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Review

Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review

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ABSTRACT

N-acetylcysteine (NAC) is recognized for its role in acetaminophen overdose and as a mucolytic. Over the past decade, there has been growing evidence for the use of NAC in treating psychiatric and neurological disorders, considering its role in attenuating pathophysiological processes associated with these disorders, including oxidative stress, apoptosis, mitochondrial dysfunction, neuroinflammation and glutamate and dopamine dysregulation. In this systematic review we find favorable evidence for the use of NAC in several psychiatric and neurological disorders, particularly autism, Alzheimer's disease, cocaine and cannabis addiction, bipolar disorder, depression, trichotillomania, nail biting, skin picking, obsessive-compulsive disorder, schizophrenia, drug-induced neuropathy and progressive myoclonic

Abbreviations: ABC, Aberrant Behavior Checklist; AD, Alzheimer's disease; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; ADHD, attention deficit hyperactivity disorder; ADL, Activities of Daily Living; ADP, adenosine diphosphate; AE, adverse effects; AIMS, Abnormal Involuntary Movement Scale; ALL, acute lymphoblastic leukemia; ALS, amyotrophic lateral sclerosis; AN, animal naming test; ASD, autism spectrum disorder; ASRS, ADHD Self Report Scale; ATP, adenosine triphosphate; BAS, Barnes Akathisia Scale; BDRS, Bipolar Depression Rating Scale; BE, benzoylecgonine; BID, twice daily; BP, blood pressure; BPAD, bipolar disorder; BSCS, Brief Substance Craving Scale; CCQ-Brief, Cocaine Craving Questionnaire-Brief; CGI, Clinical Global Impression; CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity; CLOX-1, Clock Drawing Executive Test; CO, carbon monoxide; COWA, Controlled Oral Word Association Test; CSSA, Cocaine Selective Severity Assessment; DA, dopamine; DBPC, Double Blind Placebo Control Trial; DE, detrimental; Dep, depressive disorder; DNA, deoxyribonucleic acid; DRS-2, Dementia Rating Scale-2; DTE, dithioerythritol; DTT, dithiothreitol; ESRS, Extrapyramidal Symptom Rating Scale; F, female; FDA, Food and Drug Administration; FTQ, Fagerström Tolerance Questionnaire; g/d, grams per day; G, grams; GAF, Global Assessment of Functioning; GI, gastrointestinal; GOR, grade of recommendation; G-SAS, Gambling Symptom Assessment Scale; GSH, glutathione; GSSG, glutathione disulphide; GTCS, Generalized Tonic Clonic Seizures; HA, headache; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; HIV, human immunodeficiency virus; 5-HT, serotonin; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; IU, international units; LIFE-RIFT, Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool; LOE, level of evidence; LPS, lipopolysacchride; LTD, long term depression; LTP, long term potentiation; M, male; MADRS, Montgomery–Asberg Depression Scale; MAOI, monoamine oxidase inhibitor; MAP, methamphetamine; MCQ, Marijuana Craving Questionnaire; MDD, major depressive disorder; μg, micrograms; mg, milligrams; MGH-HPS, Massachusetts General Hospital Hair Pulling Scale; MMSE, Mini-Mental Status Examination; MNWS, Minnesota Nicotine Withdrawal Scale; mRNA, messenger ribonucleic acid; NA, nucleus accumbens; NAC, N-acetylcysteine; NACA, N-acetylcysteine amide; NAM, N-acetylmethionine; NE, neutral effect; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NIMH-TSS, National Institute of Mental Health Trichotillomania Severity Scale; NMDA, N-methyl D-aspartate; NPI, Neuropsychiatric Inventory; NR, not reported; OCD, obsessive compulsive disorder; OR, odds ratio; PANSS, Positive and Negative Syndrome Scale; PB, placebo; PFC, pre-frontal cortex; PG, pathological gambling; PG-YBOCS, Pathological Gambling-Yale-Brown Obsessive Compulsive Scale; PICO, Problem-Intervention-Comparison-Outcomes Framework; PITS, Psychiatric Institute Trichotillomania Scale; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; QSU, Questionnaire of Smoking Urges; RBS-R, Repetitive Behavior Scale-Revised; RCT, randomized controlled trial; ROS, reactive oxygen species; SAS, Simpson–Angus Scale; SC, single case report or series; SD, standard deviation; SDS, Sheehan Disability Scale; SLE, systemic lupus erythematosus; SLICE-LIFE, Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation; SMD, spinal muscular dystrophy; SN, sensorineural; SOFAS, Social and Occupational Functioning Assessment Scale; SQ, subcutaneous; SR, systematic review; SRS, Social Responsiveness Scale; SSRI, selective serotonin reuptake inhibitor; SU, substance use; TBI, traumatic brain injury; TID, three times daily; TMT, Timed Trail Making Test A and B; TNF, tumor necrosis factor; TSC, Trichotillomania Scale for Children; TTM, trichotillomania; UDS, urine drug screen; ULD, Unverricht–Lundborg Disease; VAS, Visual Analog Scale; Vit, vitamin; Wk, weeks; Y-BOCS, Yale Brown Obsessive Compulsive Scale; YMRS, Young Mania Rating Scale.

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epilepsy. Disorders such as anxiety, attention deficit hyperactivity disorder and mild traumatic brain injury have preliminary evidence and require larger confirmatory studies while current evidence does not support the use of NAC in gambling, methamphetamine and nicotine addictions and amyotrophic lateral sclerosis. Overall, NAC treatment appears to be safe and tolerable. Further well designed, larger controlled trials are needed for specific psychiatric and neurological disorders where the evidence is favorable.

Contents

1. Introduction

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N-acetylcysteine (NAC) is acetyl derivative of the amino acid cysteine (Arakawa and Ito, 2007). It is widely available as an over-the-counter nutritional supplement with antioxidant properties (Berk et al., 2013). NAC is considered a well-tolerated and safe medication that has been used all across the world in variety of medical conditions for past several decades (LaRowe et al., 2006). It is widely recognized for its role as an antidote of acetaminophen overdose (Green et al., 2013). For acetaminophen overdose, NAC has been FDA approved as oral 72-h protocol since 1985 in the United States (Yarema et al., 2009). Outside of the Unites States, the 20-h intravenous protocol has been preferable and FDA approved the intravenous form for use in acetaminophen overdose in the United States in 2004 (Yarema et al., 2009). It is also used as a mucolytic in chronic obstructive pulmonary disease (Dekhuijzen and van Beurden, 2006), a renal protectant in contrast-induced nephropathy (Quintavalle et al., 2013), as a preventive agent for atrial fibrillation (Liu et al., 2014) and as adjunct therapy in HIV-infection (De Rosa et al., 2000). Additionally it has shown to inhibit replication of the seasonal influenza A virus and could be a potential treatment in influenza A infection (Geiler et al., 2010).

Over the past decade, there has been a growing interest in using NAC to treat psychiatric and neurological disorders. Evidence based on preclinical research studies suggest that NAC may modulate pathophysiological processes that are involved in multiple psychiatric and neurological disorders, including oxidative stress, neurogenesis and apoptosis, mitochondrial dysfunction, neuroinflammation and dysregulation of glutamate and dopamine neurotransmitter systems (Dean et al., 2011; Samuni et al., 2013). In addition, it is also believed to have a role in long-term neuroadaptation and metaplasticity that is very important in a number

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of psychiatric disorders (Moussawi et al., 2009; Reichel et al., 2011).

Over the past decade, clinical reports have documented the outcome of treatment with NAC for a multitude of psychiatric and neurological disorders, including schizophrenia, bipolar disorder, skin picking, trichotillomania, obsessive-compulsive disorder, autism and addiction to nicotine, cannabis, cocaine, methamphetamine, gambling (Berk et al., 2013); as well as epilepsy, amyotrophic lateral sclerosis, neuropathy (Bavarsad Shahripour et al., 2014) and traumatic brain injury (Hoffer et al., 2013). Given the growing number of studies on its use as a treatment intervention in psychiatry and neurology, along with a very good safety and tolerability profile, we aimed to systematically review the literature and critically evaluate the level of evidence concerning the use of NAC for treating psychiatric and neurological disorders. Such a systematic evaluation has allowed us to produce a grade of recommendation for each psychiatric and neurological disorder. To this end, this manuscript can help us understand in which disorders NAC may be clinically useful, in which disorders NAC may not be useful and in which disorders more studies are required to make such a judgment. We particularly concentrate on the evidence for any adverse effects during the use of NAC in controlled clinical trials to assess whether NAC is safe for the treatment of psychiatric and neurological disorders.

2. Method

The PICO (Problem-Intervention-Comparison-Outcomes) framework was used to conduct this review (Richardson et al., 1995). The goal was to identify research studies that reported NAC as a treatment to improve all common psychiatric and neurological disorders. We did not compare NAC treatment to other treatment and we considered all clinical study designs. Our primary goal was to consider improvement in all outcomes reported in the clinical studies review as well as determine the prevalence of adverse effects with NAC treatment.

2.1. Search strategy

A systematic online literature search of PUBMED, Ovid Medline, Psych info, Google Scholar, CINAHL, EmBase, Scopus, Cochrane and ERIC databases from inception through March 2015 was conducted using search terms – "N-acetylcysteine", "acetylcysteine" or "NAC" AND broad search term – "psychiatry", "psychiatric disorder", "mental illness", "neurology", "neurological disorder" or "addiction" OR specific psychiatric and neurological disorder – "autism", "autistic disorder", "ASD", "Asperger's", "pervasive developmental disorder", "depressive disorder", "major depression", "bipolar disorder", "mania", "hypomania", "psychosis", "schizophrenia", "anxiety", "attention deficit hyperactivity disorder", "ADHD", "obsessive compulsive disorder", "OCD", "methylphenidate", "amphetamine", "methamphetamine", "cocaine", "cannabis", "marijuana", "heroin", "prescription pills", "opioids", "benzodiazepine", "nicotine", "pathological gambling", "trichotillomania", "nail biting", "skin picking", "impulse control disorder", "amyotrophic lateral sclerosis", "ALS", "epilepsy", "seizures", "traumatic brain injury", "TBI", "stroke", "neuropathy", "Parkinson's disease", "Huntington's disease", or "multiple sclerosis". The references cited in the identified publications were searched for additional studies.

2.2. Study selection

One reviewer screened titles and abstracts of all potentially relevant publications. All the abstracts were divided into five reviewers. All the reviewers independently went through their section to select articles based on inclusion and exclusion criteria. Studies were initially included if they met all of the following criteria: (a) human clinical trials that included randomized controlled trials, non-randomized trials, case studies and/or case series, (b) studies on psychiatric and neurological disorders, and (c) reported a direct clinical effect of NAC as an outcome. Studies were excluded if they: (a) did not involve humans, (b) did not present new or unique data (review articles, letter to the editor, duplicate article), (c) did not measure a clinical outcome related to effect of NAC, or (d) only reported a non-clinical measure.

2.3. Level of evidence ratings

Although we considered conducting a meta-analysis on each psychiatric and neurological disorder, the lack of standard outcomes and the limitations in study design prevented a meta-analysis of any identified disorder. As an alternative, we provide a grade of recommendation (GOR) for each psychiatric and neurological disorder based on the level of evidence (LOE) for each study. Using a well-established scale (Howick et al., 2011), each study was individually assessed to determine the LOE, ranging from level 1 to 5 (see Table 1). After assessing all identified studies for each disorder, a GOR ranging from A (solid evidence) to D (limited, inconsistent or inconclusive evidence) was assigned (see Table 2) to each disorder. Since a treatment could be a GOR of D for several reasons, we specified if the treatment received this rating because the evidence was a single case-report or series (SC), demonstrated a neutral effect (NE) or was found to be possibly detrimental (DE).

2.4. Data analysis and synthesis

We summarized and synthesized the information about various psychiatric and neurological disorders in several ways. A GOR for each psychiatric and neurological disorder is summarized based on the LOE for each study identified in Table 3. Since the GOR is based on the quality of the clinical study and not necessarily the outcome, we outline whether NAC should be recommended for the specific psychiatric and neurological disorder based on both the strength of the evidence and the outcome of the studies. A study was given 1 point for positive outcomes on all primary and secondary measures and 0 for negative outcomes on all measures. The studies were given 0.5 point if the study was positive for few but not all outcomes (either primary or secondary) or positive in subgroup analysis only. Based on points, the percentage positive of total studies was calculated. If the overall percentage was less that 50%, independent of the GOR, then the recommendation for treatment was 'NO' to use NAC for that specific disorder based on current research. If 100% of the studies were positive and GOR was either A or B, then the recommendation for treatment was 'YES' to use NAC for that specific disorder. For percentage positive between 50% and 100% or GOR was either C or D, then recommendation for treatment was 'MIXED'. If there was only one study on a disorder, the recommendation for clinical treatment was 'NONE' as it is not advisable to base treatment on one study. Number of studies was based on actual trial conducted and not number of articles to avoid duplication. For each psychiatric and neurological disorder, a table provides the details of each study along with the LOE grading and point based on outcomes. In addition, the text discusses the summary of all the studies for each disorder. Following the discussion of the potential effectiveness of NAC, a section discusses the reported adverse effects based on the reports from the controlled clinical trials. Finally the discussion synthesizes this information to summarize the potential clinical use of NAC in psychiatric and neurological disorders along with its mechanism of action.

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Table 1
Levels of evidence.

Level	Description
1a	SR or meta-analysis of RCTs with homogeneity or Cochrane review with favorable findings
1b	Prospective high-quality RCT (medium sized with *N* between 50 and 100 or large sized with *N* over 100 and/or higher validity trials based on adequate follow-up, intent to treat analysis, baseline similarity, equal treatment and dropout rates)
2a	SR of cohort (prospective, nonrandomized) studies with homogeneity
2b	Individual cohort (prospective, nonrandomized) study or low-quality RCT (small sized with *N* less than 50 and/or lower validity trials based on adequate follow-up, intent to treat analysis, baseline similarity, equal treatment and dropout rates)
3a	SR of case–control (retrospective) studies with homogeneity
3b	Individual case–control (retrospective) study
4	Open label trials, case series or reports
5	Expert opinion without critical appraisal or based on physiology or bench research

RCT, randomized controlled trial; SR, systematic review.

Table 2
Grade of recommendation.

