N-Acetyl Cysteine in Mental Health – Emerging Evidence of Therapeutic Applications
“Drug discovery is at a near standstill for treating psychiatric disorders such as schizophrenia, bipolar disorder, depression, and common forms of autism”

Former NIMH director Steven Hyman

Sci Transl Med. 2012
Psychopharmacology

- All current drugs are based on neurotransmitters as targets e.g. serotonin for mood disorders

- There is an urgent need to think more broadly about pharmacological targets in the treatment of psychiatric disorders

- Current Rx are incapable of resolving mental health conditions in terms of the newly identified neurobiological cascade they trigger e.g. inflammation, mitochondrial dysfunction, reduced, altered HPA axis etc.
A New Take on Mental Illness... in a Nutshell

Psychological Event + Vulnerability

Environmental Influences i.e. diet, infection, poor sleep, deficiencies

Prolonged & Sustained Inflammation & Oxidative Stress

Increased apoptosis, reduced neurogenesis

Inability to resolve acute episode & increased likelihood of relapse
“NAC provides a dual opportunity, first as a novel therapy, and second as a key to unlocking the pathophysiology of targeted disorders. It is noteworthy that the mechanisms of action of NAC overlap with the pathophysiology of a diverse range of neuropsychiatric disorders, including autism, addiction, depression, schizophrenia, bipolar disorder, and Alzheimer’s and Parkinson’s diseases. Determining precisely how NAC works is crucial both to understanding the core biology of these illnesses, and to opening the door to other adjunctive therapies operating on these pathways.”
Basic Biochemistry of NAC (Samuni et al 2013)

- Acetylated form of Cysteine
- Conveys greater stability in GIT than Cysteine
- In this form does not compete with other amino acids for uptake in GIT or BBB
Basic Biochemistry of NAC (Samuni et al 2013)

- Readily oxidised
- Forming & breaking of disulphide bridges in proteins
- Forms metal ion complexes
Cysteine is the Rate Limiting Component of GSH

Cysteine

Glutathione
Glutathione’s Role in the Brain

- **Predominant endogenous free radical scavenger**
- Consistent evidence of depleted brain GSH concentrations across a range of mental health conditions
- **The links between neuropsychiatric disorders & reduced GSH levels were first documented back in the 1934!**
- NAC has some direct scavenging properties as well, however, its potency in this respect is the subject of much debate
Mechanisms of Action of NAC

Targets

- Glutamate
  - NMDA and AMPA effects
  - Regulates extracellular glutamate
  - Cystine glutamate antiporter

Dopamine
- Facilitates dopamine release
- Blocks dopamine ROS
- Reverses mitochondrial toxicity

Mitochondrial dysfunction
- Normalises lactate

Oxidative stress
- Direct scavenging
- ↑ glutathione

Inflammation
- ↓ IL-6 and TNF alpha
- Increased levels of cytokines
- Altered gene expression in monocytes and dendritic cells

Neurogenesis apoptotic markers
- Attenuates CA++ influx and BCL-2
- ↑ neuronal sprouting & regeneration

Berk TIPS 2013
Diverse Applications Due to Multiple Mechanisms?
(Deepmala et al 2015, Samuni et al 2013)

Proposed Target of Actions
- Oxidative Stress
- Mitochondrial dysfunction
- Inflammation

Related Psychiatric Conditions
- AD, ASD, BPAD, Depression, Drug induced neuropathy, OCD, Schizophrenia
- AD, ASD, BPAD, TBI, Schizophrenia
- BPAD, Depression, Schizophrenia, TBI
Depression and Oxidative Stress: Meta-Analysis

Forest plot of effect sizes of associations between depression and oxidative stress

Diverse Applications Due to Multiple Mechanisms?
(Deepmala et al 2015, Samuni et al 2013)

Proposed Target of Actions
- Abnormal Glutamate Signalling
- Abnormal Dopamine Signalling

