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- ***N-Acetyl Cysteine*** (NAC; brand name of nebulized form is Mucomyst)
  - General
    - Go to www.vitacost.com and search for "NAC Source Naturals"; discuss with Dr. Wilson, but usual dose is two 1000 mg tabs/day
    - Glutathione is the major antioxidant in the brain that plays a key role in defending against oxidative damage
    - Glutathione appears to play an active role in the neuroprotective effects of lithium and Depakote
    - Glutamate modulator
    - Acts on glutamate/cysteine exchanger
    - NAC is an orally bioavailable precursor to glutathione; 90% is metabolized by the liver
    - 2-8 grams/day
    - Half-life 5.6 hours (11 hours in neonates)
    - FDA-approved since 1963
  - Used for:
    - Bipolar disorder and schizophrenia
      - 2011-2012: study in bipolar depression
      - Berk et al, 2007, RCT, DB, multicenter trial, as an adjunct in bipolar disorder, 75 adults, 1 gram twice-a-day, 6 months: safe and effective; at the end of 6 months, there was a 4 week washout period where NAC was tapered off during which all positive effects were lost
      - Berk et al, 2007, RCT, DB, multicenter trial, as adjunct in schizophrenia, 140 adults, 1 gram twice-a-day, 6 months: safe and effective; side effect: mild nausea
      - Geller et al, 1998
      - Can help in treatment of mania as well
      - Can take 4-8 weeks for benefits
    - Unipolar depression, three studies 2005-2013
      - Cornelius et al, 2005
      - Cornelius et al, 2010
      - Levin et al, 2013
    - Behavioral disturbance in autism, RCT, 33 youth aged 3.2-10.7 (Hardan et al, 2012)
      - 3000 mg/day
      - Well tolerated, limited side effects
      - Significant improvement in irritability
    - Trichotillomania

- positive randomized controlled study in adults (with NAC 3+ times more effective than placebo
- negative study in children (Bloch et al, 2013)
  - Side effects:
    - Nausea 30% vs. 63% placebo
    - Diarrhea 5% (1 subject) vs. 5% placebo
    - Fatigue 0% vs. 11% placebo
    - Insomnia 0% vs. 5% placebo
    - Rash 5% (1 subject) vs. 0% placebo
    - Depression 5% (1 subject) vs. 0% placebo

- Nail biting (case reports)
- ADHD, several studies 2005-2010
  - Sohlkhah et al, 2005
  - Riggs et al, 2007
  - Thurstone et al, 2010
  - McRae et al, 2010
  - Riggs et al, 2010
- OCD
  - See below
- Cocaine dependence
  - Decreases propensity to seek cocaine
  - No effect on reinforcing properties of cocaine
  - Can decrease tendency to relapse
- Marijuana dependence in teens (Grey et al, 2012)
  - Over 8 weeks
  - 1200-2400 mg/day
  - Well tolerated, effective
- Other substance use disorders
- Kidney protection during certain imaging procedures or to help prevent/minimize kidney damage from certain medications
- Pulmonary conditions
  - Cystic fibrosis
  - Emphysema/COPD
  - Insterstitial lung disease
  - Bronchitis/pneumonia/TB/bronchiectasis
- Liver protection (e.g., in Tylenol overdose)
- Polycystic ovarian syndrome (helped decrease BMI as well as other symptoms of PCOS)
- Diabetes
- Lupus
- AIDS (helps immune functioning)
- Influenza (in animal and studies)
- Blepharitis
- Autism (possibly)

        - Hearing loss (in animals)
        - Dementia (possibly, when used with B vitamins)
    - Side effects and risks
        - Nausea, vomiting (at mega doses)
        - Diarrhea
        - Rotten egg smell (from pills)
        - If used in nebulizer
            - Cough
            - Bronchospasm/anaphylaxis
            - Runny nose
        - Rash/urticarial
            - Allergic reaction is more notable in i.v. administration of NAC and can include, especially with repeated dosing
                - Bronchospasm/difficulty breathing
                - Drop in blood pressure
                - Rash
                - Angioedema
                - Nausea/vomiting
        - Very large doses in mice (at doses dramatically higher than those used in humans)
            - Increase blood pressure in lungs (pulmonary hypertension)
    - Drug-drug interactions
        - Decrease in carbamazepine level
        - Exaggerated hypotensive reaction to nitroglycerine

N-Acetylcysteine in depressive symptoms and functionality: a systematic review and meta-analysis
Brisa S Fernandes, Olivia M Dean, Seetal Dodd, Gin S Malhi, Michael Berk
Journal of Clinical Psychiatry 2016, 77 (4): e457-66