Grade	Description
A	At least one level 1a study *or* two level 1b studies
B	At least one level 1b, 2a, or 3a study, *or* two level 2b or 3b studies
C	At least one level 2b or 3b study, *or* two level 4 studies
D	Level 5 evidence, *or* troublingly inconsistent or inconclusive studies of any level, *or* studies reporting no improvements
N	No studies identified

3. Results

3.1. Evidence of effectiveness of NAC in the treatment of psychiatric and neurological disorders

A total of 65 publications met inclusion and exclusion criteria. These studies included several psychiatric and neurological disorders, including addiction to cocaine, nicotine, methamphetamine, cannabis and gambling, Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis (ALS), anxiety disorder, attention deficit hyperactivity disorder (ADHD), autism, bipolar disorder (BPAD), depressive disorder, epilepsy, impulse control disorder including trichotillomania, skin picking and nail biting, neuropathy, obsessive compulsive disorder (OCD), schizophrenia, and traumatic brain injury (TBI). Each of these disorders is reviewed in a separate section below. Fig. 1A–M outlines the flow diagrams of article screening and selection for each disorder (see Appendix 1).

There were four sets of publications (a total of 13 published studies) that examined the same population but with different outcome measures. One set in schizophrenia with two publications (Berk et al., 2008a, 2011a, 2011b); one set in BPAD with six publications (Berk et al., 2008b; Dean et al., 2012; Magalhaes et al., 2011a, 2011b, 2012, 2013); one set in cocaine addiction with two publications (LaRowe et al., 2006, 2007); and one set in cannabis addiction with three publications (Gray et al., 2012; McClure et al., 2014; Roten et al., 2013;). There was one publication that reported outcomes related to two different disorders – nicotine and pathological gambling addiction and hence this publication is discussed in both the sections (Grant et al., 2014).

3.1.1. Addiction

NAC has been used in several clinical trials examining various addictions, including cannabis, cocaine, methamphetamine, nicotine, and pathological gambling (Table 4).

Table 3
Overall ratings of NAC based on clinical studies presented by condition.

Psychiatric and neurological condition	Uncontrolled studies Positive% (positive/total)	Controlled studies Positive% (positive/total)	Grade of recommendation	Recommendation for treatment
Addiction – cannabis	50% (0.5/1)	50% (0.5/1)	B	Mixed
Addiction – cocaine	100% (1/1)	50% (1.5/3)	B	Mixed
Addiction – methamphetamine		25% (0.5/2)	B	No
Addiction – nicotine		33% (2/6)	B	No
Addiction – pathological gambling	100% (1/1)	25% (0.5/2)	B	No
Alzheimer's disease	100% (2/2)	50% (0.5/1)	C	Mixed
Amyotrophic lateral sclerosis	50% (1/2)	0% (0/2)	B	No
Anxiety	100% (1/1)		D – SC	None
Attention-deficit hyperactivity disorder		100% (1/1)	C	None
Autism	100% (2/2)	50% (1.5/3)	B	Mixed
Bipolar disorder	100% (1/1)	50% (1/2)	A	Mixed
Depressive disorder	100% (1/1)	50% (0.5/1)	B	Mixed
Epilepsy	75% (3/4)		C	Mixed
Impulse control-nail biting	100% (2/2)	50% (0.5/1)	C	Mixed
Impulse control-skin picking	100% (4/4)		C	Mixed
Impulse control-trichotillomania	100% (4/4)	50% (1/2)	B	Mixed
Neuropathy	100% (1/1)	100% (1/1)	C	Mixed
Obsessive compulsive disorder	100% (1/1)	50% (0.5/1)	C	Mixed
Schizophrenia	100% (1/1)	75% (1.5/2)	B	Mixed
Traumatic brain injury		100% (1/1)	B	None

SC, Single Case Report.

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Table 4
Addiction.

Study	Participants # Group (M, F); age (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Controlled studies							
Cannabis							
Gray et al. (2012)	NAC: 58 (39M, 19F); 18.9 (1.5) PB: 58 (45M, 13F); 18.8 (1.5)	2.4 g/d NAC or PB for 8 wk	DBPC parallel	Urine cannabinoid testing	OR in favor of NAC	Vivid dreams, irritability, severe heartburn	1b/0.5
Roten et al. (2013)	NAC: 45 (gender NR); 15–21 PB: 44 (gender NR); 15–21			MCQ	No significant differences		
Cocaine							
LaRowe et al. (2006)	13 (6M, 7F); 37.1 (7.6)	1.2 g/d NAC or PB, every 12 h dosing for 4 doses	DBPC crossover	CSSA, craving, self-reported use	Reduced CSSA, craving and self-reported use	Pruritus, headache, flatu-lence/diarrhea, abdominal cramps, local rash, fatigue, elevated BP, sweating, chest pain, dizziness	2b/0.5
LaRowe et al. (2007)	15 (7M, 8F); 37.4 (7.1)			Physiologic response to cue, motivational measures	Reduced viewing time, desire and interest. No change in physiologic response and craving		
Amen et al. (2011)	6 (4M, 2F); 41.8 (7.4)	2.4 g/d NAC or Baclofen for 16 days	Single blind cross over	VAS ratings of rush, high, craving	NAC reduced cravings. No effect on rush, high	NR	2b/0.5
LaRowe et al. (2013)	2.4 g NAC: 33 (25M, 8F); 43 (9) 1.2 g NAC: 40 (30M, 10F); 44 (10) PB: 38 (28M, 10F); 43 (9)	2.4 g/d or 1.2 g/d NAC or PB for 8 wk	DBPC parallel	Quantitative levels of BE, BSCS, CSSA, days to relapse	No significant effect; improved BSCS, CSSA, days to relapse only in initially abstinent individuals	Gastrointestinal AE, headaches, dizziness, insomnia	1b/0.5
Methamphetamine							
Grant et al. (2010)	NAC: 14 (8M, 6F); 37.2 (8.2) PB: 17 (14M, 3F); 36.1 (6.6)	Up to 2.4 g/d NAC + 200 mg Naltrexone or PB for 8 wk	DBPC parallel	Penn Craving Scale, CGI, UDS, frequency of use	No significant differences	None	2b/0
Mousavi et al. (2015)	32 (26M, 6F); 29.2 (4.9)	1.2 g/d NAC or placebo for 4 wk	DBPC crossover	CCQ-Brief, daily use, UDS, side effects	Significant improvement on NAC during treatment but no carryover effects	Not significant	2b/0.5
Nicotine							
Bernardo et al. (2009)	Nicotine, alcohol and caffeine in BPAD NAC: 38 (15M, 23F); 44.6 (11.2) PB: 37 (15M, 22F); 46.6 (13.8)	1–2 g NAC or PB for 24 wk	DBPC parallel	CGI-SU (alcohol, tobacco, caffeine)	No change in alcohol and tobacco use; significant decrease in caffeine use in NAC group at 2 wk	NR	1b/0.5
Knackstedt et al. (2009)	NAC: 14 (9M, 5F); 51.3 (10.1) PB: 15 (10M, 5F); 48.6 (10.5)	2.4 g/d NAC or PB for 4 wk	DBPC parallel	Daily use, CO levels, QSU-Brief (craving), MNWS (withdrawal)	No significant differences	NR	2b/0.5
Schmaal et al. (2011)	NAC: 10 (42% M); 21.4 (2.07) PB: 12 (40% M); 20.25 (1.14)	3.6 g/d NAC or PB for 3 days and 1.8 g the 4th day	DBPC parallel	QSU-Brief (craving), MNWS (withdrawal), VAS reward	Reduced MNWS, VAS reward; no effect on craving	Mild stomach problems	2b/0.5

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Table 4 (*Continued*)

Study	Participants # Group (M, F); age (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Grant et al. (2014)	28 (23M, 5F); 47.6 (10.9) NAC: 13 PB: 15	1.2–3.0 g/d NAC or PB for 12 wk	DBPC parallel	Fagerström test for nicotine dependence, HDRS, HARS at 6, 12 and 24 wk	Improvement at 6 wk but not at 12 and 24 wk	NR	2b/0.5
McClure et al. (2014)	Cigarette smokers from Gray et al. (2012); 32M, 36F; 18.8 (1.4) NAC: 34 PB: 34	2.4 g/d NAC or PB for 8 wk	DBPC parallel	Cigarettes/day; QSU-Brief; modified FTQ	No significant differences	NR	2b/0
Prado et al. (2015)	Treatment resistant tobacco use disorder NAC: 17 (7M, 10F); 51.9 (7.02) PB: 14 (2M, 12F); 50.8 (11.8)	3 g/d NAC or PB for 12 wk	DBPC parallel	Cigarettes/day, CO levels, quit rates, HDRS	Significant difference in all outcomes	Not significant	2b/1
Pathological gambling							
Grant et al. (2007)	NAC: 6; gender and age NR PB: 7; gender and age NR	1.8 g/d NAC or PB for 6 wk	DBPC parallel	PG-YBOCS	Reduced PG-YBOCS but not statistically significant	Mild flatulence	2b/0
Grant et al. (2014)	28 (23M, 5F); 47.6 (10.9) NAC: 13 PB: 15	1.2–3.0 g/d NAC or PB for 12 wk	DBPC parallel	PG-YBOCS, HDRS, HARS at 6, 12 and 24 wk	No effect at 6 and 12 wk but improved PG-YBOCS at 24 wk	NR	2b/0.5
Uncontrolled studies							
Cannabis							
Gray et al. (2010)	Cannabis dependent: 24 (18M, 6F); 19 (0.16)	2.4 g/d NAC for 4 wk	Open label	Daily marijuana use, MCQ, urine cannabinoid levels	Significant decrease over 4 weeks in use and cravings. No change in urine cannabinoid levels	Mild–moderate AE in 63% – abdominal discomfort, muscle aches, insomnia, headaches, runny nose, nausea, restlessness, dizziness	4/0.5
Cocaine							
Mardikian et al. (2007)	*N* = 23 (22M, 1F); 40 (1.4)	1.2–3.6 g/d NAC for 28 days	Open label	Cocaine use, side effect, CSSA	Reduced CSSA and cocaine use	Pruritus, headache, flatulence/diarrhea, abdominal cramps, local rash, fatigue, elevated BP, sweating, chest pain, dizziness	4/1
Pathological gambling							
Grant et al. (2007)	*N* = 27 (15M, 12F); 50.8 (12.1)	Up to 1.8 g/d NAC for 8 wk	Open label	PG-YBOCS, G-SAS, CGI, SDS	Reduced PG-YBOCS	Mild flatulence	4/1

AE, adverse effects; BE, benzoylecgonine; BP, blood pressure; BPAD, bipolar disorder; BSCS, Brief Substance Craving Scale; CCQ-Brief, Cocaine Craving Questionnaire-Brief; CSSA, Cocaine Selective Severity Assessment; CGI, Clinical Global Impression; CO, carbon monoxide; DBPC, Double Blind Placebo Control Trial; FTQ, Fagerström Tolerance Questionnaire; G-SAS, Gambling Symptom Assessment Scale; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; MCQ, Marijuana Craving Questionnaire; MNWS, Minnesota Nicotine Withdrawal Scale; NR, not reported; OR, odds ratio; PB, placebo; PG-YBOCS, Pathological Gambling-Yale-Brown Obsessive Compulsive Scale; QSU, Questionnaire of Smoking Urges; SDS, Sheehan Disability Scale; SU, substance use; UDS, Urine Drug Screen; VAS, Visual Analog Scale.

3.1.1.1. Cannabis. A large DBPC trial (*N* = 116; LOE 1b) which treated cannabis dependent adolescents and young adults with 2.4 g/day of NAC or placebo along with brief weekly cessation counseling and contingency management for 8 weeks demonstrated that significantly more NAC treated individuals demonstrated a negative urine cannabinoid tests (Gray et al., 2012). Secondary outcome measure of self-reported days of cannabis use favored NAC but was not statistically significant. Further analysis performed on a

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subset of the participants ($N = 89$) found a decrease in self-reported marijuana craving in both groups, but no statistically significant difference between groups (Roten et al., 2013). A small open-label uncontrolled study ($N = 24$; LOE 4) found significant improvements in number of days used and cravings, but no significant changes were seen in urine cannabinoid levels (Gray et al., 2010).

Thus, there is one level 1b study that suggests partial improvement in clinical measures of cannabis use. This provides a GOR of B, but this must be considered carefully as it is not clear how NAC affects cannabinoid metabolism. If NAC hastens the elimination of cannabinoid then it might be more likely for an individual to have a negative urine test. In addition, concurrent use of psychotherapeutic intervention along with NAC treatment could have decreased the individual effect of NAC on cannabis use. Further studies will be needed to investigate these possibilities.

3.1.1.2. Cocaine. A three-arm DBPC ($N = 111$; LOE 1b) treated treatment-seeking cocaine dependent adults with NAC 2.4 g/day, NAC 1.2 g/day or placebo for 8 weeks (LaRowe et al., 2013). No significant effects were found in any of the outcome measures – quantitative levels of benzoylecgonine in urine, a cocaine metabolite, Brief Substance Craving Scale (BSCS) and Cocaine Selective Severity Assessment (CSSA). A positive effect of NAC on the BSCS, CSSA and days to relapse was found in a very small subgroup of individuals who were abstinent at the beginning of the trial. Additionally, riboflavin, the compound added to both the NAC and the placebo to measure compliance, is a co-factor for the enzyme glutathione peroxidase – an enzyme that is essential in glutathione antioxidant metabolism and one of the metabolic targets of NAC. Thus, it is possible the addition of riboflavin to the treatment capsules in both groups could have reduced any effect of NAC. The results were mixed for two other small controlled trials ($N = 15, 6$; LOE 2b) (LaRowe et al., 2007; Amen et al., 2011). A small 4 week open-label uncontrolled safety study ($N = 23$; LOE 4) found that NAC significantly reduced self-reported craving and abstinence scores on the CSSA, the number of use days and total dollar amount spent on use (Mardikian et al., 2007).

Thus, with at least one LOE 1b study a GOR of B is assigned to NAC for treatment for cocaine addiction symptoms. However, the largest study to date was overall negative and other controlled studies were rather small. This limits the confidence to which these results can be generalized. Thus, it is clear that other larger well-designed controlled clinical studies are needed to follow-up on these initial studies.

3.1.1.3. Methamphetamine. One small sized DBPC trials ($N = 31$; LOE 2b) compared progressive increasing doses of NAC (up to 2.4 g/day) along with Naltrexone (up to 200 mg/day) vs. placebo for 8 weeks in non-treatment-seeking subjects with methamphetamine dependence (Grant et al., 2010). The study found no statistical difference in the Penn rating scale for craving, frequency of use, urine toxicology results or Clinical Global Impression – Severity (CGI-S). This study was limited by a high dropout rate. Another recent small DBPC cross over trial ($N = 32$; LOE 2b) found significant decrease in Cocaine Craving Questionnaire-Brief (CCQ-Brief) scores in the NAC (1.2 g/day) group when compared to placebo among the 23 treatment seeking completers. The effect was no longer significant when cross treatment was done with placebo indicating NAC's limited effect on relapse prevention (Mousavi et al., 2015).