Related Psychiatric Conditions
- Addictions, ASD, OCD, Schizophrenia
- ADD, ADHD, BPAD, Depression, Schizophrenia
Figure 2
Berk et al. The promise of N-acetylcysteine in neuropsychiatry. Trends in Pharmacological Sciences March 2013, Vol. 34, No. 3
### Assessing The Evidence for Specific Psychiatric Conditions (Deepmala et al 2015)

#### Table 3

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

NAC in Bipolar Disorder (Berk et al 2008, Deepmala et al 2015, Maegelhaes et al 2013)

- 3 studies: 2 controlled
- 2/3 produced positive outcomes (1 controlled/1 uncontrolled)

Most Noteworthy (Berk et al 2008)

- DBPC trial (n=75) in BPAD maintenance phase administered NAC 2g/d as adjunct for 24wks
- NAC treatment produced significant reductions on both depression & mania scores
- Failed to show any significant differences in the frequency of or latency to new episodes of either depression or mania
ARCHIVAL REPORTS

N-Acetyl Cysteine for Depressive Symptoms in Bipolar Disorder—A Double-Blind Randomized Placebo-Controlled Trial

Michael Berk, David L. Copolov, Olivia Dean, Kristy Lu, Sue Jeavons, Ian Schapkaitz, Murray Anderson-Hunt, and Ashley I. Bush

Background: Treatment-resistant subthreshold depression is a major problem in bipolar disorder. Both depression and bipolar disorder are complicated by glutathione depletion. We hypothesized that treatment with N-acetyl cysteine (NAC), a safe, orally bioavailable precursor of glutathione, may improve the depressive component of bipolar disorder.

Methods: A randomized, double-blind, multicenter, placebo-controlled study of individuals \( n = 75 \) with bipolar disorder in the maintenance phase treated with NAC (1 g twice daily) adjunctive to usual medication over 24 weeks, with a 4-week washout. The two primary outcomes were the Montgomery Asberg Depression Rating Scale (MADRS) and time to a mood episode. Secondary outcomes included the Bipolar Depression Rating Scale and 11 other ratings of clinical status, quality of life, and functioning.

Results: NAC treatment caused a significant improvement on the MADRS (least squares mean difference [95% confidence interval]: \(-8.05 [-13.16, -2.95], p = .002\)) and most secondary scales at end point. Benefit was evidenced by 8 weeks on the Global Assessment of Functioning Scale and Social and Occupational Functioning Assessment Scale and at 20 weeks on the MADRS. Improvements were lost after washout. There was no effect of NAC on time to a mood episode (log-rank test: \( p = .968 \)) and no significant between-group differences in adverse events. Effect sizes at end point were medium to high for improvements in MADRS and 9 of the 12 secondary readouts.

Conclusions: NAC appears a safe and effective augmentation strategy for depressive symptoms in bipolar disorder.

Key Words: Bipolar disorder, clinical trial, depression, glutathione, risk for schizophrenia, where there is a decrease in brain glutathione (18)
Most noteworthy features of noteworthy study!

- Several subgroup analyses revealed
  - BPAD II subjects had more pronounced benefits for every outcome including Young Mania Rating Scale (YMRS)
  - Subjects with mania or hypomania at baseline administered NAC demonstrated improvement in YMRS while their counterparts worsened according to BDRS
  - More NAC treated individuals had complete remission however this failed to reach statistical significance
NAC in Bipolar Disorder: Effect sizes (MMRM, week 24)

Week 24

MADRS  BDRS  CGIBP  CGI-D  YMRS  RIFT  SLICE
Favors NAC

Q-LES-Q  GAF  SOFAS
Favors Placebo

Favors Placebo

Effect Size
-1.04
-0.83
-0.81
-0.62
-0.66
-1.11
-0.93

Favors NAC

0.95
0.82
0.83

Adjusted Effect Size (95% CI)

Berk Biological Psychiatry 2008
NAC in Depression (Berk et al 2014, Carvalho et al 2013, Deepmala et al 2015)

- 2 studies: 1 controlled & 1 uncontrolled (case series)
- Both produced positive results but not on every outcome measured