OBJECTIVE: To assess the utility of N-acetylcysteine administration for depressive symptoms in subjects with psychiatric conditions using a systematic review and meta-analysis.
DATA SOURCES: A computerized literature search was conducted in MEDLINE, Embase, the Cochrane Library, SciELO, PsycINFO, Scopus, and Web of Knowledge. No year or country restrictions were used. The Boolean terms used for the electronic database search were (NAC OR N-acetylcysteine OR acetylcysteine) AND (depression OR depressive OR depressed) AND (trial). The last search was performed in November 2014.
STUDY SELECTION: The literature was searched for double-blind, randomized, placebo-controlled trials using N-acetylcysteine for depressive symptoms regardless of the main psychiatric condition. Using keywords and cross-referenced bibliographies, 38 studies were identified and examined in depth. Of those, 33 articles were rejected because inclusion criteria were not met. Finally, 5 studies were included.
DATA EXTRACTION: Data were extracted independently by 2 investigators. The primary outcome measure was change in depressive symptoms. Functionality, quality of life, and manic and anxiety symptoms were also examined. A full review and meta-analysis were performed. Standardized mean differences (SMDs) and odds ratios (ORs) with 95% CIs were calculated.
RESULTS: Five studies fulfilled our inclusion criteria for the meta-analysis, providing data on 574 participants, of whom 291 were randomized to receive N-acetylcysteine and 283 to placebo. The follow-up varied from 12 to 24 weeks. Two studies included subjects with bipolar disorder and current depressive symptoms, 1 included subjects with MDD in a current depressive episode, and 2 included subjects with depressive symptoms in the context of other psychiatric conditions (1 trichotillomania and 1 heavy smoking). Treatment with N-acetylcysteine improved depressive symptoms as assessed by Montgomery-Asberg Depression Rating Scale and Hamilton Depression Rating Scale when compared to placebo (SMD = 0.37; 95% CI = 0.19 to 0.55; P < .001). Subjects receiving N-acetylcysteine had better depressive symptoms scores on the Clinical Global Impressions-Severity of Illness scale at follow-up than subjects on placebo (SMD = 0.22; 95% CI = 0.03 to 0.41; P < .001). In addition, global functionality was better in N-acetylcysteine than in placebo conditions. There were no changes in quality of life. With regard to adverse events, only minor adverse events were associated with N-acetylcysteine (OR = 1.61; 95% CI = 1.01 to 2.59; P = .049).
CONCLUSIONS: Administration of N-acetylcysteine ameliorates depressive symptoms, improves functionality, and shows good tolerability.

N-Acetylcysteine in the Treatment of Pediatric Tourette Syndrome: Randomized, Double-Blind, Placebo-Controlled Add-On Trial
Michael H Bloch, Kaitlyn E Panza, Alisa Yaffa, Pedro G Alvarenga, Ewgeni Jakubovski, Jilian M Mulqueen, Angeli Landeros-Weisenberger, James F Leckman
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BACKGROUND: Current pharmacological treatments for Tourette Syndrome (TS), such as antipsychotic agents and α-2 agonists, are moderately effective in the treatment of tics, but have substantial side effects that limit their use. N-acetylcysteine (NAC) modulates glutamatergic systems, and has been used safely as an antioxidant agent with minimal side effects for decades. NAC has been increasingly studied for the treatment of other obsessive-compulsive spectrum disorders. We aim to examine the efficacy of NAC for the treatment of pediatric TS in a double-blind, placebo-controlled, add-on study.
METHODS: Thirty-one children and adolescents 8-17 years of age with TS were randomly assigned to receive NAC or matching placebo for 12 weeks. Our primary outcome was change in severity of tics as measured by the Yale Global Tic Severity Scale (YGTSS), Total tic score. Secondary measures assessed comorbid obsessive-compulsive disorder (OCD), depression, anxiety, and attention-deficit/hyperactivity disorder (ADHD). Linear mixed models in SAS were used to examine differences between NAC and placebo.
RESULTS: Of 31 randomized subjects, 14 were assigned to placebo (two females; 11.5 + 2.8 years) and 17 to active NAC (five females; 12.4 + 1.4 years) treatment. No significant difference between NAC and placebo was found in reducing tic severity or any secondary outcomes.
CONCLUSIONS: We found no evidence for efficacy of NAC in treating tic symptoms. Our findings stand in contrast to studies suggesting benefits of NAC in the treatment of other obsessive-compulsive spectrum disorders in adults, including OCD and trichotillomania, but are similar to a recent placebo-controlled trial of pediatric trichotillomania that found no benefit of NAC.