Thus, there are two LOE 2b trials studying the effect of NAC on methamphetamine dependence resulting in a GOR of B, but these studies were inconsistent, so an unequivocal recommendation for the use of NAC treatment for methamphetamine dependence cannot be made at this point and further larger controlled trials are needed.

3.1.1.4. Nicotine. A medium sized DBPC trial ($N = 75$; LOE 1b) treated individuals with BPAD I and II with 1–2 g/day NAC or placebo for 24 weeks and measured change in tobacco, alcohol and caffeine use. There was a significant decrease in caffeine use in the NAC group at 2 weeks, but not at any other visit. The biggest limitation of this study was that the clinical cohort was individuals with BPAD and the overall rates of substance use disorder in this cohort were low. This affected the power of this study specific to substance use disorder and might have affected the overall results (Bernardo et al., 2009). An analysis of the cigarette smokers in a DBPC study ($N = 68$; LOE 2b) on cannabis cessation (Gray et al., 2012) demonstrated no effect of 2.4 g/day of NAC on the number of cigarettes smoked per day on Smoking Urges-Brief or Modified Fagerström Tolerance Questionnaire scores (McClure et al., 2014). Three small sized trials ($N = 29, 22, 28$; level 2b) reported either negative or mixed results on use of NAC in nicotine use disorder (Grant et al., 2014; Knackstedt et al., 2009; Schmaal et al., 2011). In a recent pilot study ($N = 34$; LOE 2b), there was a significant reduction in both the number of cigarettes used and exhaled carbon monoxide, which was complimented by higher cessation rates in the NAC (47.1%) than the placebo (21.4%) group (Prado et al., 2015). Overall there is one LOE 1b and at least two LOE 2b studies resulting in a GOR of B but there is little evidence of effectiveness of the NAC for nicotine addiction. The studies which demonstrated some differences showed inconsistent effects. Thus, a recommendation for the use of NAC for nicotine cannot be made at this time.

3.1.1.5. Pathological gambling. A small 8 week open-label uncontrolled trial ($N = 27$; LOE 4) treated individuals with pathological gambling with 1.8 g/day of NAC for 8 weeks and found improvement in the Pathological Gambling-Yale-Brown Obsessive Compulsive Scale (PG-YBOCS), Gambling Symptom Assessment Scale (G-SAS), CGI and Sheehan Disability Scale (SDS) (Grant et al., 2007). A few responders from this open-label trial completed a 6 week DBPC withdrawal trial ($N = 13$; LOE 2b) but results were not statistically significant. The selection of responders and the withdrawal study design may have reduced the effect that could have been detected from the controlled study. For example, by selecting responders, the study may have selected a higher number of individuals with a placebo response. Another small DBPC trial ($N = 28$; LOE 2b) did not find improvement in any outcome measures during 12 weeks of treatment phase of the study but showed improvement at 24 week follow-up (Grant et al., 2014). However, only 11 individuals completed the follow-up visits, suggesting a significant bias due to high dropouts. Thus, with two LOE 2b studies, the GOR is B but there is only limited evidence for the effectiveness of NAC for gambling addiction.

3.1.1.6. Addiction overall. Overall, the evidence for NAC as a treatment for addiction is rather limited. Although several controlled studies were positive for cocaine, the largest and most meticulously performed study was only positive for a small subset of participants that were abstinent at the beginning of the trial. There is some evidence for cannabis but this is limited due to inconsistent findings. Other addictions have limited evidence that NAC is a useful treatment. However, many of the studies conducted were rather preliminary in nature and hence making recommendations for or against the use of NAC in addiction is somewhat preliminary.

3.1.2. Alzheimer's disease

In the largest DBPC trial to date ($N = 43$; LOE 2b), patients with probable AD who were treated with either 50 mg/kg/day of NAC or placebo for 24 weeks showed improvement in some, but not all cognitive testing (Adair et al., 2001). An attempt was made to do a small DBPC using 0.6 g NAC with 400 μg folic acid, 6 mg

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vitamin B12, 30 IU α-tocopherol, 400 mg S-adenosyl methionine and 500 mg acetyl-L-carnitine daily vs. placebo for 9 months in 12 institutionalized patients with moderate to late-stage probable AD (Remington et al., 2009). Unfortunately everyone in the placebo group dropped-out by 6 months, making the study a small uncontrolled case-series ($N = 6$; LOE 4). This treatment delayed the decline in the Dementia Rating Scale-2 (DRS-2) and Clock Drawing Test (CLOX-1) tests and resulted in improvements in the Neuropsychiatric Inventory and AD Cooperative Study – Activities of Daily Living. Another case report ($N = 1$; LOE 4) described a man with probable AD and hyperhomocysteinemia who demonstrated impressive clinical improvements when NAC was added to hydroxocobalamin and 5 mg folinic acid (McCaddon and Davies, 2005).

Since there is only one LOE 2b trial, the GOR is C for AD. The results of studies are mixed and high-quality controlled studies would be very helpful in documenting a potential therapeutic effect of NAC in AD (Table 5).

3.1.3. Amyotrophic lateral sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disorder, caused by degeneration of central and peripheral motor neurons (Williams and Windebank, 1991). The largest DBPC ($N = 110$; LOE 1b) failed to show any benefit of subcutaneous 50 mg/kg/day of NAC in survival and/or disease progression when compared to placebo in individuals with ALS (Louwerse et al., 1995). Similarly another small sized case control study ($N = 36$; LOE 3b) concluded no benefit in survival with NAC along with other antioxidants (Vyth et al., 1996). There are two uncontrolled open label studies with mixed results ($N = 51, 11$; LOE 4) (De Jong et al., 1987; Küther and Struppler, 1987). With one level 1b study the GOR for ALS is B but since 100% of the controlled studies and 75% of overall studies were negative, NAC does not seem to be a recommended treatment option for increasing survival in ALS at this time (Table 6).

3.1.4. Anxiety

One case study ($N = 1$; LOE 4) reported significant improvement as evident by drop in CGI-S from 5 to 2 after 8 week treatment with NAC in a 17 yo male with generalized anxiety disorder and social phobia who previously failed both multiple selective serotonin reuptake inhibitors and cognitive behavioral therapy (Strawn and Saldana, 2012). As there is only one case report, a GOR D is assigned and hence it is difficult to make any recommendations for NAC treatment for anxiety at this point (Table 7).

3.1.5. ADHD

A small sized DBPC study ($N = 24$; LOE 2b) examined the effect of NAC (2.4 g/day or 4.8 g/day), compared to placebo on ADHD within a systemic lupus erythematosus (SLE) population (Garcia et al., 2013). NAC reduced ADHD symptoms as measured by the ADHD Self-Report Scale Symptom Checklist (ASRS). With one LOE2b study, a GOR of C is assigned but this evidence must be tempered with the fact that the study population suffered from SLE and thus cannot be generalized as a treatment for typical ADHD (Table 8).

3.1.6. Autism

In a small sized DBPC study ($N = 29$; Level 2b), Aberrant Behavior Checklist Irritability Subscale (ABC-I) scores significantly decreased over the study period in the NAC group as compared to the placebo group (Hardan et al., 2012). Although other secondary outcomes improved, no significant improvement was found in the CGI-improvement (CGI-I) or CGI-S. In another small sized DBPC study ($N = 40$; Level 2b), the NAC add-on to risperidone group showed a decrease in ABC-I as compared to the placebo group but did not affect any of the core autism symptoms. It should be noted that the treatment group started out with a significantly higher ABC-I at the beginning of the trial (Ghanizadeh and Moghimi-Sarani, 2013). Similar findings were seen in a recent 10 week small sized DBPC trial ($N = 40$; Level 2b) on NAC treatment adjunctive to risperidone on irritability and hyperactivity subscales (Nikoo et al., 2015).

Two case studies (LOE 4) reported improvements in core and associated ASD behaviors with NAC treatment. (Ghanizadeh and Derakhshan, 2012; Marler et al., 2014). Given that there are three LOE 2b studies of autism, a GOR of B is given to NAC for the treatment in children with autism. Clearly NAC is a promising treatment for irritability in children with autism. Larger clinical trials are needed to confirm these findings and potentially investigate whether other core or associated autism symptoms may respond to NAC treatment (Table 9).

3.1.7. Bipolar disorder

Several controlled and uncontrolled studies have investigated NAC in treating and preventing symptoms during the maintenance phase of BPAD (Table 10). In the first multicenter DBPC trial ($N = 75$; LOE 1b), when compared to placebo, the NAC group demonstrated a significant improvement on the Montgomery–Asberg Depression Scale (MADRS), Bipolar Depression Rating Scale (BDRS) and nine out of 12 secondary outcome measures in individuals in the maintenance phase of BPAD (Berk et al., 2008a, 2008b). However, the study failed to show any significant differences between the two groups in the frequency of or latency to new episodes of either depression or mania (Berk et al., 2008a, 2008b).

Several subgroup analyses of the abovementioned study have been done to examine other outcome measures. No intergroup differences were found on cognitive outcomes examined in one subgroup analysis ($N = 46$) using digit span, word learning, trail making and verbal fluency (Dean et al., 2012). The interaction between symptoms, functioning level and medical comorbidities using a self-reported checklist was examined in another subgroup analysis ($N = 74$) and showed advantage of NAC treatment in functioning over the placebo treatment in individuals with medical comorbidities as compared to individuals without medical comorbidities (Magalhaes et al., 2012).

A small subgroup analysis ($N = 17$) of individuals who had a major depressive episode at baseline, showed that NAC treatment significantly improved measures of symptom severity, functioning, quality of life and response rate at the end of 24 weeks (Magalhaes et al., 2011b). In another subgroup analysis ($N = 14$) of individuals who had BPAD II, changes were more pronounced for every outcome including Young Mania Rating Scale (YMRS) in the NAC treatment group, as compared to the placebo group (Magalhaes et al., 2011a). Another small subgroup analysis examined individuals ($N = 15$) with a manic or hypomanic episode at baseline and reported improvement in YMRS in the NAC group and a worsening of BDRS in the placebo group. More participants in NAC group had complete symptom remission although it was not statistically significant (Magalhaes et al., 2013).

Subsequent studies focused specifically on depressive symptoms of BPAD. A large 8 week open-label run-in ($N = 149$; LOE 4) to a DBPC trial included individuals with BPAD and a recent episode of moderate depression. The study showed robust improvement in BDRS, functioning and quality of life on NAC add-on to usual treatment (Berk et al., 2011a, 2011b). Participants in the above study with a MADRS ≥ 12 at baseline were randomized ($N = 149$; LOE 1b) to NAC or placebo add-on treatment for 24 weeks. The primary outcome measure, latency to a mood episode, was not significantly different between the treatment and placebo groups (Berk et al., 2012).

Thus, there are two LOE 1b studies in BPAD with one of the two positive for NAC as an effective treatment for BPAD symptoms, resulting in a GOR of A. The negative study was a withdrawal study

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Table 5
Alzheimer's disease (AD).

Study	Participants # Group (M, F); age in year (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Controlled studies							
Adair et al. (2001)	NAC: 23 PB: 20 Age and gender NR	50 mg/kg/d NAC in 3 divided doses for 24 wk or PB	DBPC parallel	MMSE, ADL, cognitive battery	Improvement in some cognitive tests	Transient headache	2b/0.5
Uncontrolled studies							
McCaddon and Davies (2005)	65 yo M with probable AD and hyperhomocysteinemia	0.6 g/d NAC + hydroxocobalamin and 5 mg folinic acid	Case report	Symptoms	Less agitated; improved recognition, compliance, memory and communication	NR	4/1
Remington et al. (2009)	Institutionalized moderate-to-late stage AD NAC: 6 PB: 6, all dropped out by 6 months	0.6 g NAC + other vitamins for 9 mo or PB for 6 mo	Case series	DRS-2, CLOX-1, NPI, ADCS-ADL	Improved NPI and ADL. Slower CLOX-1 and DRS-2 decline	NR	4/1

ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; ADL, Activities of Daily Living; AE, adverse effects; DBPC, Double Blind Placebo Controlled; DRS-2, Dementia Rating Scale-2; CLOX-1, Clock Drawing Executive Test; GI, gastrointestinal; MMSE, Mini-Mental Status Examination; NPI, Neuropsychiatric Inventory; NR, not reported; PB, placebo.

which measured time to new mood episode. This could suggest that the initial 8-week open-label treatment was enough time to optimally reverse physiological processes and that further prolonged treatment was not necessary to provide an advantage of the NAC treatment. However, the primary outcome measure in the withdrawal study was not significant in the other large DPBC study, suggesting that time to new mood episode is not a clinical characteristic of BPAD that is effectively treated by NAC. This may indicate that NAC may lessen symptoms of BPAD but may not affect the frequency of cycling between mood states. Clearly NAC treatment for BPAD seems promising and deserves further investigation.

Table 6
Amyotrophic lateral sclerosis (ALS).

Study	Participants # Group (M, F); age (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Controlled studies							
Louwerse et al. (1995)	Acetylcysteine: 54 (29M, 25F); 58 (11) PB: 56 (32M, 24F); 57 (9.6)	50 mg/kg/d SQ acetylcysteine or PB for 12 mo	DBPC Parallel	Survival	No significant difference in survival or reduction in disease progression	NR	1b/0
Vyth et al. (1996)	ALS: 36 Controls: 107 Age and gender NR	SQ NAC ± Vit C and E, NAM, DTT, DTE for 3–4.2 yr	Case control	Survival	No effect on survival	Gastric pain, nausea, abdominal discomfort	3b/0
Uncontrolled studies							
De Jong et al. (1987)	ALS: 40 Spinal muscular dystrophy: 11 Age and gender NR	Everyone: 100 ml of 5% NAC, SQ/d for 6–24 mo 26 (not stable on NAC alone): DTT 10 (hypersensitivity to NAC): prednisone	Open label	Increased, equal or drop less than 10% in Norris score, vital chest capacities	62% were stable at 6 mo and 52% at 24 mo	Hypersensitivity	4/1
Küther and Struppler (1987)	*N* = 11 (6M, 5F); 35–68 yo	50 ml of 5% NAC, SQ/d and Vit C for 1–12 mo	Open label	Contracture, muscle strength, Norris score, vital capacity	No significant difference	Pain, swelling, SC granuloma, and abscess at the injection site, rhinorrhea, leg edema, allergic reaction	4/0

AE, adverse effects; DBPC, Double Blind Placebo Controlled; DTE, dithioerythritol; DTT, dithiothreitol; NAM, N-acetylmethionine; NR, not reported; PB, placebo; SQ, subcutaneous; Vit, vitamin.