**Most noteworthy** (Berk et al 2014)

- DBPCT (n= 252) individuals with MDD 12 wks
- Administered 2g/d NAC as adjunct
- Statistically significant improvement in multiple outcomes compared with placebo but MADRS scores, response and remission rates did not become statistically significant until 16 wks
The Efficacy of Adjunctive N-Acetylcysteine in Major Depressive Disorder: A Double-Blind, Randomized, Placebo-Controlled Trial

Michael Berk, MBBCh, MMed (Psych), FF(Psych)SA, PhD; Olivia M. Dean, PhD; Sue M. Cotton, PhD; Susan Jeavons, PhD; Michelle Tanious, BMedSci (Hons), BPsych (Hons); Kristy Kohlmann, BSc (Hons); Karen Hewitt, RN; Kirsteen Moss, PGDip App Psych; Christine Allwang, MD; Ian Schapkaitz, MBBCh; Jenny Robbins, RN; Heidi Cobb, BSc (Hons); Felicity Ng, MBBS; Seetal Dodd, MSc, PhD; Ashley L. Bush, MBBS, PhD; and Gin S. Malhi, MBChB, BSc (Hons), MD

ABSTRACT

Objective: Major depressive disorder (MDD) is one of the most common psychiatric disorders, conferring considerable individual, family, and community burden. To date, treatments for MDD have been derived from the monoamine hypothesis, and there is a paucity of emerging antidepressants, especially with novel mechanisms of action and treatment targets. N-acetylcysteine (NAC) is a redox-active glutathione precursor that decreases inflammatory cytokines, modulates glutamate, promotes neurogenesis, and decreases apoptosis, all of which contribute to the neurobiology of depression.

Method: Participants with a current episode of MDD diagnosed according to DSM-IV-TR criteria (N = 252) were treated with NAC or placebo in addition to treatment as usual for 12 weeks and were followed to 16 weeks. Data were collected between 2007 and 2011.

Results: The omnibus interaction between group and visit for the Montgomery-Asberg Depression Rating Scale (MADRS), the primary outcome measure, was not significant (F_{15,209} = 1.98, P = .067), and the groups did not separate at week 12 (t_{360.1} = −1.12, P = .265). However, at week 12, the scores on the Longitudinal Interval Follow-Up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT) differed from placebo (P = .03). Among participants with a MADRS score ≥ 25, NAC separated from placebo at weeks

Considerable attention has been paid recently to the weak pipeline of emerging agents in psychiatry, and in particular, the paucity of truly novel antidepressant agents.¹ New insights into the putative biology of depression have indicated alternative mechanisms of action for the development of novel antidepressants, including inflammation and oxidative stress. Glutathione, a tripeptide consisting of glutamate, glycine, and cysteine, is the dominant free radical scavenger within the brain that buffers reactive oxidative species. N-acetylcysteine can reliably enhance the synthesis of glutathione by increasing the availability of cysteine, the rate-limiting synthetic step.²,³ N-acetylcysteine also has other actions germane to the known pathophysiology of depression, such as enhancing neurogenesis, blocking apoptosis, reducing inflammation, protecting against mitochondrial toxicity, and modulating glutamate,⁴,⁵ which make N-acetylcysteine a promising translational bridge between these pathways and the development of targeted therapies.

Clinically, N-acetylcysteine has demonstrated efficacy in the treatment of schizophrenia, mood symptoms in bipolar disorder, smoking and cannabis cessation, gambling, and autism.⁶⁻¹⁰ We therefore aimed to test its efficacy in the acute
NAC in Depression (Berk et al 2014)

Most noteworthy features of noteworthy study!

- Berk’s data suggests that the greatest clinical improvement seen at 6mo
- Prof. Berk would like to see future studies go for 1-2 years to capture the full impact of long-term supplementation
- **NAC works best in severe depression e.g. Montgomery Asberg Rating Score of > 25**
- Sub-group analyses reveal better efficacy in middle-aged rather than young patients

- 3 studies: 1 uncontrolled, 2 controlled
- Consistently positive results

**Most noteworthy** (Berk et al. 2008)

- DBPC trial (n=140)
- Administered 2g/d NAC for 4mo
- Improvement on CGI & PANSS & qualitative measures
- No statistically significant improvement on GAF, SOFAS, BAS, SAS, AIMS
FIGURE 2. Comparison of the negative subscale scores of PANSS (mean [SD]) over time between the 2 study groups. The asterisk symbol indicates $P < 0.05$ for time x treatment interaction.

