studies from the substance-use disorder literature have demonstrated that NAC may have effectiveness at 3600 mg/day [52••, 65, 66]. Due to the tolerability of NAC and efficaciousness in some studies at 3600 mg/day, future studies should attempt to use this higher dose. Additionally, while the current review focuses on NAC due to its glutamatergic and antioxidant roles, other well-tolerated nutraceuticals like vitamin D have been explored in the treatment of addictive, compulsive, and impulsive disorders due to their antioxidant and dopaminergic effects [25, 79–81].

Conclusions

In summary, behavioral addictions share features with substance use disorders and impulse control disorders, and preliminary data from small trials and case series have suggested efficacy of NAC in gambling disorder, repetitive SIB, and compulsive sexual behaviors. Larger studies of NAC in these behaviors and conditions are warranted. More mixed results have been present in studies of BED, although those studies were limited by small sample sizes and NAC doses. Studies of NAC in problematic use of the internet, problematic video gaming, repetitive stealing or kleptomania, and problematic shopping/buying are lacking. Given similarities between these behaviors/conditions and formal behavioral addictions and involvement of glutamate in these behaviors, future studies of NAC in these behaviors and conditions are indicated. Future studies should also assess the mechanistic effects of NAC using ^{1}H-MRS and other techniques and explore the potential of other nutraceuticals like vitamin D (calcitriol).

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Author Contribution GAA and MNP conceived the project. NRG, FF, and BK conducted the literature search. NRG, FF, and BK drafted the original manuscript with GAA and MNP critically revising. All authors read and approved the final manuscript.

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Declarations

Conflict of Interest The authors declare no conflicts of interest with the content of this manuscript. Dr. Potenza has consulted for Opiant Therapeutics, Game Day Data, Baria-Tek, the Addiction Policy Forum, AXA and Idorsia Pharmaceuticals; has been involved in a patent application with Yale University and Novartis; has received research support from Mohegan Sun Casino and the National Center for Responsible Gaming; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders or other health topics; has consulted for and/or advised gambling and legal entities on issues related to impulse-control/addictive disorders; has provided clinical care in a problem gambling services program; has performed grant reviews for research-funding agencies; has edited journals and journal sections; has given academic lectures in grand rounds, CME events, and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. The other authors do not report disclosures.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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•• Of major importance

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