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Table 7
Anxiety.

Study	Participants # Group (M, F); age (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Uncontrolled Studies							
Strawn and Saldana (2012)	17 yo M with generalized anxiety and social phobia	1.2 g/d NAC for 4 wk then 2.4 g/d for 4 wk	Case report	CGI; subjective anxiety levels	Improved CGI; decreased subjective anxiety	None	4/1

AE, adverse effects; CGI, Clinical Global Impression.

3.1.8. Depressive disorder

A large randomized controlled trial ($N = 252$; LOE 1b) in individuals with major depressive disorder (MDD) and MADRS score ≥ 18 showed improvement in multiple outcome measures – in the NAC group when compared to placebo add on treatment to usual treatment for 12 weeks (Berk et al., 2014). There is also a case series ($N = 2$; LOE 4) that showed successful and sustained improvement of depressive symptoms on NAC augmentation in two patients with MDD who had responded only partially to a trial of monoamine oxidase inhibitors (MAOI) tranylcypromine (Carvalho et al., 2013) (Table 11).

With one level 1b study, the GOR is B. Since the randomized controlled trial was not positive for all the outcome measures, the recommendations for NAC treatment for MDD is still mixed and further controlled studies and longer follow-up for assessing consistent improvement are needed. Overall NAC seems to be a promising treatment option for mood disorders. It has shown to have positive effect on mood in an unrelated RCT that studied NAC for idiopathic pulmonary fibrosis, and found no benefit for that indication. However, on a measure of well-being, the SF 36, there were significant between group differences favoring the NAC group (Martinez et al., 2014). The SF 36 has shown a tight correlation with more traditional mood scales (Elliott et al., 2003).

3.1.9. Epilepsy

All the studies have been in progressive myoclonus epilepsy, Unverricht–Lundborg Disease (ULD) (Table 12). ULD is an autosomal recessive neurodegenerative disorder (21q22.3) that typically begins between 6 and 15 years of age characterized by myoclonus and tonic–clonic seizures, followed by the development of dysarthria, cognitive dysfunction and ataxia. Most patients have marked impairment in daily life functioning and marked disability (Lehesjoki and Koskiniemi, 1998). In first case series ($N = 4$; LOE-4) of use of adjunctive treatment with NAC in ULD, four siblings were treated with 4–6 g/day of NAC over 26–30 months for ULD and showed remarkable improvement in symptoms and basic daily functioning (Hurd et al., 1996). Similar responses to 6 g/day NAC were seen in a 40-year-old male with ULD with marked improvement in walking, myoclonus, generalized seizures, talking and daily living skills ($N = 1$; LOE-4). Symptoms clearly worsened when he refused his medications for 1 week when parents were on vacation. Improvement was seen back within 2 days as soon as he restarted his medicines and was sustained for 10 month of follow-up (Selwa, 1999). Another case series (LOE-4) also showed positive response to 4–6 g/day NAC in the majority of the five cases of progressive myoclonic epilepsies (four with ULD and one with Lafora Body disease) (Ben-Menachem et al., 2000). Mixed response ranging from dramatic improvement in some individuals, partial or failed improvement in some and significant side effects including possible neutropenia and sensorineural hearing loss in some were reported in a subsequent case series ($N = 4$; LOE-4) (Edwards et al., 2002). With four case studies/series (LOE-4), the GOR is C. The results of the case series are mixed and some serious adverse events are mentioned in these studies therefore the recommendation for use of NAC in progressive myoclonus epilepsy is mixed and further controlled studies are needed.

3.1.10. Impulse control disorder

Several controlled and uncontrolled trials were conducted on various impulse control disorders including trichotillomania, skin picking disorder and nail biting disorder (Table 13).

3.1.10.1. Nail biting. A DBPC study ($N = 42$; LOE 2b) on nail-biting in children showed greater increase in nail length after 1 month of treatment with NAC compared to placebo but this difference was not significant at the end of second month (Ghanizadeh et al., 2013). Two case series ($N = 4$; LOE 4) reported improvement in nail biting frequency with NAC (Berk et al., 2009; Odlaug and Grant, 2007). Thus with one level 2b and two level 4 studies, the GOR is C but considering the results of controlled trial was not consistently positive over time, there is only limited evidence on effectiveness of NAC on nail biting disorder and further controlled studies are required.

3.1.10.2. Skin picking. An interesting open-label prospective case-series ($N = 35$; LOE 4) of individuals with Prader–Willi syndrome demonstrated a significant improvement in skin-picking symptoms and skin lesions in the majority of individuals with 12 week NAC treatment (Miller and Angulo, 2014). Several adult case series ($N = 5$; LOE 4) have reported decrease in the frequency of skin picking behavior with NAC treatment (Grant et al., 2012; Odlaug and

Table 8
Attention-deficit hyperactivity disorder (ADHD).

Study	Participants # Group (M, F); age (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Controlled studies							
Garcia et al. (2013)	Participants with ADHD and SLE; 45.9 (1.8) NAC, 2.4 g/d: 9 NAC, 4.8 g/d: 9 PB: 6 Controls: 22; 48.0 (1.5)	2.4 g/d or 4.8 g/d or PB for 3 mo	DBPC – three arms	ASRS	Improved ASRS Scores	None	2b/1

ASRS, ADHD Self Report Scale; AE, adverse effects; DBPC, Double Blind Placebo Controlled.

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Table 9
Autism.

Study	Participants # Group (M, F); age in year (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Controlled studies							
Hardan et al. (2012)	NAC: 14 (12M, 2F); 7 (2.1) PB: 15 (15M, 0F); 7.2 (2.2)	0.9 g NAC: 1×/d × 4 wk then 2×/d × 4 wk then 3×/d × 4 wk or PB	DBPC parallel	Primary: ABC Irritability Secondary: ABC-Stereotype, SRS, RBS-R, CGI	Improved ABC Irritability, SRS cognition, autism mannerisms and RBS-R stereotypies but no effect on other SRS subscales or CGI	Gastrointestinal AE	2b/0.5
Ghanizadeh and Moghimi-Sarani (2013)	NAC: 20 (13M, 7F); 8.8 (3.1) PB: 20 (12M, 8F); 7.9 (2.4)	Risperidone with add-on 1.2 g NAC/d or PB for 8 wk	DBPC parallel	ABC-Irritability, lethargy, social withdrawal, stereotype behavior, hyperactivity, noncompliance and inappropriate speech subscale	Significant improvement in irritability only and no change in other secondary outcome measures	Not significant	2b/0.5
Nikoo et al. (2015)	NAC: 20 (16M, 4F); 7.5 (2.6) PB: 20 (17M, 3F); 7.6 (2.6)	Risperidone with add-on 0.6–0.9 g/d NAC or PB for 10 wk	DBPC parallel	ABC-Irritability, lethargy, social withdrawal, stereotype behavior, hyperactivity, noncompliance and inappropriate speech subscale at 5 and 10 wk	Significant improvement in irritability and hyperactivity subscale but no change in other secondary outcome measures	Not significant	2b/0.5
Uncontrolled studies							
Ghanizadeh and Derakhshan (2014)	8 yo M with autism, nail-biting, hyperactivity and inattentiveness	0.8 g NAC/d for 30 days	Case report	VAS for social interactions, communication, verbal skills and aggression	Improvement on all VAS measures, improved nail-biting, hyperactivity and inattentiveness	Mild abdomen pain	4/1
Marler et al. (2014)	4 yo M with severe self-injurious behavior	0.45 g/d titrating to 1.8 g/day over 3 wk	Case report	Frequency and severity of self-injurious behavior	Improvement in self-injurious behavior	None	4/1

ABC, Aberrant Behavior Checklist; AE, adverse effects; CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity; DBPC, Double Blind Placebo Controlled; NAC, N-acetylcysteine; NR, not reported; PB, placebo; RBS-R, Repetitive Behavior Scale-Revised; SRS, Social Responsiveness Scale; VAS, Visual Analog Scale.

Grant, 2007; Silva-Netto et al., 2014). With four level 4 studies, the GOR is C. All the studies showed positive effect so NAC seems like a promising treatment option for skin picking but further controlled studies are needed.

3.1.10.3. Trichotillomania. In a medium sized DBPC trial ($N = 50$; LOE 1b), significant improvements were found on the Massachusetts General Hospital Hair Pulling Scale, the Psychiatric Institute Trichotillomania Scale and the CGI in participants who received NAC as compared to the placebo group (Grant et al., 2009). In another DBPC trial ($N = 39$; LOE 2b), no significant differences in improvement between NAC and placebo groups were found in children and adolescents with trichotillomania (Bloch et al., 2013). The authors suggest that their study findings may differ from previous studies due to a younger aged sample or more severe trichotillomania symptoms among the placebo group in their study. Four case series ($N = 6$; LOE 4) in adults reported improved hair growth with NAC (Odlaug and Grant, 2007; Rodrigues-Barata et al., 2012; Silva-Netto et al., 2014; Taylor and Bhagwandas, 2014). Thus, with one level 1b, one level 2b and four level 4 studies, the GOR is B. The results however are mixed as only one out of two controlled trials was positive for improvement. Larger clinical trials are needed to confirm the effectiveness of NAC in trichotillomania.

3.1.10.4. Impulse control disorder overall. The GOR is B given the one level 1b study but this must be tempered with the fact that one other DBPC study did not find positive results and another DBPC was positive only at one time point. However, there were some limitations to the negative DBPC studies, and seven uncontrolled studies have documented positive results. Thus, further studies

Table 10
Bipolar disorder (BPAD).

Study	Participants # Group (M, F); age in year (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Controlled studies							
Berk et al. (2008b)	NAC: 38 (15M, 23F); 44.6 (11.2) PB: 37 (15M, 22F); 46.6 (13.8)	1 g NAC BID for 24 wk or PB	DBPC parallel	MADRS, BDRS, YMRS, CGI, GAF, SOFAS, SLICE-LIFE, LIFE-RIFT, Q-LES-Q	Moderate-to-large effect on MADRS and BDRS	Changed energy, headaches, increased joint pain, heartburn, 3 serious AE	1b/1
Magalhaes et al. (2011a)	BPAD II NAC: 7 (4M, 3F); 43 (29) PB: 7 (3M, 4F); 52 (54)				Significant improvement in the YMRS. More participants achieved remission in depression and mania symptoms	Mild HA in 1, sweating in 1, increased thirst in 1	
Magalhaes et al. (2011b)	BPAD with major depressive episode at baseline NAC: 10 (5M, 5F); 43 (15.39) PB: 7 (3M, 4F); 42.86 (15.39)				Significant improvement on MADRS, BDRS, GAF, RIFT and Q-LES-Q. Significantly more patients with treatment response	Mild HA in 3, diarrhea and abdominal pain in 2	
Magalhaes et al. (2013)	BPAD with manic or hypomanic episodes at baseline NAC: 8 (4M, 4F); 50 (20) PB: 7 (3M, 4F); 38 (36)				Significant improvement in YMRS within NAC group; more symptom remission	1 NAC patient withdrew due to AE	
Magalhaes et al. (2012)	BPAD with medical comorbidities NAC: 38 (15M, 23 F); 44.6 (11.2) PB: 36 (14M, 22F); 46.6 (13.8)			Self-reported medical comorbidities, MADRS, BDRS, YMRS, CGI, GAF, SOFAS, SLICE/LIFE, LIFERIFT, Q-LES-Q	Only all the functional outcomes were better with medical comorbidity	NR	
Dean et al. (2012)	NAC: 21 (8M, 13F); 44.6 (12.5) PB: 25 (10M, 15F); 46.4 (13.1)			Digit span, word learning, trail making, verbal fluency	No effect	NR	
Berk et al. (2012)	BPAD with depressive symptoms at baseline (MADRS $\geq$ 12) NAC: 76 (16M, 60F); 47.1 (10.9) PB: 73 (32M, 41F); 44.4 (11.8)	1 g NAC BID for 24 wk or PB	DBPC withdrawal	MADRS, BDRS, YMRS, CGI, GAF, SOFAS, SLICE/LIFE, LIFERIFT, Q-LES-Q	No effect	NR	1b/0
Uncontrolled studies							
Berk et al. (2011a, 2011b)	BPAD with depressive symptoms at baseline (MADRS $\geq$ 12) 149 (48M, 101F); 45.8 (11.4)	1 g NAC BID for 8 wk	Open label	BDRS, MADRS, YMRS, CGI, GAF, SOFAS, SLICE/LIFE, LIFERIFT,Q-LES-Q	Significant improvement in all outcome measures	NR	4/1

AE, adverse effects; BDRS, Bipolar Depression Rating Scale; CGI-S, Clinical Global Impression Severity Scale; DBPC, Double Blind Placebo Controlled; GAF, Global Assessment of Functioning; LIFE-RIFT, Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool; MADRS, Montgomery–Asberg Depression Scale; NR, not reported; PB, placebo; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; SLICE/LIFE, Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation; SOFAS, Social and Occupational Functioning Assessment Scale; YMRS, Young Mania Rating Scale.

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Table 11
Depressive disorder.

Study	Participants # Group (M, F); age in year (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Controlled studies							
Berk et al. (2014)	MDD (MADRS ≥ 18) NAC: 127 (43M, 84F); 49.9 (13.0) PB: 125 (50M, 75F); 50.5 (12.5)	1 g BID NAC for 12 wk or PB add on to usual treatment	DBPC parallel	MADRS, CGI-I, CGI-S, HARS, GAF, SOFAS, SLICE/LIFE, LIFERIFT, Q-LES-Q at 12 wk and 4 wk after treatment discontinuation (16 wk)	No significant effect on MADRS, response rate, remission rate at 12 wk but significant effect at 16 wk; LIFE-RIFT improved at 12 wk; no significant change in GAF and SOFAS	Gastrointestinal and musculoskeletal AE	1b/0.5
Uncontrolled studies							
Carvalho et al. (2013)	Severe treatment resistant MDD on tranylcypromine Case 1: 22 yoM Case 2: 43 yo F	2 g BID NAC for 8 wk	Case series	HDRS and CGI-I	Improvement in and CGI in both the cases	NR	4/1

AE, adverse effects; CGI-I, Clinical Global Impression Improvement Scale; CGI-S, Clinical Global Impression Severity Scale; DBPC, Double Blind Placebo Controlled; GAF, Global Assessment of Functioning; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; LIFE-RIFT, Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool; MADRS, Montgomery–Asberg Depression Scale; MDD, major depressive disorder; NR, not reported; PB, placebo; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; SLICE/LIFE, Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation; SOFAS, Social and Occupational Functioning Assessment Scale.

will be needed to help clarify the role of NAC in impulse control disorders as NAC may be a promising treatment.