TABLE 3. Frequency of the Adverse Effects in the 2 Study Groups

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>N-acetylcysteine + Risperidone</th>
<th>Placebo + Risperidone</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness, n</td>
<td>7</td>
<td>4</td>
<td>0.48</td>
</tr>
<tr>
<td>Constipation, n</td>
<td>4</td>
<td>3</td>
<td>1.00</td>
</tr>
<tr>
<td>Dizziness, n</td>
<td>6</td>
<td>4</td>
<td>0.71</td>
</tr>
<tr>
<td>Vomiting, n</td>
<td>5</td>
<td>2</td>
<td>0.40</td>
</tr>
<tr>
<td>Increased appetite, n</td>
<td>4</td>
<td>4</td>
<td>1.00</td>
</tr>
<tr>
<td>Nausea, n</td>
<td>6</td>
<td>3</td>
<td>0.45</td>
</tr>
<tr>
<td>Headache, n</td>
<td>5</td>
<td>3</td>
<td>0.69</td>
</tr>
<tr>
<td>Dry mouth, n</td>
<td>5</td>
<td>2</td>
<td>0.40</td>
</tr>
<tr>
<td>Increased blood pressure, n</td>
<td>4</td>
<td>1</td>
<td>0.34</td>
</tr>
<tr>
<td>Diarrhea, n</td>
<td>6</td>
<td>3</td>
<td>0.45</td>
</tr>
</tbody>
</table>

**boldface values indicate the significant $P$ values ($< 0.05$).**
Qualitative methods in early phase clinical trials

<table>
<thead>
<tr>
<th>Theme</th>
<th>Number of Transitions</th>
<th>P Value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Improvement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved insight</td>
<td>62</td>
<td>.000</td>
</tr>
<tr>
<td>Adequate self-care</td>
<td>81</td>
<td>.000</td>
</tr>
<tr>
<td>Diminished perceptual abnormalities</td>
<td>15</td>
<td>.513</td>
</tr>
<tr>
<td>Reduction in self-harm thoughts</td>
<td>3</td>
<td>.083</td>
</tr>
<tr>
<td>Improved social interactivity</td>
<td>57</td>
<td>.007</td>
</tr>
<tr>
<td>Motivation and volition</td>
<td>86</td>
<td>.000</td>
</tr>
<tr>
<td>Thought reorganization</td>
<td>17</td>
<td>.054</td>
</tr>
<tr>
<td>Mood reactivity and euthymia</td>
<td>38</td>
<td>.013</td>
</tr>
<tr>
<td>Psychomotor stability</td>
<td>21</td>
<td>.023</td>
</tr>
<tr>
<td>Diminished delusional thoughts</td>
<td>23</td>
<td>.051</td>
</tr>
<tr>
<td><strong>Persistence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysthymia</td>
<td>24</td>
<td>.029</td>
</tr>
<tr>
<td>Affective flattening</td>
<td>4</td>
<td>.059</td>
</tr>
<tr>
<td>Auditory hallucinations</td>
<td>51</td>
<td>.021</td>
</tr>
<tr>
<td>Impaired insight</td>
<td>14</td>
<td>.367</td>
</tr>
<tr>
<td>Self-neglect and poor hygiene</td>
<td>5</td>
<td>.052</td>
</tr>
<tr>
<td>Social withdrawal</td>
<td>12</td>
<td>.023</td>
</tr>
<tr>
<td>Paranoia or delusions</td>
<td>81</td>
<td>.331</td>
</tr>
<tr>
<td>Avolition and apathy</td>
<td>16</td>
<td>.810</td>
</tr>
<tr>
<td>Ideas of reference</td>
<td>13</td>
<td>.001</td>
</tr>
<tr>
<td>Poverty of speech and thoughts</td>
<td>0</td>
<td>.083</td>
</tr>
<tr>
<td>Grandiosity</td>
<td>6</td>
<td>.000</td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>9</td>
<td>.146</td>
</tr>
</tbody>
</table>

