Supplements in Psychiatry: N-Acetylcysteine, Omega-3 Fatty Acids & Melatonin

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N-Acetylcysteine = NAC

NAC modulates Neurotransmitters:

1. Glutamate

- NAC ↑ Cysteine levels
- Cysteine exchanged by glial cells for glutamate
- Glutamate stimulates (-) metabotropic receptors which ↓ synaptic release of glutamate

2. Dopamine

- NAC alters Dopamine release in striatum
- NAC facilitates Dopamine release in mesolimbic area (frontal lobes)

NAC also helps protect cells from oxidative stress

NAC in Substance Use Disorders

Role of oxidative stress established in pathophysiology of addictions:

Cannabis Studies

Open Labile

N = 24 cannabis dependent adults

NAC dose 2400 mg per day

Decreased days/week use and “number of hits” per use

(Gray et al. Am J Addiction 2010)

NAC in Substance Use Disorders

Nicotine Dependence

1. Placebo Controlled RCT

N = 29 nicotine dependent adults

NAC dose 2400 mg per day

Inconclusive

(Knackstedt et al. Biological Psychiatry 2009)

2. Double Blind Placebo Control RTC looking at inflammatory biomarkers

N = 41 adults

NAC dose 1200 mg per day for 6 months

NAC resulted in ↓ levels of Inflammatory biomarkers

(Van Schooten et al. Cancer Epidemiology Biomarkers 2002)

NAC in Substance Use Disorders

Cocaine Dependence

2 small placebo controlled crossover studies

N = 13 & N = 15

NAC dose 2400 mg per day or Placebo for 2 days

NAC correlated with significant ↓ craving, withdrawal and self-reported use

(LaRowe et al. Am J Addictions 2006)

Follow up study N = 23 for 4 weeks

↓ $ spent on cocaine; number of days of use

(Mardikian et al. Prog Neuropsychopharm Biol Psychiatry 2007)

NAC in Impulse Control Disorders

Pathological Gambling

Open labile

N = 29 adults with pathologic addiction to gambling

NAC dose 1800 mg per day for 8 weeks

16/29 had significant reduction in gambling behavior

N = 13 of responders then randomized to NAC or Placebo for 6 weeks

83% of NAC versus 28% of placebo remained responders

(Grant et al. Biological Psychiatry 2007)

NAC in Impulse Control Disorders

Trichotillomania

- Double Blind Placebo Controlled RCT
- N = 50 (45 women and 5 men)
- NAC dose 1200 mg per day for 6 weeks followed by NAC dose of 2400 mg per day for 6 additional weeks
- Effects seen at week 9 on average
- ↓ hair pulling behaviors

(Grant et al. Arch Gen Psychiatry 2009)

Also some evidence NAC (2000 mg per day) decreases nail biting

(Berk et al. CNS Spectrum 2009)

NAC in Schizophrenia

Double blind placebo controlled randomized study

- N = 140 adults with schizophrenia (60% on clozapine)
- NAC dose 1000 mg twice per day for 6 months
- 60% completed trial
- Improvement seen in negative symptoms; global functioning; abnormal movements and akathesia
- Effects lost 1 month after discontinuing NAC

(Berk et al. Biological Psychiatry 2008)

NAC in Bipolar Disorder

Double blind placebo controlled randomized study

- N = 75 adults with Bipolar Affective Disorder
- NAC dose 2000 mg per day for 6 months
- 64% completed trial
- Improvement seen in depressive symptoms – large effect size
- Effects lost after discontinuing NAC

(Berk et al. Biological Psychiatry 2008)

NAC in Autism Disorder

Double Blind Placebo Controlled Study

- N = 33 (31 males and 2 females)
- Age range 3.2 years – 10.7 years
- NAC doses: 900 mg/day for 4 weeks then 1800 mg/day for 4 weeks then 2700 mg/day for 4 weeks
- NAC treatment associated with significant improvement in irritability and stereotypic/repetitive behaviors

(Hardan et al. Biological Psychiatry 2012)

Omega-3 Fatty Acids (Ω - 3)

Studies in patients with depression supported by epidemiological evidence showing that international variations in the prevalence of depression correlated closely with fish consumption in the national diet.

(Hibbeln JR, Lancet 1998)

Also evidence fish consumption correlated with homicide rates and post-natal depression.