3.1.11. Neuropathy

In a small sized DBPC ($N = 14$; LOE 2b) trial, 14 stage III colon cancer receiving adjunctive biweekly oxaliplatin along with fluorouracil/leucovorin chemotherapy were randomized to 1.2 g/day NAC ($N = 5$) or placebo ($N = 9$) to see the protective effect of NAC in the development of common serious adverse effect of oxaliplatin – grades 3–4 sensory neuropathy. After 12 cycles of chemotherapy, the study showed a significant benefit of NAC over placebo in preventing development of oxaliplatin induced serious sensory neuropathy (Lin et al., 2006). One other case report ($N = 1$; LOE 4) showed positive response on combination of neuro-protectants – NAC, Levocarnitine and Pyridoxine in a 46-day-old male with acute lymphoblastic leukemia (ALL) who developed severe vincristine-induced peripheral neuropathy (Baker and Lipson, 2010). With one LOE2b and one LOE 4 studies, the GOR is C but considering the small sample size of the controlled study and use of multiple antioxidants in the case study, the data is still limited to provide any recommendations for use of NAC in anticancer medicines induced neuropathy. Further large controlled studies are required (Table 14).

3.1.12. Obsessive compulsive disorder

A 12 week DBPC trial ($N = 48$; LOE 2b) treated individuals with OCD on a selective serotonin reuptake inhibitor with either placebo or NAC. Results showed significant improvement in the Yale Brown Obsessive Compulsive Scale (Y-BOCS) and CGI-S, but not the CGI-I, in the NAC group compared to the placebo group (Afshar et al., 2012). The study is limited due to high dropout rates. Significant decrease in Y-BOCS from 33 to 9 was seen with NAC add on treatment to Fluvoxamine in a case report ($N = 1$; LOE 4), with childhood onset OCD (Lafleur et al., 2006).

Since there is only one LOE 2b study, the GOR is C for OCD. Also in this study not all the outcome measures were positive. So the recommendations for use of NAC in OCD is limited at this time and further larger controlled studies are needed to see the effectiveness of NAC in treatment of OCD (Table 15).

3.1.13. Schizophrenia

A large DBPC study ($N = 140$; LOE 1b) reported significantly greater improvement in the NAC group in all qualitative and a few quantitative measures (Berk et al., 2008a, 2011a, 2011b) Another small sized DBPC study ($N = 42$; LOE 2b) examining the addition of NAC to risperidone in an 8 week trial found improvement in PANSS negative and total scales (Farokhnia et al., 2013). Additionally, a case report ($N = 1$; LOE 4) documented improvements in a 24-year-old women with treatment resistant schizophrenia after 7 days of 0.6 g/day of NAC as assessed by the PANSS and CGI-S (Bulut et al., 2009). With one LOE 1b study, the GOR for use of NAC in schizophrenia is B. Clearly NAC is a novel treatment for schizophrenia but further high-quality clinical trials are needed to confirm the findings (Table 16).

3.1.14. Traumatic brain injury (TBI)

One DBPC study ($N = 80$; LOE 1b) showed positive response to NAC on top of usual treatment in blast related mild TBI in active duty service members. Use of NAC was associated with a significant improvement in mild TBI symptoms, neuropsychological testing results, and complete symptom resolution when compared to placebo. Early treatment initiation within 24 h of the injury independently showed improvement in symptoms (Hoffer et al., 2013). Since there is one LOE 1b study, the GOR is B for NAC use in TBI. Even though the study is positive, it is hard to make recommendation based on just one positive study. Early treatment with NAC seems to be a promising treatment for mild TBI and further controlled trials showing consistent improvements on NAC are needed (Table 17). In a related traumatic neurodegenerative model, NAC has shown preliminary promise in a study of the prevention of noise induced hearing loss. While the study was negative on the primary outcome,

Table 12
Epilepsy.

Study	Participants # Group (M, F); age (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Uncontrolled studies							
Hurd et al. (1996)	Siblings with ULD Case 1: 33 yo M Case 2: 35 yo F Case 3: 38 yo M Case 4: 39yo M	4–6 g/d NAC for 1 and 2: 30 mo 3 and 4: 26 mo	Case series	Symptoms and functioning	1: Improved verbalization, conversation skills, basic daily functioning, understanding abilities 2: Improved basic living skills – eating, toileting, walking 3 and 4: Improved turning in bed, speaking few words	One case had diarrhea	4/1
Selwa (1999)	40 yo M with ULD	3 g BID NAC for 10 mo	Case report	Overall symptoms	Improved tremors, myoclonus, talking and walking	NR	4/1
Ben-Menachem et al. (2000)	Progressive myoclonic epilepsies Case 1: 22 yo F Case 2: 20 yo F Case 3: 24 yo M Case 4: 30 yo M Case 5: 21 yo F	NAC: 1 and 2: 4–6 g/d for 60 mo 3: 6 g/d for 3 mo 4: 4–6 g/d for 24 mo 5: 4 g/d for 6 mo	Case series	Overall symptoms	1: Improved ataxia, GTCS, myoclonus and functioning 2: Improved myoclonus, GTCS and functioning 3: Improved myoclonus and general cognition but patient died 3 mo later due to other medical complications 4: Improved walking, myoclonus, ataxia and self-care 5: Improved myoclonus, GTCS, absence seizures, ataxia and mental function for 3 mo then deterioration (NAC stopped at 6 mo)	None	4/0.5
Edwards et al. (2002)	ULD Case 1: 38 yo F Case 2: 30 yo F Case 3: 48 yo F Case 4: 35 yo M	NAC: 1: 3.6 g/d for 12 mo 2: 3.6 g/d for 24 mo 3: 3 g/d for 5 wk 4: 3 g/d for 3 mo	Case series	Seizures, ataxia and other symptoms	1: Improved GTCS but not myoclonus and ataxia 2: Dramatically improved myoclonus, ataxia, and alertness 3: Slightly improved myoclonus 4: Improved myoclonus only for initial 2 mo	1: Possible neutropenia 2: None 3: SN deafness (NAC stopped in 5 wk) 4: Nausea, epigastric pain	4/0.5

AE, adverse effects; GTCS, Generalized Tonic Clonic Seizures; NR, not reported; SN, sensorineural; ULD, Unverricht–Lundborg Disease.

the rate of threshold shifts, there was significance in a secondary outcome and post hoc analyses (Kopke et al., 2015).

3.2. Adverse effects reported in controlled clinical trials

It is important to consider the adverse effects profile of any new treatment. It is difficult to judge the significance of adverse effects (AEs) reported in uncontrolled trials and controlled trials provide a more objective indication of significant AEs. However, rather rare AEs may not be statistically significant in controlled clinical trials, thus it is important to consider all reported possible AEs. Here we consider both AEs from controlled clinical trials as well as those reported in uncontrolled trials.

For the most part, controlled trials did not report significant AEs in the NAC treated groups as compared to the placebo group. Adverse effects involved different systems including gastrointestinal, neurological, psychological/behavioral, musculoskeletal, dermatological, and other systems. Details of AE specific to a particular disorder are tabulated in Table 18. The largest rate of AEs were seen in an open-label study on cannabis in which 63% of the participants reported mild to moderate AEs, primarily consisting of abdominal discomfort, muscle pains, insomnia, headache, nasal congestion, runny nose, nausea, weight loss, restlessness, and dizziness (Gray et al., 2010). Very few studies reported severe AEs leading to discontinuation of NAC including full body rash in a TTM DBPC (Bloch et al., 2013); aggression in a child with nail biting (Ghanizadeh et al., 2013); and SN deafness in a case of ULD (Edwards et al., 2002). In studies of ALS where subcutaneous injections were used, swelling, granuloma, and an abscess at injection sites were reported along with hypersensitivity reactions (De Jong et al., 1987; Küther and Struppler, 1987). Serious AE of possible neutropenia was reported in a case series on ULD (Edwards et al., 2002). Interestingly, in a study on schizophrenia Extrapyramidal Symptoms Rating Scale (ESRS) were significantly lower for the NAC + risperidone group as compared to the placebo + risperidone

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Table 13
Impulse control disorder.

Study	Participants # Group (M, F); age (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Controlled studies							
Nail biting							
Ghanizadeh et al. (2013)	NAC: 21 (13M, 8F); 9.3 (2.8) PB: 21 (15M 6F); 10.8 (3.1)	0.8 g/d NAC or PB for 8 wk	DBPC parallel	Total length of all nails	Greater nail growth in 1st but not in 2nd month	Headache, agitation, isolation, aggression	2b/0.5
Trichotillomania							
Grant et al. (2009)	NAC: 25 (1M, 24F); 32.7 (10.5) PB: 25 (4M, 21F); 35.8 (13.6)	1.2 g/d NAC × 6 wk, then 2.4 g/d NAC for 6 wk or PB	DBPC parallel	MGH-HPS, PITS, CGI	Improved MGH-HPS, PITS and CGI	None	1b/1
Bloch et al. (2013)	NAC: 20 (3M, 17 F); 14.0 (2.4) PB: 19 (2M, 17 F); 13.1 (3.1)	2.4 g/d NAC or PB for 12 wk	DBPC parallel	MGH-HPS, TSC, NIMH-TSS, CGI	No significant difference between groups	Full body rash in 1	2b/0
Uncontrolled studies							
Grooming behaviors – nail biting, skin picking and trichotillomania							
Odlaug and Grant (2007)	Case 1: 28 yo M with nail-biting and trichotillomania Case 2: 40 yo F with trichotillomania Case 3: 52 yo F with skin picking	NAC: 1: 1.2 g/d for 2 wk 2: 2.4 g/d for 5 mo 3: 1.8 g/d for 4 mo	Case series	Frequency of engaging in grooming behaviors	Improvement in grooming behavior frequency	Mild flatulence in case 1	4/1
Nail biting							
Berk et al. (2009)	BPAD and nail biting Case 1: 46 yo F Case 2: 44 yo F Case 3: 46 yo M	NAC: 1: 1 g BID for 7 mo 2: 1 g BID for 2 mo 3: Dose NR for 28 wk	Case series	Nail biting frequency (self-report)	Improved nail biting frequency	None	4/1
Skin picking							
Grant et al. (2012)	24 yo F	Dose NR for 1 yr	Case report	Skin picking frequency (self-report)	Improved skin picking frequency	None	4/1
Miller and Angulo (2014)	Prader–Willi syndrome and skin-picking 35 (23F, 12M); 5–39 yo	0.450–1.2 g/d NAC for 12 wk	Open-label	Number of skin lesions	71% complete resolution of skin-picking and remainder had significant improvement in skin-picking	Abdominal cramping, diarrhea and flatulence	4/1
Silva-Netto et al. (2014)	Case 1: 45 yo F with skin picking and trichotillomania Case 2: 40 yo F with skin-picking Case 3: 31 yo F with skin-picking	NAC: 1: 1.2–1.8 g/d; duration NR 2: 1.2 g/d for 10 mo 3: 1.2 g/d; duration NR	Case series	Symptoms	1: Improved trichotillomania and skin-picking 2: Improved skin-picking 3: Improved skin-picking	NR	4/1
Trichotillomania							
Rodrigues-Barata et al. (2012)	Case 1: 23 yo F Case 2: 19 yo F	NAC: 1: 1.2 g/d for 6 mo 2: 1.2 g/d for 3 mo	Case series	Regrowth of hair	Complete regrowth achieved	None	4/1
Taylor and Bhagwandas (2014)	58 yo F	1.2 g/d NAC for 32 wk	Case report	Regrowth of hair	Improved hair growth	NR	4/1

AE, adverse effects; BPAD, bipolar disorder; CGI, Clinical Global Impression; DBPC, Double Blind Placebo Controlled; MGH-HPS, Massachusetts General Hospital Hair Pulling Scale; NIMH-TSS, National Institute of Mental Health Trichotillomania Severity Scale; NR, not reported; PITS, Psychiatric Institute Trichotillomania Scale; TSC, Trichotillomania Scale for Children.

group suggesting that it might be protective against adverse effects of other psychiatric medications when used as an adjunctive therapy (Farokhnia et al., 2013).

For the most part, NAC, especially oral formulation was found to be safe with a low incidence of AEs in most studies. The excellent safety profile of NAC and favorable treatment effects support it as an excellent novel treatment for psychiatric and neurological disorders especially in oral formulation.

4. Discussion

NAC has been investigated as a novel treatment for a wide range of psychiatric disorders and a few neurological disorders. Studies suggest that NAC is a favorable treatment for several disorders while the evidence of its effectiveness for other disorders is less clear. The exact reason of this differential response is not obvious. NAC works through several different metabolic pathways.

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Table 14
Neuropathy.

Study	Participants # Group (M, F); age (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Controlled studies							
Lin et al. (2006)	Participants with stage III colorectal cancer on postoperative oxaliplatin with a fluorouracil/leucovorin regimen NAC: 5 (4M, 1F); 58 (41–75) PB: 9 (5M, 4F); 65 (43–78)	1.2 g NAC or PB, 90 min before oxaliplatin administration for 18 mo	DBPC parallel	Development of neuropathy	Positive effect in preventing oxaliplatin induced neuropathy	NR	2b/1
Uncontrolled studies							
Baker and Lipson (2010)	46 yo M with ALL and vincristine induced peripheral neuropathy	50 mg BID NAC, 150 mg TID Levocarnitine and 35 mg/d Pyridoxine for 5 mo	Case report	Motor function	Motor function returned to near normal	NR	4/1

AE, adverse effects; DBPC, Double Blind Placebo Controlled; NR, not reported; PB, placebo.

Table 15
Q11 Obsessive compulsive disorder (OCD).

Study	Participants # Group (M, F); age (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Controlled studies							
Afshar et al. (2012)	Participants with OCD on SSRI NAC: 24 (6M, 18F); 30.62 (5.35) PB: 24 (6, 18); 31.25 (4.70)	0.6 g/d NAC titrated to 2.4 g/d depending on CGI or PB for 12 wk	DBPC parallel	Y-BOCS CGI-S CGI-I	Significant improvement in Y-BOCS and CGI-S but not CGI-I	Nausea, vomiting, diarrhea	2b/0.5
Uncontrolled studies							
Lafleur et al. (2005)	58 yo F with OCD on Fluvoxamine 300 mg daily	0.6 g/d NAC titrated up to 3 g/d for 7 wk	Case report	Y-BOCS	Marked decrease in Y-BOCS	Few episode of mild, brief right hand tingling and single day of dry mouth	4/1

AE, adverse effects; CGI-I, Clinical Global Impression Improvement Scale; CGI-S, Clinical Global Impression Severity Scale; DBPC, Double Blind Placebo Controlled; PB, placebo; SSRI, selective serotonin reuptake inhibitor; Y-BOCS, Yale Brown Obsessive Compulsive Scale.