\(^a\)Using Wilcoxon signed rank test.
NAC in Addictions (Deepmala et al 2015)

- RCTs have looked at a variety of addictions:
  - Cannabis
  - Cocaine
  - Methamphetamine?
  - Nicotine?
  - Pathological Gambling?
- Most consistent demonstrated efficacy is in cocaine addiction

- 4 studies: 3 controlled, 1 uncontrolled
- Consistently positive

Most Noteworthy (La Rowe et al 2013)

- DBPC parallel trial (n=73)
  - 33 subjects administered 2.4g/day for 8 wks
  - 40 subjects administered 1.2g/day for 8 wks
- Improved BSCS, CSSA an days to relapse in individuals abstinent at baseline
A Double-Blind Placebo-Controlled Trial of N-Acetylcysteine in the Treatment of Cocaine Dependence

Steven D. LaRowe, PhD,1,2 Peter W. Kalivas, PhD,3 Joyce S. Nicholas, PhD,3,4 Patrick K. Randall, PhD,2 Pascale N. Mardikian, MD,2 Robert J. Malcolm, MD2

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4Division of Biostatistics and Epidemiology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina

Background: There remains no FDA approved medication for the treatment of cocaine dependence. Preclinical studies and early pilot clinical investigations have suggested that N-acetylcysteine (NAC) may be useful in the treatment of the disorder.

Objective: The present report assessed the efficacy of NAC in the treatment of cocaine dependence.

Methods: Cocaine-dependent volunteers (n = 111) were randomized to receive daily doses of 1,200 mg of NAC, 2,400 mg of NAC, or placebo. Participants were followed for 8 weeks (up to three visits weekly). At each of these visits, urine samples were collected, along with self-reports of cocaine use. Urine samples were assessed for N-acetylcysteine (NAC) may be a candidate medication for the treatment of this disorder. Previous research has shown that following chronic cocaine administration,1−3 basal extracellular glutamate levels within the nucleus accumbens are reduced, which contributes to the reinstatement of cocaine-seeking behaviors in animal models of relapse.1,4 NAC, a cystine prodrug, can prevent reinstated cocaine-seeking behaviors by normalizing basal glutamate levels via activation of the cystine-glutamate exchanger.1,4 Research on the administra-
Quintero 2013 Role of nucleus accumbens glutamatergic plasticity in drug addiction. Neuropsychiatr Dis Treat. 2013;9:1499-1512. Figure 1
Additional Reasons to Use NAC in Addiction

- **In vitro studies suggest that NAC**
  - Restoration of Glt1 transporters & normalization of neuronal membrane potential
  - Antioxidant support via GSH
  - Reverses methamphetamine induced apoptotic cell death
  - Reverses MDMA induced cell death in the hippocampus

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NAC in OCD (Oliver et al 2015)

- 3 combined case reports and studies in OCD and 8 in OCRD always as an adjunct to medications
- Evidence limited by sample size & other methodological issues
- Preliminary evidence supports the use of NAC as an adjunct in moderate to severe OCD & OCRD
- Doses of 2.4g – 3g/day for a minimum of 12 weeks necessary to determine efficacy
N-Acetyl Cysteine in the Treatment of Obsessive Compulsive and Related Disorders: A Systematic Review

Georgina Oliver¹, Olivia Dean¹,²,³, David Camfield⁴,⁵,⁶, Scott Blair–West¹, Chee Ng¹, Michael Berk¹,²,³,⁴, Jerome Sarris¹,⁴