(Hibbeln JR, World Rev Nut & Diet 2001; J Affective Disor 2002)

Omega-3 Fatty Acids (Ω - 3)

Ω3FA

- Cannot be synthesized – must come from diet and are have anti-inflammatory properties
- Ω6FA much more common in western diet and is pro-inflammatory
- Higher ratios of Ω6FA/ Ω3FA promotes neuroinflammation
- ↑ Ω3FA concentrations alter cell membrane fluidity and proteins (receptors) in the membrane
- ↑ Ω3FA concentrations have been shown to affect serotonin and dopamine neurotransmission especially in the frontal cortex

Ω3FA and ADHD

Studies of youth with ADHD have demonstrated alterations in Ω3FA concentrations in plasma and erythrocyte membranes.

Meta-analysis of children with ADHD and Ω3FA supplementation:

- Included 10 randomized placebo-controlled trials
- N = 699 youth
- Duration range 4 weeks to 4 months
- EPA doses ranged from 0 mg to 750 mg per day
- DHA doses ranged from 0 to 480 mg per day

Ω3FA and ADHD

Meta-analysis of children with ADHD and Ω3FA supplementation:

- Small but significant effect size (.31) favoring Ω3FA
- Similar effects for both inattention and hyperactivity
- Higher doses of EPA within supplements were significantly associated with increased efficacy

(Bloch et al. Journal of Am Acad of Child & Adol Psychiatry 2011)

Intervention Studies - Pharmacology

Omega-3 Fatty Acids (PUFA)

(Amminger, Arch Gen Psych 2010)

N = 81 Help Seeking Prodromal Patients (ages 12 to 25)

PUFA vs. Placebo (3 months treatment/9 additional months F/U)

12 month Conversion Rates:

- 2/41 (5%) PUFA
- 11/40 (28%) Placebo

Melatonin

- Neurohormone secreted by the Pineal gland
- Discovered in 1958 by dermatologist and named due to effects on skin melanocytes
- Concerned with biological timing
- Secreted at night & associated with sleep, lowered core body temperature, and other night time events.
- The period of melatonin secretion has been described as ‘biological night’

Melatonin

- Main function in mammals is to ‘transduce’ information about the length of the night, for the organization of day-length dependent functions

- Exogenous melatonin has acute sleepiness-inducing and temperature-lowering effects during ‘biological daytime’

- It is most effective around dusk and dawn

- it will shift the phase of the human circadian clock (sleep, endogenous melatonin, core body temperature, cortisol) to earlier (advance phase shift) or later (delay phase shift) times.

Arendt et al. Sleep Medicine Reviews (2005)

Melatonin – Jet Lag/Shift Work

For Eastern Travel:

- Want to phase advance sleep cycle
- 1 – 5 mg Melatonin at 1600 (departing time zone) for 3 nights
- 1 – 5 mg Melatonin 2 hrs. before sleep in new time zone

For Westward Travel:

- Want to phase delay sleep cycle
- 1 – 5 mg Melatonin at bedtime (departing time zone) for 3 nights
- 1 – 5 mg Melatonin 2 hrs. before sleep in new time zone

Arendt et al. Sleep Medicine Reviews (2005)

Melatonin – Blindness

Appears to be useful in some individuals with blindness

Arendt et al. Sleep Medicine Reviews (2005)

Melatonin – Elderly

Age-related changes in circadian system occur

Age-related sleep changes:

- ↑ sleep latency
- ↓ sleep efficiency
- ↑ night and early morning awakenings
- More problems falling back asleep after awakenings

Melatonin (dose ranges .5 to 6 mg) times 30 minutes to 2 hours prior to sleep onset have been effective (inconsistent in research findings)

Melatonin – ADHD

- Initial insomnia common problem with children with ADHD
- 30% of medication-free children with ADHD have chronic sleep-onset insomnia
- Stimulants may increase sleep latency by as much as 30 minutes
- 60% of children have some (many transient) problems with initial insomnia
- Children with ADHD are 2-4X more likely to be prescribed sleep medications compared with children without ADHD

Melatonin – ADHD

- Randomized Double Blind Placebo Controlled Trial
- N = 105 Medication-Free Children with ADHD with Sleep Onset Insomnia (SOI)
- SOI defined:
  - Complaints of sleep-onset problems by parents and/or child
  - Occur at least 4 days/week for 1 year
  - Sleep onset later than 8:30 PM for 6 year old and 15 minutes per year for older children
  - Average sleep latency exceeding 30 minutes
- Ages 6 -12 years
- Melatonin dose was 3mg (< 40 kg) or 6 mg (> 40 kg) for 4 weeks

Melatonin – ADHD

- Sleep onset advanced by 27 minutes with Melatonin
- Sleep onset delayed by 10 minutes with placebo
- Total asleep time increased with Melatonin by 20 minutes
- Total asleep time decreased 14 minutes with placebo
- No effect of improved sleep on ADHD behaviors, cognition, quality of life
- No adverse events