Table 16
Schizophrenia.

Study	Participants # Group (M, F); age in year (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Controlled studies							
Berk et al. (2008a, 2008b) Berk et al. (2011a, 2011b)	140 (98M, 32F); 36.6 (10.9) NAC: 69 (48M, 21F) PB: 71 (50M, 21F)	2 g/day NAC or PB for 4 mo	DPBC parallel	PANSS, CGI, GAF, SOFAS, BAS, SAS, AIMS	Improvement on CGI, PANSS but no other outcome measures Qualitative analysis showed improved mental state	Not significant	1b/0.5
Farokhnia et al. (2013)	NAC: 21 (9M, 12F); 32.2 (6.1) PB: 21 (11M, 10F); 33.4 (7.0)	2 g/d NAC or PB + risperidone for 8 wk	DBPC parallel	PANSS, HDRS	Improvement in PANSS negative and total scales	None	2b/1
Uncontrolled studies							
Bulut et al. (2009)	24 yo F	0.6 g/d for 67 days	Case report	PANSS, CGI-S	Decrease in PANSS and CGI-S	None	4/1

AE, adverse effects; AIMS, Abnormal Involuntary Movement Scale; BAS, Barnes Akathisia Scale; CGI-S, Clinical Global Impression Severity Scale; DPBC, Double Blind Placebo Controlled; GAF, Global Assessment of Functioning; HDRS, Hamilton Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; PB, placebo; SAS, Simpson–Angus Scale; SOFAS, Social and Occupational Functioning Assessment Scale.

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Table 17
Traumatic brain injury (TBI).

Study	Participants # Group (M, F); age (SD)	Treatment	Study design	Outcome measure	Effect of NAC	AE	Level/point
Controlled studies							
Hoffer et al. (2013)	Mild TBI secondary to blast exposure 80M, 1F; 18–43 yo NAC: 40 PB: 41	4 g loading dose NAC then 2 g BID for 4 days then 1.5 g BID or PB for 7 days	DBPC parallel	Resolution of dizziness, hearing loss, headache, memory loss, sleep disturbance and neurocognitive dysfunction (COWA, AN, TMT)	Significant improvement in all measures	NR	1b/1

AE, adverse effects; AN, Animal Naming; COWA, Controlled Oral Word Association test; DPBC, Double Blind Placebo Controlled; NR, not reported; PB, placebo; TMT, Timed Trail Making Test A and B.

This differential response may be due to different metabolic pathways underlying the pathophysiology of various psychiatric and neurological disorders and the differential effect of NAC on these pathways. Studies on most of the psychiatric disorders, including autism, AD, schizophrenia, cocaine addiction, cannabis addiction, BPAD, MDD, trichotillomania, nail biting and OCD, demonstrated mixed results. For other psychiatric disorders, specifically methamphetamine, nicotine, and pathological gambling addictions, the evidence for the effectiveness of NAC was negative overall. No recommendations could be made for two psychiatric disorders – anxiety and ADHD. Study on anxiety was only preliminary (i.e., case report) while the evidence for ADHD was based on a very specific population (SLE) hence not fully representative of idiopathic ADHD. The majority of the psychiatric disorders were assigned a GOR of B or C. Thus, the recommendations for use of NAC in the majority of psychiatric disorders are still limited based on the number and the quality of studies that have been conducted and available for review at the time of this review. In terms of neurological disorder, for mild TBI there was one positive DBPC study making NAC a potentially promising treatment option, but it is difficult to give a specific recommendation based on a single study. NAC showed positive response in anticancer medicines induced neuropathy in a small controlled trial and a case study making it a favorable treatment option for this indication, but since the sample size of the controlled study was very small, it is hard to give any specific recommendation based on the limited current evidence. Similarly evidence of use was mixed ranging from dramatic to partial or no improvement along with AEs in progressive myoclonus epilepsy. For ALS the evidence of the effectiveness of NAC in survival was negative overall. While larger controlled trials are needed to establish effectiveness of NAC, based on the evidence so far and excellent safety profile, NAC appears to be a favorable and novel treatment option for several psychiatric and neurological disorders and these results are encouraging.

The presumed mechanisms of action of NAC may make clinical sense for its use in psychiatric and neurological disorder. NAC has been demonstrated to work on multiple pathways that have been implicated in various psychiatric and neurological disorders – oxidative stress, mitochondrial dysfunction, inflammatory mediators, neurotransmission, and neural plasticity (Bavarsad Shahripour et al., 2014; Berk et al., 2013; Dean et al., 2011; Moussawi et al., 2009). Potential mechanisms of action are summarized below.

4.1. Potential mechanisms of action

4.1.1. Oxidative stress

Oxidative stress refers to a pathological state which occurs when the level of reactive oxygen species (ROS) is elevated to a level at which cellular damage can occur. This can be due to abnormally high levels of ROS, a deficit of cellular protective mechanisms, or both (Gandhi and Abramov, 2012; Smaga et al., 2012). Oxidative stress is involved in the pathogenesis of multiple psychiatric and neurological disorders including BPAD (Fullerton et al., 2010; Kunz et al., 2008), autism (James et al., 2004, 2006, 2008, 2009; Melnyk et al., 2012; Rose et al., 2012a, 2012b), depression (Behr et al., 2012; Smaga et al., 2012), schizophrenia (Kunz et al., 2008; Okusaga, 2014; Wu et al., 2013), OCD (Selek et al., 2008), AD (Markesbery, 1999), ULD (Arakawa and Ito, 2007), ALS (Louwerse et al., 1995) and drug induced neuropathy (Baker and Lipson, 2010; Lin et al., 2006). The brain is uniquely vulnerable to ROS, due to its high oxygen metabolism and limited antioxidant capabilities (Smaga et al., 2012). Highly reactive compounds like hydroxyl radical, hydrogen peroxide, superoxide and peroxynitrite cause oxidative cellular dysfunction through processes like lipid peroxidation, inactivation of enzymes, malfunction of the mitochondrial respiratory chains, DNA modification and/or cell death (Maes et al., 2011; Smaga et al., 2012). Postmortem brain specimens in several psychiatric disorders have shown oxidative damage (Gawryluk et al., 2011). Protective antioxidant mechanisms such as superoxide dismutase, catalase, glutathione (GSH) reductase and glutathione peroxidase neutralize reactive species (Maes et al., 2011; Smaga et al., 2012). Reduction in GSH has been shown in depression (Bilici et al., 2001), BPAD (Andreazza et al., 2009) and schizophrenia (Altuntas et al., 2000) supporting the role of redox imbalance in psychiatric disorders.

NAC provides cysteine that is rate limiting amino acid in GSH production (Dringen and Hirrlinger, 2003). GSH carries a free thiol group that acts as a reducing agent. GSH reduces the superoxide radical into hydrogen peroxide which can then be neutralized to water by catalase activity. During this processes, GSH becomes oxidized into glutathione disulphide (GSSG). The cysteine/cysteine cycle can also serve as a direct free radical scavenging system (Banjac et al., 2008; Vene et al., 2011). Several preclinical studies have shown direct and indirect antioxidant effects of NAC, for example, NAC significantly improves antioxidant defenses in alcohol treated rats (Achat-Mendes et al., 2007; Flora, 1999; Fukami et al., 2004; Seiva et al., 2009; Smaga et al., 2012; Wan et al., 2006).

4.1.2. Mitochondrial dysfunction

Mitochondrial dysfunction occurs in several psychiatric disorders (Shao et al., 2008) including schizophrenia (Robicsek et al., 2013), BPAD (Konradi et al., 2004), autism (Rossignol and Frye, 2012), AD (Wang et al., 2014) and TBI (Lifshitz et al., 2004). The role of mitochondrial dysfunction in the pathophysiology of psychiatric disorders is supported by the fact that psychiatric symptoms are common in mitochondrial disorders (Anglin et al., 2012a, 2012b, 2012c, 2012d). Mitochondria are the site for multiple redox reaction in order to generate adenosine triphosphate (ATP) energy and hence are a major source of ROS in the cell that can lead to oxidative injury (Sullivan et al., 2007). NAC has been shown to have direct effects on mitochondrial functioning in different

Table 18
Reported adverse effects (AE) of N-acetylcysteine.

AE	Addiction					AD	ALS	Anxiety	ADHD	Autism	BPAD	Dep	Epilepsy	Impulse control disorder			Neuropathy	OCD	Schizophrenia	TBI
	Cannabis	Cocaine	MAP	Nicotine	PG									Nail biting	Skin picking	TTM				
Gastrointestinal AE																				
Mild abdominal pain/discomfort	x			x			x			x	x		x							
Flatulence		x			x										X					
Abdominal cramps		X	x											x	X					
Nausea, heart burns, vomiting, diarrhea	x	x	x	x			x				x		x		x			x		
General GI symptoms			x									x								
Neurological/psychological/behavioral AE																				
Headaches		x	x			x					x			x						
Tingling																		x		
Vivid dreams	x																			
Insomnia	X																			
Irritability/agitation	x													x						
Other system AE																				
Elevated BP		x																		
Purities/local rash		x																		
Hypersensitivity							x													
Injection site reaction							X													
Allergic reaction			x				x													
Fatigue/change in energy		x									x							x		
Dry mouth/increased thirst/sweating			x								x									
Muscle/joint pain	x										x									
General musculoskeletal symptoms												x								
Nasal congestion/runny nose	x						x													
Restlessness	x																			
Dizziness	x	x																		
Neutropenia													x							
Chest pain		x																		
Leg edema							x													
Severe AE needing discontinuation																				
Full body rash																x				
Severe aggression														x						
Other severe AE	x										x			x						
SN deafness													x							

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ADHD, attention deficit hyperactivity disorder; BP, blood pressure; BPAD, bipolar disorder; Dep, depressive disorder; GI, gastrointestinal; MAP, methamphetamine; OCD, obsessive compulsive disorder; PG, pathological gambling; SN, sensorineural; TBI, traumatic brain injury; TTM, trichotillomania.

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disorders. As mentioned above NAC is the precursor of the most abundant intracellular antioxidant, GSH, and also acts as a direct free radical scavenger and hence plays a very important role in reducing the incidence and burden associated with oxidative injury. NAC has shown to improve mitochondrial functioning in animal models of inflammatory bowel disease through regeneration of mitochondrial membrane potential and hence decreases membrane permeability and apoptosis (Amrouche-Mekkioui and Djerdjouri, 2012). Similarly the effect of NAC on mitochondrial membrane potential along with oxidative injury has been shown in lung epithelial cells (Tobwala et al., 2013). NAC has shown similar effect on mitochondrial functioning in an animal model of myocardial infarction (Basha and Priscilla, 2013) and Huntington disease related mitochondrial dysfunction (Sandhir et al., 2012).

4.1.3. Inflammatory mediators

Several psychiatric disorders have been associated with a derangement of inflammatory cytokines including interleukin (IL)-1β, IL-2, IL-6, interferon (IFN), tumor necrosis factor α (TNF α), the soluble IL-6 receptor (sIL-6R), and the IL-1 receptor antagonist (IL-1RA) including depression (Dowlati et al., 2010), BPAD (Tsai et al., 2014) and schizophrenia (Drexhage et al., 2010). Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), proinflammatory cytokines, and intercellular adhesion molecule-1 (ICAM-1) are upregulated after TBI (Chen et al., 2008). Treatment with cytokines IL-2 and IFN α in diseases such as cancer are associated with high rates of depression (Capuron et al., 2000, 2001, 2004). Cytokines activate brain macrophages that lead to the release of inflammatory mediators resulting in oxidative stress and neurotoxicity (Rajkowska and Miguel-Hidalgo, 2007).

NAC has anti-inflammatory properties through several cellular processes. It is a GSH precursor and direct antioxidant, and hence inhibits upstream events leading to NF-κB activation (Baeuerle and Henkel, 1994) and other proinflammatory cytokines. This inhibition of proinflammatory transcription factor NF-κB by NAC down regulates expression of several proinflammatory genes (Yang et al., 2002). NAC directly inhibits the inflammatory cytokines TNFα, IL-1β and IL-6, at the protein and mRNA levels, in LPS-activated macrophage cell lines (Palacio et al., 2011) along with a direct effect on brain macrophages through increased GSH production, antioxidant properties and cysteine/glutamate exchange and hence regulating glutamergic excitatory neuronal damage and redox reactions (Kigerl et al., 2012).

By suppressing the activation of NF-κB, NAC has shown to reduce lung inflammation (Blackwell et al., 1996). NAC has also been shown to reduce IL-6 levels in dialysis patients (Nascimento et al., 2010), TNF α and IL-1β in cardiac injury after aortic aneurysm repair (Mahmoud and Ammar, 2011), and multiple other inflammatory cytokines in burn patient (Csontos et al., 2012). NAC is as effective as an anti-inflammatory agent in animal models of traumatic brain injury (Chen et al., 2008) and ischemia (Khan et al., 2004), lipopolysaccharide-induced pulmonary edema (Gatti et al., 1993), lethal endotoxemia (Victor et al., 2003) and hypoxia-ischemic brain injury in neonatal rat brains (Jatana et al., 2006).

4.1.4. Glutamate neurotransmission

Abnormal glutamate signaling has been shown in multiple psychiatric illnesses including schizophrenia (Kantrowitz and Javitt, 2010a, 2010b), OCD (Chakrabarty et al., 2005), autism (Rubenstein and Merzenich, 2003) and addiction, primarily cocaine addiction (Baker et al., 2003; Bauzo et al., 2012; Carlezon and Nestler, 2002; Cornish and Kalivas, 2000, 2001; Pierce et al., 1996). Vesicular release of glutamate at Prefrontal Cortex-Nucleus Accumbens (PFC-NA) synapses contributes to the basal tone of glutamate. This is negatively regulated by extrasynaptic glutamate activation of extrasynaptic group II metabotropic autoreceptors mGluR2/3 (Baker et al., 2002a, 2002b; Kupchik et al., 2012). Extracellular glutamate is regulated primarily by cystine–glutamate exchangers (System Xc^-) located on glial cells (Baker et al., 2002a; Bauzo et al., 2012; Pow, 2001). These transporters exchange extracellular cystine for intracellular glutamate (Kupchik et al., 2012; McBean, 2002). System Xc^- also plays a very important role in GSH production and hence plays an important role in regulating oxidative stress. Glutathione is synthesized by uptake of L-cystine in the glial cells that is released later out of the cell as GSH via the Cys_2/CysH shuttle (Dringen et al., 1999; Kranich et al., 1998; Wang and Cynader, 2000).