¹Department of Psychiatry, The Melbourne Clinic, The University of Melbourne, Melbourne, ²Innovation in Mental and Physical Health and Clinical Treatment: Strategic Research Centre, School of Medicine, Deakin University, Geelong, ³The Florey Institute of Neuroscience and Mental Health, ⁴Centre for Human Psychopharmacology, Swinburne University, Melbourne, ⁵Illawarra Health & Medical Research Institute (IHMRI), ⁶School of Psychology, University of Wollongong, Wollongong, Australia

Objective: Obsessive compulsive and related disorders are a collection of debilitating psychiatric disorders in which the role of glutamate dysfunction in the underpinning neurobiology is becoming well established. N–acetyl cysteine (NAC) is a glutamate modulator with promising therapeutic effect. This paper presents a systematic review of clinical trials and case reports exploring the use of NAC for these disorders. A further objective was to detail the methodology of current clinical trials being conducted in the area.

Methods: PubMed, Web of Science and Cochrane Library Database were searched for human clinical trials or case reports investigating NAC in the treatment of obsessive compulsive disorder (OCD) or obsessive compulsive related disorders. Researchers with known involvement in NAC studies were contacted for any unpublished data.

Results: Four clinical trials and five case reports/series were identified. Study durations were commonly 12–weeks, using 2,400–3,000 mg/day of NAC. Overall, NAC demonstrates activity in reducing the severity of symptoms, with a good tolerability profile and minimal adverse effects. Currently there are three ongoing randomized controlled trials using NAC for OCD (two adults and one pediatric), and one for excoriation.

Conclusion: Encouraging results have been demonstrated from the few pilot studies that have been conducted. These results are detailed, in addition to a discussion of future potential research.

KEY WORDS: Obsessive–compulsive disorder; Trichotillomania, acetylcysteine; Glutamate; Review, systematic,
## NAC in OCD (Oliver et al 2015)

Table 1. N-acetyl cysteine (NAC) in the treatment of obsessive compulsive disorder (OCD): clinical trials and case reports

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study design</th>
<th>Co-morbidities</th>
<th>NAC dose</th>
<th>Concurrent medication</th>
<th>Outcome measures</th>
<th>Baseline Y-BOCS</th>
<th>Endpoint Y-BOCS</th>
<th>Outcome/effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lafleur et al</td>
<td>2006</td>
<td>Case report (n=1)</td>
<td>MDD</td>
<td>3,000 mg daily, titrated from 600 mg over 6 weeks</td>
<td>SSRI</td>
<td>Y-BOCS and HAM-D</td>
<td>32</td>
<td>9</td>
<td>Large reduction in OCD severity, noted improvement in quality of life</td>
</tr>
<tr>
<td>Van Ameringen et al</td>
<td>2013</td>
<td>Retrospective case reports (n=6)</td>
<td>Tourette’s syndrome, MDD, dysthymia, MDE, panic disorder with agoraphobia social phobia, GAD, substance abuse, excoriation, TTM, ADHD</td>
<td>Mean dose=2,833.3 (±408.2) mg/day, titrated from 500 mg for 8 weeks</td>
<td>SSRI, benzodiazepines, hypnotic, antihistamine, anticonvulsants (glutamate modulating agents)</td>
<td>Y-BOCS, CGI-S and CGH</td>
<td>29.3*</td>
<td>28*</td>
<td>NAC not significant in ameliorating OCD symptoms in 5 of the 6 patients.</td>
</tr>
<tr>
<td>Atshar et al</td>
<td>2013</td>
<td>12 week RDBPCT (n=39)</td>
<td>None recorded</td>
<td>2,400 mg daily, titrated from 600 mg over 2 weeks</td>
<td>SSRIs</td>
<td>Y-BOCS, CGI-S and CGH</td>
<td>27.70 (Tx group): 27.62 (control group)</td>
<td>16.83 (Tx group): 21.89 (control group)</td>
<td>Cohen’s d=1.31</td>
</tr>
</tbody>
</table>

*Pooled data of patients within case series.