Antioxidant treatment of the glutathione deficiency in bipolar disorder with n-acetyl cysteine: a double blind randomized placebo controlled trial. M Berk DL Copolov a, 0 Dean a,b K Lu a C S Jeavons', I Schapkaitz " MA Hunt Al Bush **Background:** Oxidative stress is documented to occur in bipolar disorder. Existing mood stabilisers have effects on oxidative biology. Glutathione is the body's major endogenous free radical scavenger. N-acetyl cysteine (NAC) is a tolerable, orally bioavailable precursor of glutathione. **Methods:** In a randomized, double-blind, multi-center, placebo-controlled study, we evaluated 75 individuals with bipolar disorder who were treated with NAC (1 gram BID) as an add-on to their usual mood stabilizer medication over a 6 month period, followed by a 4 (± 2) week washout. At the one month post discontinuation visit there was no longer any significant difference between the groups on any of the outcome measures. There were no significant between group differences in treatment emergent adverse events. A calculation of effect sizes revealed significant improvements in the medium range, from 0.3930 to 0.64. **Conclusions:** NAC is a novel, efficacious and tolerable therapeutic option for bipolar disorder, which is safe affordable and readily available. In particular, it ameliorates depressive symptoms in the maintenance phase, addressing a major unmet need.

A Double-Blind, Randomized, Controlled Pilot Trial of N-Acetylcysteine in Veterans With Posttraumatic Stress Disorder and Substance Use Disorders
Sudie E Back, Jenna L McCauley, Kristina J Korte, Daniel F Gros, Virginia Leavitt, Kevin M Gray, Mark B Hamner, Stacia M DeSantis, Robert Malcolm, Kathleen T Brady, Peter W Kalivas
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OBJECTIVE: The antioxidant N-acetylcysteine is being increasingly investigated as a therapeutic agent in the treatment of substance use disorders (SUDs). This study explored the efficacy of N-acetylcysteine in the treatment of posttraumatic stress disorder (PTSD), which frequently co-occurs with SUD and shares impaired prefrontal cortex regulation of basal ganglia circuitry, in particular at glutamate synapses in the nucleus accumbens.
METHODS: Veterans with PTSD and SUD per DSM-IV criteria (N = 35) were randomly assigned to receive a double-blind, 8-week course of N-acetylcysteine (2,400 mg/d) or placebo plus cognitive-behavioral therapy for SUD (between March 2013 and April 2014). Primary outcome measures included PTSD symptoms (Clinician-Administered PTSD Scale, PTSD Checklist-Military) and craving (Visual Analog Scale). Substance use and depression were also assessed.
RESULTS: Participants treated with N-acetylcysteine compared to placebo evidenced significant improvements in PTSD symptoms, craving, and depression (β values < -0.33; P values < .05). Substance use was low for both groups, and no significant between-group differences were observed. N-acetylcysteine was well tolerated, and retention was high.

CONCLUSIONS: This is the first randomized controlled trial to investigate N-acetylcysteine as a pharmacologic treatment for PTSD and SUD. Although preliminary, the findings provide initial support for the use of N-acetylcysteine in combination with psychotherapy among individuals with co-occurring PTSD and SUD.

Randomized, Double-Blind, Placebo-Controlled Trial of N-Acetylcysteine Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder

Daniel L C Costa, Juliana B Diniz, Guaraci Requena, Marinês A Joaquim, Christopher Pittenger, Michael H Bloch, Euripedes C Miguel, Roseli G Shavitt

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OBJECTIVE: To evaluate the efficacy of serotonin reuptake inhibitor (SRI) augmentation with N-acetylcysteine (NAC), a glutamate modulator and antioxidant medication, for treatment-resistant obsessive-compulsive disorder (OCD).

METHODS: We conducted a randomized, double-blind, placebo-controlled, 16-week trial of NAC (3,000 mg daily) in adults (aged 18-65 years) with treatment-resistant OCD, established according to DSM-IV criteria. Forty subjects were recruited at an OCD-specialized outpatient clinic at a tertiary hospital (May 2012-October 2014). The primary outcome measure was the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores. To evaluate the variables group, time, and interaction effects for Y-BOCS scores at all time points, we used nonparametric analysis of variance with repeated measures. Secondary outcomes were the severity scores for anxiety, depression, specific OCD symptom dimensions, and insight.

RESULTS: Both groups showed a significant reduction of baseline Y-BOCS scores at week 16: the NAC group had a reduction of 4.3 points (25.6 to 21.3), compared with 3.0 points (24.8 to 21.8) for the placebo group. However, there were no significant differences between groups ($P = .92$). Adding NAC was superior to placebo in reducing anxiety symptoms ($P = .02$), but not depression severity or specific OCD symptom dimensions. In general, NAC was well tolerated, despite abdominal pain being more frequently reported in the NAC group (n [%]: NAC = 9 [60.0], placebo = 2 [13.3]; $P < .01$).

CONCLUSIONS: Our trial did not demonstrate a significant benefit of NAC in reducing OCD severity in treatment-resistant OCD adults. Secondary analysis suggested that NAC might have some benefit in reducing anxiety symptoms in treatment-resistant OCD patients.