Studies have shown both increased and decreased glutamate levels in different psychiatric disorders specifically schizophrenia (Baker et al., 2008) and addiction (Schmaal et al., 2012). Increased glutamatergic release from a wide range of glutamatergic projections extending from the PFC to the NA is seen in animal models of active drug seeking and reinstatement (Baker et al., 2003; Cornish and Kalivas, 2000; Di Ciano and Everitt, 2001; Everitt and Wolf, 2002; Goldstein and Volkow, 2002; McFarland and Kalivas, 2001; Park et al., 2002). Studies have also shown reduced basal glutamate levels in the NA associated with substance withdrawal (Baker et al., 2003; Hotsenpiller et al., 2001; Kupchik et al., 2012; McFarland et al., 2003; Pierce et al., 1996). Excess of glutamate can lead to NMDA activation leading to increased excitatory neuronal damage and degeneration (Barger and Basile, 2001; Piani and Fontana, 1994; Sattler and Tymianski, 2001). Excitatory glutamate related injuries have been shown to have a role in several neurodegenerative disorder including epilepsy, trauma, ALS and AD (Lipton and Rosenberg, 1994). Studies have shown that the activation of group I mGlus receptors can be neurotoxic by increased excitatory signals or neuroprotective by inhibiting the ROS generation and intracellular GSH loss (Allen et al., 2000; Deng et al., 2004). NAC is rapidly converted into cystine after administration and enters cell through this cysteine transporters to activate system Xc^- (Kau et al., 2008; Kupchik et al., 2012). NAC dose-dependently increases extracellular glutamate by restoring cystine–glutamate exchange via system Xc^- and thus bringing extracellular glutamate to normal range (Baker et al., 2003; Madayag et al., 2007). This normalization of extracellular glutamate by NAC restores tone onto presynaptic inhibitory metabotropic glutamate autoreceptors in the NA and blunts the increased glutamate release (Baker et al., 2003; Moran et al., 2005). NAC also provides the rate limiting component, cysteine for GSH production and hence has role in modulation of NMDA related injury via effect on GSH or its derivatives (Gilbert et al., 1991; Leslie et al., 1992; Varga et al., 1997). Both these actions of NAC together affect the excitatory neuronal damage and glutamate homeostasis. Magnetic resonance spectroscopy data suggests that NAC normalizes glutamate in cocaine addiction, increases brain glutathione, and alters neural markers, including glutamate–glycine and myoinositol (Das et al., 2013; Holmay et al., 2012; Schmaal et al., 2012).

4.1.5. Long term neuroadaptation

Dysregulated glutamate homeostasis can lead to impaired synaptic potentiation and plasticity and thus altered metaplasticity (Moussawi et al., 2009). Metaplasticity refers to the ability to generate synaptic plasticity (ability of synapses to strengthen or weaken over time in response to their activity level) and can be adaptive or maladaptive. This change in synaptic plasticity happens when a priming activity like substance administration alters the capacity of a subsequent high or low frequency stimulation in inducing long-term potentiation (LTP) or long term depression (LTD)(Abraham, 2008). Several studies found that rats withdrawn from cocaine self-administration had a marked deficit in LTP and LTD in the NA core following stimulation of PFC and NAC treatment restored the ability to induce LTP and LTD by stimulating mGluR2/3

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and mGluR5, respectively (Kupchik et al., 2012; Moussawi et al., 2009). Neuroplasticity is important in mental health and maladaptive neuroplasticity could lead to psychiatric disorders (Kays et al., 2012). This mechanism is worth further exploration in different psychiatric disorders

4.1.6. Dopamine neurotransmission

Dopamine (DA) has been linked to the pathophysiology of schizophrenia, addiction, BPAD, depression, and ADHD (Berk et al., 2007; Heinz and Schlagenhauf, 2010; Hyman et al., 2006; Malhi and Berk, 2007; Wu et al., 2012). The reciprocal interaction between dopamine and glutamate in brain has been an area of focus in understanding the pathology of psychiatric illnesses including drug addiction (Sesack et al., 2003) especially methamphetamine addiction. Methamphetamine releases high levels of DA. DA itself has the potential to cause oxidative injury and hence dysregulation of DA transmission can lead to neurotoxicity (Hastings, 2009). Repeated administration of methamphetamine damages DA nerve terminals (Cadet et al., 2003; Davidson et al., 2001; Fukami et al., 2004; Fumagalli et al., 1998) as evident by a marked reduction of DA transporter demonstrated using positron emission tomography in the brain of methamphetamine abusers (Fukami et al., 2004; Sekine et al., 2001, 2003; Volkow et al., 2001a, 2001b, 2001c). NAC influences glutamergic neurotransmission regulation of DA release from presynaptic terminals (Baker et al., 2002a, 2002b). Also NAC as a GSH precursor acts as an important intracellular antioxidant (Schulz et al., 2000) and hence seems to have a significant role in regulating DA induced neurotoxicity in different psychiatric disorders.

4.1.7. Serotonergic neurotransmission

Serotonin (5HT) transmission has been target of multiple psychopharmacological agents and derangement has been shown to be associated with multiple psychiatric disorder including affective disorders (Jobe et al., 1998), schizophrenia (Abi-Dargham, 2007), autism (Cook et al., 1997), addiction (Jones and Kauer, 1999; Müller et al., 2007) and OCD (Baumgarten and Grozdanovic, 1997). Role of NAC on serotonergic transmission has not been explored in details as of yet. A recent study showed the effect of NAC in animal model of psychosis by blocking hallucinogenic effect of serotonergic receptor 5-HT_{2A}R agonist. This action seem to be mediated by increased cysteine-glutamate antiporter followed by mGluR2 autoreceptors activations hence showing complex interaction between glutamatergic and serotonergic neurotransmission (Lee et al., 2014)

4.2. Dosage and formulations

The daily dosage of NAC ranged from 0.6 g to 6 g/day with majority of the studies using 2.0–2.4 g/day dosing. All the studies used oral formulation of NAC with the exception of the four studies in ALS that used subcutaneous formulation. The shortest duration of treatment reported was 2 days in cocaine addiction (LaRowe et al., 2007) and longest was 60 month in a case of progressive myoclonic epilepsy (Ben-Menachem et al., 2000). Both of these studies showed positive outcomes. The majority of the studies had 8 weeks follow-up and few had 3–6 months follow-up.

N-acetylcysteine is FDA-approved for acetaminophen poisoning for 72-h oral and 21-h intravenous regimens. Seventy two-hour oral regimen consists of 18 doses – loading dose of 140 mg/kg and maintenance dose of 70 mg/kg every 4 h to a total dose of 1330 mg/kg. Total recommended intravenous dose is 300 mg/kg (OnlineTM, 2011). This dose is much higher than used in the studies in our review. In initial studies on ALS, 50 mg/kg/day subcutaneous dose was used (Louwerse et al., 1995). Similarly in the study on the use of NAC in AD, 50 mg/kg/day in three divided doses were used (Adair et al., 2001). So if a patient is 50 kg the total dose would be 2.5 g. The rationale for this dose was not clearly stated in the studies but due to precautionary reasons the dose may have been decided to be a little lower than one used for acetaminophen toxicity. This dose was fairly well tolerated in these studies with some gastrointestinal side effects along with hypersensitivities and local site reaction related to subcutaneous formulation in the ALS studies (Louwerse et al., 1995). In a follow-up AD case series, a much lower dose of 0.6 g/day of NAC was used as an adjunct to Vitamin B12 and folate (McCaddon and Davies, 2005) and it showed positive effects. It was followed by a trial in severe OCD in which, based on earlier study dosing, 0.6 g/day was initiated and based on the response it was titrated to 3 g/day over 6 weeks (Lafleur et al., 2006). These case reports were followed by a crossover study to specifically assess the safety and tolerability of three doses of NAC – 1.2 g/day, 2.4 g/day and 3.6 g/day. The study did not show any significant difference between the three doses in terms of side effects or effect but the retention rate appeared more in favor of the higher doses of NAC (Mardikian et al., 2007). Also one three-arm DBPC did not show any differential response between NAC 1.2 g/day or 2.4 g/day in treatment-seeking cocaine dependent adults (LaRowe et al., 2013). One ADHD study and few addiction studies used higher doses of NAC in the range of 3–4.8 g with no clear signal of higher efficacy (Garcia et al., 2013; Grant et al., 2014; LaRowe et al., 2007; Mardikian et al., 2007). Studies on ULD used a higher dose 3–6 g/day. No clear association with increased efficacy with the higher dose was seen. In one study increasing the dose from 4 g to 6 g/day led to cold sores and possible neutropenia that was reversed on lowering the dose to 2.4 g/day. One other patient developed sensorineural hearing loss on 3 g/day dose of NAC (Edwards et al., 2002). Several case reports/series have shown positive responses with gradual titration to the range of 1.8–2.4 g/day of NAC (Marler et al., 2014; Odlaug and Grant, 2007; Strawn and Saldana, 2012). Hence most of the studies used the dose around 2–2.4 g/day based on the effect and safety profile. Overall the dose range between 2 and 2.4 g/day seems to be effective and well tolerated.

4.3. Potential adverse effects

For the most part, oral NAC seemed to be fairly well tolerated with no significant between group differences in most of the controlled trials. Gastrointestinal (GI) symptoms were the most common AEs and have been reported in autism, addiction, ALS, epilepsy, grooming disorder and OCD studies. Adverse effects included mild abdominal pain (Ghanizadeh and Derakhshan, 2012; Hardan et al., 2012), mild abdominal discomfort, heartburn, flatulence, cramps (Edwards et al., 2002; LaRowe et al., 2006; Odlaug and Grant, 2007; Vyth et al., 1996), nausea, vomiting and diarrhea (Afshar et al., 2012; Hurd et al., 1996). The largest rate of AEs was seen in an open-level studies on cannabis in which 63% of the participants reported mild to moderate AEs, primarily abdominal discomfort (Gray et al., 2010).

Neurological side effects were also commonly reported ranging from headaches (Adair et al., 2001; Ghanizadeh et al., 2013; Mardikian et al., 2007); to right hand tingling in a case of OCD (Lafleur et al., 2006). On the contrary lower rates in Extrapyramidal Symptoms Rating Scale was seen in NAC + risperidone group as compared to the placebo + risperidone group suggesting protective effects of NAC on AEs related to concomitant psychiatric medications when used as adjunctive therapies (Farokhnia et al., 2013). There were few incidents of dermatological AEs including self-limited non-dose dependent pruritus in one study (Mardikian et al., 2007). One child developed full body rash that required discontinuation of the NAC treatment (Bloch et al., 2013). Elevated blood pressure was reported in two studies (LaRowe et al., 2006; Mardikian et al., 2007). Other miscellaneous AEs reported were fatigue (LaRowe et al., 2006), a single day of dry mouth (Lafleur

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et al., 2006), muscle pains, insomnia, nasal congestion, runny nose, restlessness, and dizziness (Gray et al., 2010), and vivid dreams and irritability (Grant et al., 2012).

Very few studies reported severe AEs leading to discontinuation of NAC treatment. In a TTM DBPC study one child discontinued the NAC treatment after experiencing a full body rash which dissipated after discontinuing NAC (Bloch et al., 2013). A child with nail biting discontinued treatment due to aggression (Ghanizadeh et al., 2013). In a large DBPC study on cannabis one individual discontinued NAC for severe AEs (Grant et al., 2012). Two rare AE were reported in a ULD case series – neutropenia on 6 g of NAC that improved once the dose was dropped down to 2.4 g daily and SN deafness leading to discontinuation of NAC at 5 weeks and it was not resolved till 9 month of follow-up (Edwards et al., 2002). It is important to consider that different formulations of NAC may have various additives and fillers that also could cause AEs. The few and lack of consistent reports of particular severe AEs suggest that NAC is generally considered a well-tolerated and safe medication overall.

In animal literature serious AEs of pulmonary hypertension has been reported (Palmer et al., 2007) and also seizures have been reported on overdose (Bailey et al., 2004). None of the clinical studies in this review reported these AEs. Serious anaphylactic reactions have also been reported mostly associated with intravenous administration of NAC (Mroz et al., 1997). There were more AEs in ALS studies that used a subcutaneous formulation including an injection site granuloma and an abscess along with hypersensitivity and allergic reactions (De Jong et al., 1987; Küther and Struppler, 1987). No hypersensitivity or allergic reaction was seen in oral formulation. No clear association could be seen between AEs and dose or type of disease. Overall across studies it seems to be safe and well tolerated with a low incidence of serious AEs.

5. Conclusion

The use of NAC has been studied in several psychiatric and neurological disorders and seems to be a novel treatment approach. Data is still limited in terms of quantity and quality of studies for most of the disorders but overall the effect trends in a positive direction for many disorders. NAC treatment appears safe, tolerable and affordable. It's a medication worth exploring further. Further well designed, larger controlled trials are needed for different psychiatric and neurological disorders. In addition, studies to elucidate which of its many mechanisms of action are responsible for its efficacy are required.