ADHD, attention deficit hyperactivity disorder; CGH, Clinical Global Impression Scale-Improvement; CGI-S, Clinical Global Impression Scale-Severity; GAD, generalised anxiety disorder; HAM-D, Hamilton Depression Scale; MMD, major depressive disorder; MDE, major depressive episode; RDBPCT, randomized, double-blind, placebo controlled trial; SSRI, selective serotonin reuptake inhibitor; TTM, trichotillomania; Tx, treatment; Y-BOCS, Yale Brown Obsessive Compulsive Scale.
NAC in Impulse Control or Obsessive Compulsive Related Disorders (Deepmala et al 2015)

- Several small studies, case reports etc. Have used NAC in compulsive:
  - Nail biting
  - Skin picking
  - Trichotillomania
- Mixed findings with approx. 50% studies demonstrating clinical efficacy
**NAC for Prevention?**

- Results of animal studies comparing NAC to imipramine found comparable anti-depressant activity.
- These results also inferred that NAC may play a role in prevention of at risk individuals (rodents reared and kept in isolation) transitioning into active mental illness.
- There is no human data to confirm this at this time.
CASE ILLUSTRATION
22YO MALE DEPRESSION & ANXIETY
Case Illustration

- Anxiety since childhood but particularly marked at 16-17yo both free floating & specifically cue based (social)
  - Diagnosed at 20yo
  - Tx Effexor-XR 225mg
- Ongoing features of anxiety:
  - Diarrhoea, sweating of palms/brow, occasionally palpitations, hx heartburn/reflux
- Depression developed at 18yo
  - Anhedonia, lost interest/desire for surfing
  - Sad & crying ("cut off"), reclusive sadness
Response to Medication

- Before medication strong suicidal ideation
- Effexor has reduced this with no current plan or intention & significantly less crying
- However, initial DASS scores at presentation revealed ongoing severe anxious & depressive features
- Marked withdrawal symptoms from single missed dose “brain zapps” also along hands/arms, altered cognition described as “numb”, itchy skin & nightmares
Case Illustration - Immunity

- Multiple antibiotics in recent years: Wisdom teeth extraction, B.hominis infection, ear infections
- Antibiotics often followed by oral thrush (3 episodes)
- Confirmed past exposure to CMV & EBV
- Reports feeling ‘fluey’ often – fatigued, feverish, sore body but without clear infectious cause
### Haematology

<table>
<thead>
<tr>
<th>Date</th>
<th>17/02/12</th>
<th>07/06/12</th>
<th>10/07/12</th>
<th>26/10/12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time F-Fast</strong></td>
<td>1755</td>
<td>0710 F</td>
<td>1550</td>
<td>1215</td>
</tr>
<tr>
<td><strong>Lab Id.</strong></td>
<td>586549081</td>
<td>588073594</td>
<td>589219057</td>
<td>590127620</td>
</tr>
</tbody>
</table>