Conflict of interest

Michael Berk, MBBch, MMed(Psych), FF(Psych)SA, FRANZCP, PhD, has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol-Myers Squibb, Eli Lilly, Glaxo SmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier and Woolworths, has been a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay and Wyeth, and served as a consultant to Astra Zeneca, Bioadvantex, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck Merck and Servier. He is co-inventor of two provisional patents regarding the use of NAC and related compounds for psychiatric indications, which, while assigned to the Mental Health Research Institute, could lead to personal remuneration upon a commercialization event. Dr. Berk is supported by a NHMRC Senior Principal Research Fellowship 1059660. Olivia Dean, BSc, PhD is a Research Fellow and

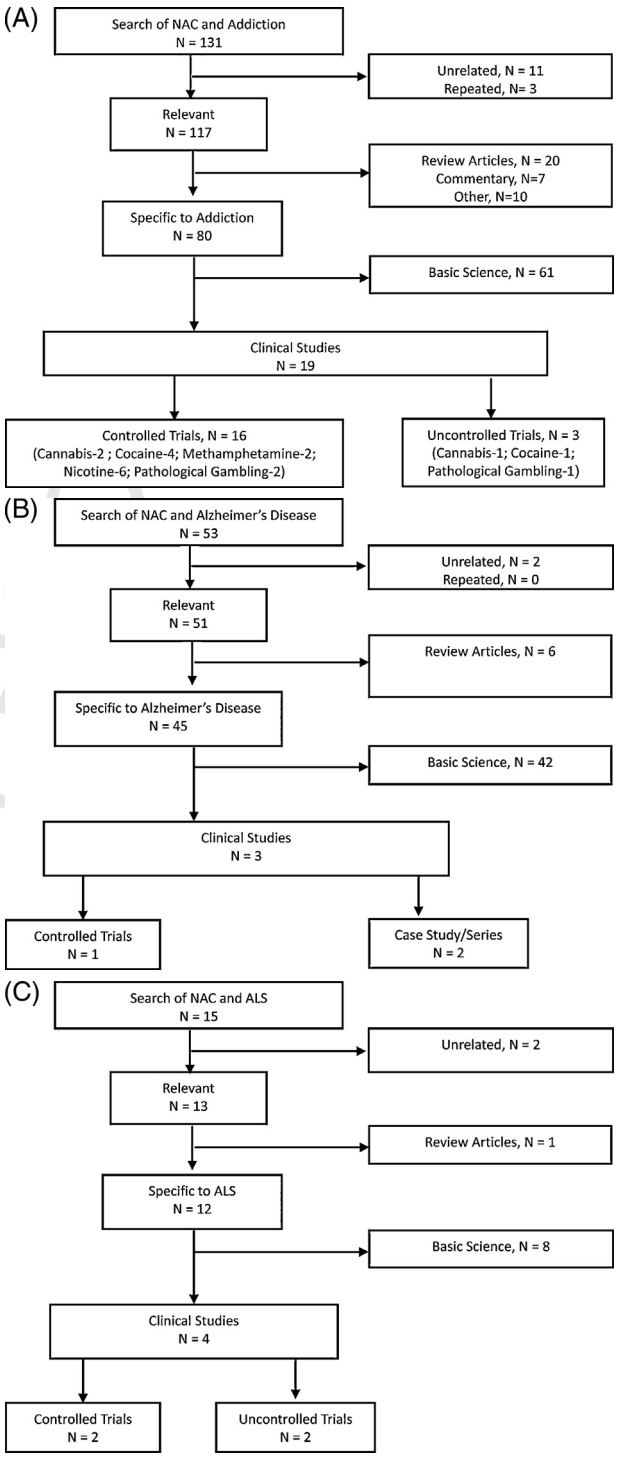

Fig. 1. Selection of studies for systematic review of NAC use in different psychiatric and neurological disorders. Flow diagram depicting inclusion and exclusion of trials for the systematic review for each disorder. (A) Selection of studies for systematic review of NAC use in addiction. (B) Selection of studies for systematic review of NAC use in Alzheimer's disease. (C) Selection of studies for systematic review of NAC use in amyotrophic lateral sclerosis (ALS). (D) Selection of studies for systematic review of NAC use in anxiety. (E) Selection of studies for systematic review of NAC use in attention deficit hyperactivity disorder (ADHD). (F) Selection of studies for systematic review of NAC use in autism. (G) Selection of studies for systematic review of NAC use in bipolar disorder (BPAD) and depression. (H) Selection of studies for systematic review of NAC use in epilepsy. (I) Selection of studies for systematic review of NAC use in impulse control disorder. (J) Selection of studies for systematic review of NAC use in neuropathy. (K) Selection of studies for systematic review of NAC use in obsessive compulsive disorder (OCD). (L) Selection of studies for systematic review of NAC use in schizophrenia. (M) Selection of studies for systematic review of NAC use in traumatic brain injury (TBI).

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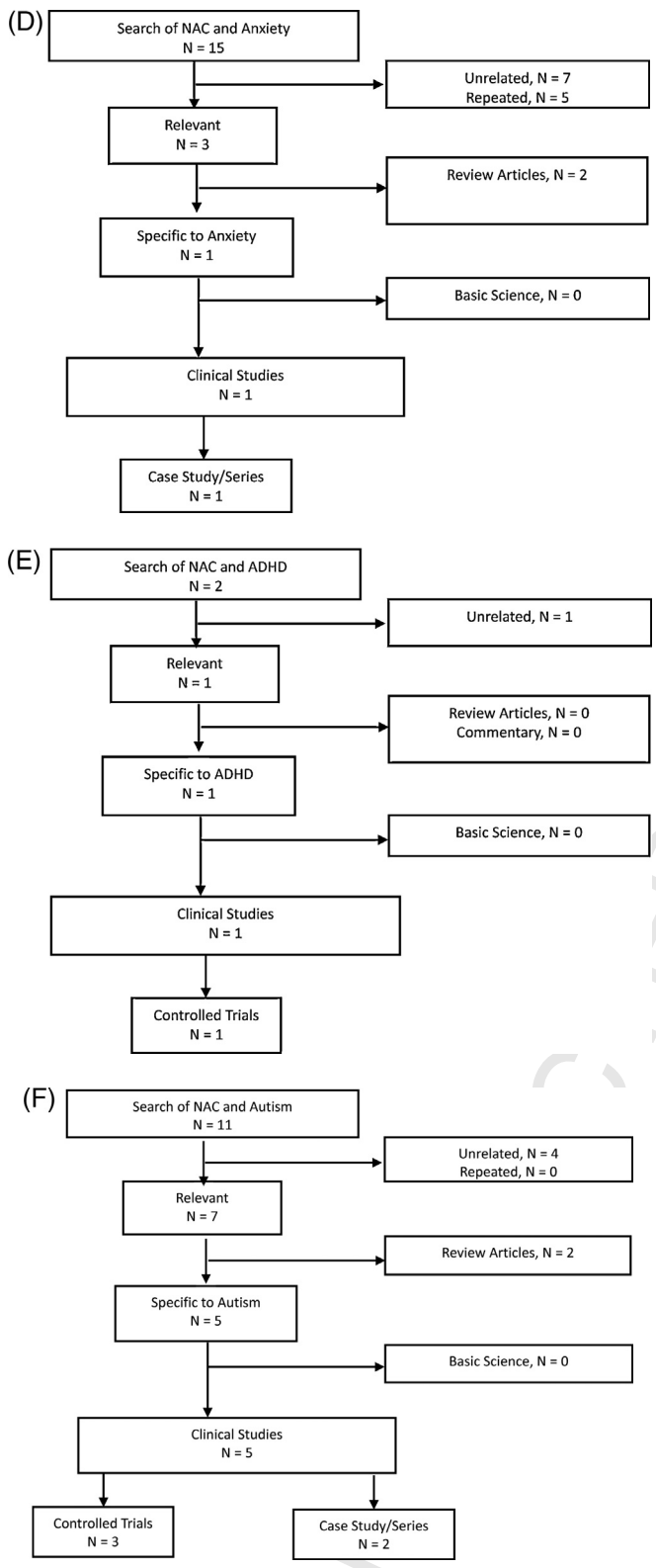

Fig. 1. (*Continued*)

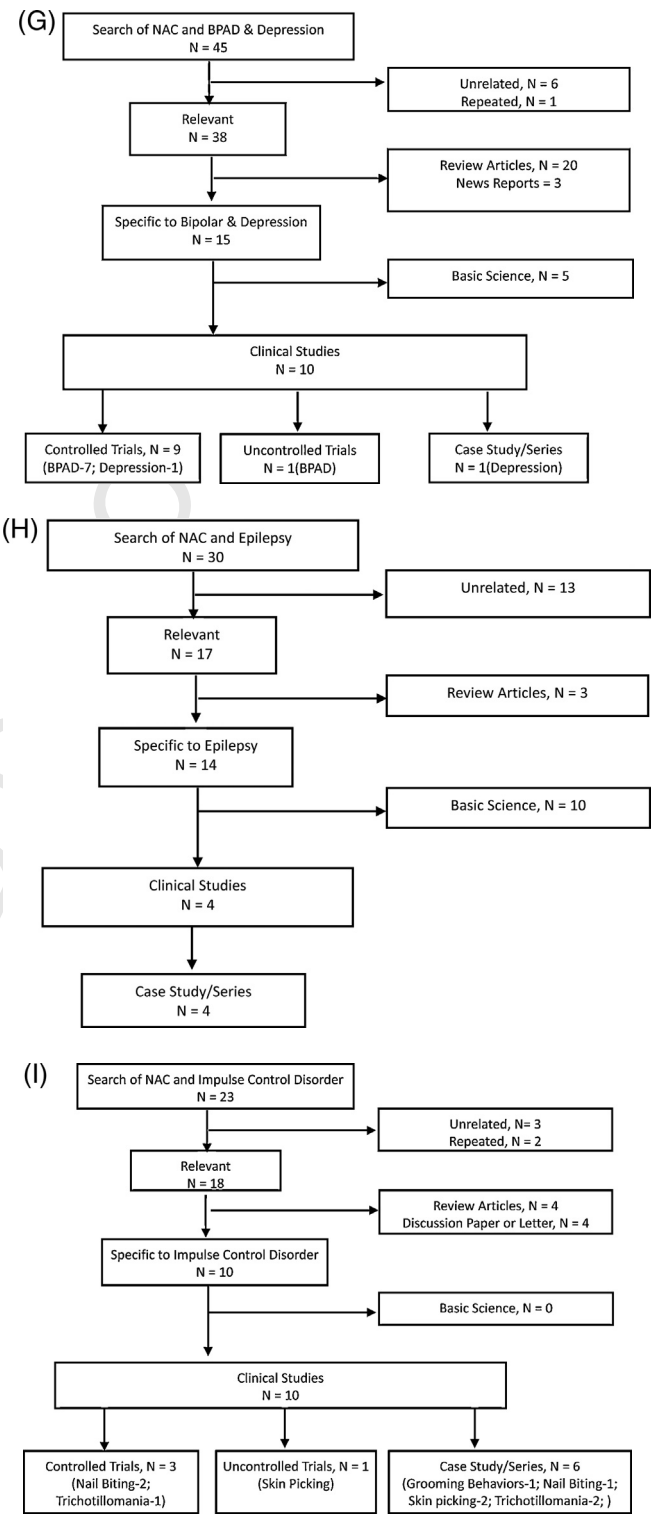

Fig. 1. (*Continued*)

has received grant support from the Brain and Behavior Research Foundation, Simons Foundation, Australian Rotary Health, Stanley Medical Research Institute, Lilly, NHMRC and an ASBD/Servier grant. She has also received in kind support from BioMedica Nutraceuticals, NutritionCare and Bioceuticals. Charles Spielholz, PhD is a consultant to BioAdvantex Pharma Inc. that manufactures NAC in a formulation for oral administration. This formulation of NAC has been approved for use in clinical trials in the United States, Switzerland and Australia. The remainders of the authors do not have any conflicts of interest associated with this publication. There has been no significant financial support for this work.

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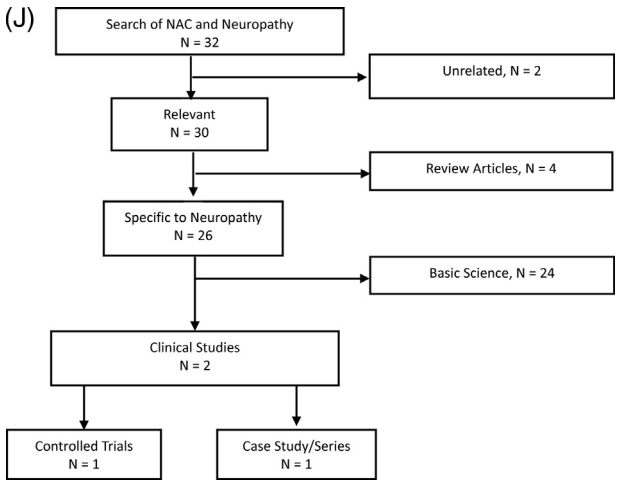

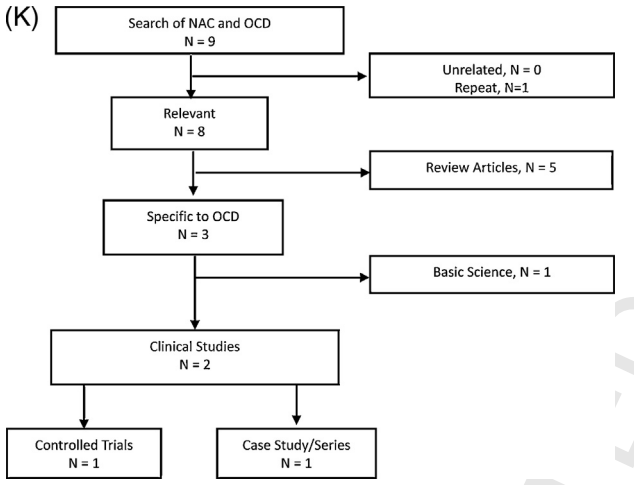

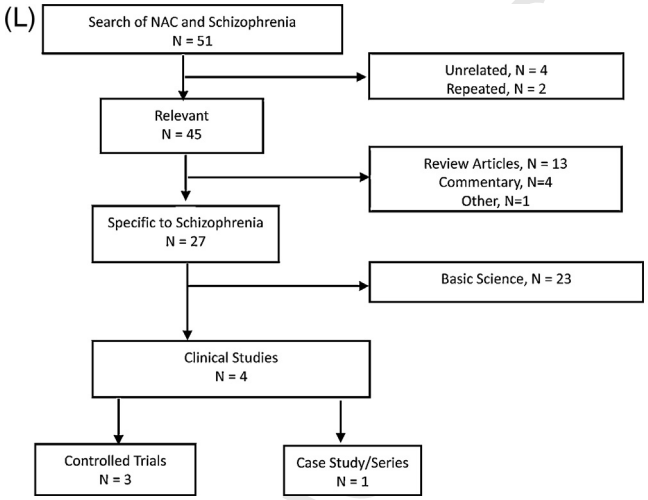

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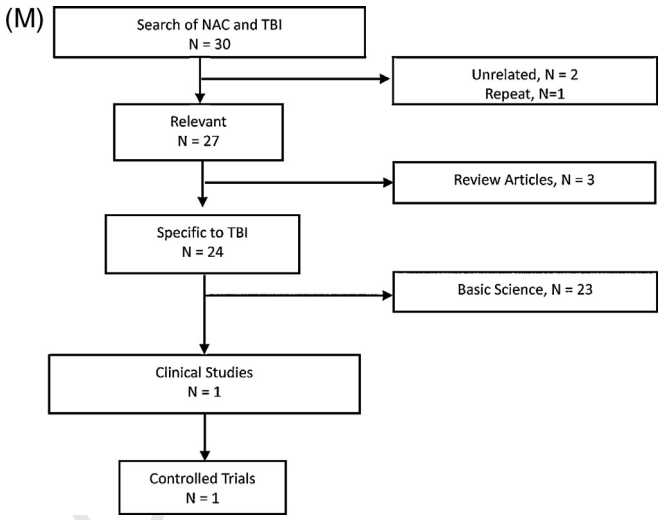

Fig. 1. (*Continued*)

Uncited references

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Patel et al. (2014) and Simon et al. (2000).

Appendix 1.

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