#### Haemoglobin
- 150 g/L (135-175)
- 145 g/L (135-175)
- 144 g/L (135-175)
- 140 g/L (135-175)

#### Haematocrit
- 0.46 (0.40-0.54)
- 0.46 (0.40-0.54)
- 0.45 (0.40-0.54)
- 0.43 (0.40-0.54)

#### RCC
- 4.9 10^12/L (4.5-6.5)
- 4.8 10^12/L (4.5-6.5)
- 4.7 10^12/L (4.5-6.5)
- 4.6 10^12/L (4.5-6.5)

#### MCV
- 93 fL (80-100)
- 96 fL (80-100)
- 94 fL (80-100)
- 94 fL (80-100)

#### WCC
- 6.7 10^9/L (3.5-10.0)
- 7.5 10^9/L (3.5-10.0)
- 8.5 10^9/L (3.5-10.0)
- 6.5 10^9/L (3.5-10.0)

#### Neutrophils
- 3.87 10^9/L (1.5-6.5)
- 4.85 10^9/L (1.5-6.5)
- 5.74 10^9/L (1.5-6.5)
- 4.01 10^9/L (1.5-6.5)

#### Lymphocytes
- 1.63 10^9/L (1.0-4.0)
- 1.90 10^9/L (1.0-4.0)
- 1.42 10^9/L (1.0-4.0)
- 1.83 10^9/L (1.0-4.0)

#### Monocytes
- 1.02 10^9/L (0-0.9)
- 0.60 10^9/L (0-0.9)
- 1.29 10^9/L (0-0.9)
- 0.58 10^9/L (0-0.9)

#### Eosinophils
- 0.09 10^9/L (0-0.6)
- 0.11 10^9/L (0-0.6)
- 0.04 10^9/L (0-0.6)
- 0.09 10^9/L (0-0.6)

#### Basophils
- 0.10 10^9/L (0-0.15)
- 0.01 10^9/L (0-0.15)
- 0.01 10^9/L (0-0.15)
- 0.02 10^9/L (0-0.15)

#### Platelets
- 322 10^9/L (150-400)
- 306 10^9/L (150-400)
- 281 10^9/L (150-400)
- 328 10^9/L (150-400)

#### ESR
- 9 mm/h (1-12)
- 2 mm/h (1-12)
- 2 mm/h (1-12)

### CRP

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#### CRP
- 2 mg/L (0-10)
- <1 mg/L (0-10)
- <1 mg/L (0-10)
Case Illustration

- First remedy started:
  - NAC 2g/day
- **Patient reports even within a week “fog is lifting”**
- Family reports “Different boy”
- **In combination with other whole health approaches (GIT esp) but no other specific mental health interventions within a year patient able to stop Effexor altogether**
- In first r’ship, has bought a house, doing well
The clinical knack of NAC

- Rapid GIT absorption from oral doses – $C_{\text{max}}$ is achieved in 1-2hrs

- Relatively low bioavailability from oral dosing i.e. 4-10% due to rapid deactylation in the intestinal mucosa & first pass liver metabolism

- Metabolised in liver to Cysteine $\rightarrow$ terminal half-life 6hrs

- Liver then produces GSH – replenishes its GSH stores before released into circulation

- **Distribution – rat studies only**
  - Highest concentrations kidney, liver then adrenal, lung, spleen, blood muscle, brain.

- **Unclear method of cellular uptake & BBB transfer for NAC itself with contradictory findings**
  - NAC taken up intact when cell membranes under oxidative stress?
  - Always converted to cysteine prior to uptake?

- **Renal clearance may account of approx. 30%**
Dosing & Compliance

- The majority of studies to date in mental health have used 2g/d however, new studies are starting to examine higher doses again particularly in more severe glutamate excess e.g. 4g/d

- Strong sour flavour – many patients actually report liking this especially all the sour lolly lovers!

- Combines well with cranberry or pomegranate juice for those that require some masking of this flavour
Interactions

- Most interactions occur only with IV administration:
  - Potentiation of Nitroglycerine
  - Chelation of zinc

- Via GSH S transferases supports the detoxification of numerous drugs and xenobiotics
  - doesn’t alter drug pharmacokinetics unless taken in IV in large doses
NAC’s Adverse Effects

- “NAC has a long-established safety record in adults and children, with FDA approval since 1963” (McClure et al 2014)

- NAC has relatively low toxicity and is associated with mild side effects such as nausea, vomiting, rhinorrhea, pruritus, flushing, constipation, tachycardia (Millea 2009, Samuni et al 2013)

- NAC can complex with zinc (demonstrated with IV use) (Stargrove 2008) – no evidence from oral doses
Theoretical Contraindications – in vitro evidence

- **Smokers** – past or present?
  - Increased progression of lung tumours in mice fed a diet rich in NAC and Vitamin E
    (Sayin et al 2014)

- Patients with **peptic ulcers** (Ziment 1988)

- Patients with **Candida infections** (Giordani et al 2002, Yilmaz & Celik 2003)
The take-home message according to Samuni et al (Biochim Biophys Acta. 2013 Aug;1830(8):4117-29.)

“The field of neuropsychiatry provides an excellent opportunity to illustrate the mechanistic complexity of NAC. This is mainly because many neuropsychiatric disorders have a multi-factorial etiology that involves inflammatory pathways, glutamatergic transmission, oxidative stress, GSH metabolism, mitochondrial function, neurotrophins and apoptosis”
References


