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Chronic *N*-acetylcysteine after cocaine self-administration produces enduring reductions in drug-seeking

A key feature of successful pharmacological treatment of psychostimulant addiction is the prevention of relapse following abstinence. During abstinence from cocaine, basal corticostriatal glutamate is dysregulated and reversal of this deficit has become a target for potential addiction pharmacotherapy. The glutamate prodrug, *N*-acetylcysteine (NAC), drives the cystine-glutamate antiporter and restores basal glutamate levels after cocaine self-administration, thus normalizing compromised corticostriatal function (Moussawi *et al*, 2011). NAC does not alter the reinforcing mechanisms associated with cocaine, but prevents drug-seeking by a reduction or reversal of the neuroplasticity required for reinstatement to cocaine-seeking (Amen *et al*, 2011; Madayag *et al*, 2007; Moussawi *et al*, 2011). For example, repeated NAC prevented cocaine-induced changes in cystine transport, basal glutamate levels, and cocaine-evoked glutamate release in the nucleus accumbens (Madayag *et al*, 2007). Further, chronic NAC restored synaptic strength as determined by both presynaptic glutamate release and postsynaptic potentiation in prefrontal projections to the nucleus accumbens (Moussawi *et al*, 2011).

These neurobiological normalizations parallel behavioral measures of decreased cocaine-seeking well into extended periods of abstinence. Following cocaine self-administration, chronic NAC (100 mg/kg) administered before daily extinction trials and during abstinence reduced cocaine-primed reinstatement, and a combination of cocaine + cue-induced reinstatement (Moussawi *et al*, 2011; Reichel *et al*, 2011). NAC not only showed efficacy when biologically available during testing, but also produced persistent decreases in cocaine-seeking 2 weeks later, when neither cocaine nor NAC was biologically present. These lasting reductions in cocaine-seeking after discontinuation of pharmacotherapy constitute a critical achievement for potential clinical efficacy of an antirelapse medication.

Although it is difficult to extrapolate preclinical findings to cocaine-dependent patients, the use of NAC has recently crossed the translational bridge from preclinical animal models of addiction to clinical trials. To date, NAC has shown promising results in subjects with cocaine, heroin, and tobacco addiction. An initial pilot open-label study demonstrated that NAC was well tolerated at doses of 1200, 2400, and 3600 mg/day. Of the subjects that finished the study, most terminated or reduced cocaine use during the treatment (Mardikian *et al*, 2007). NAC also decreased desire for cocaine in a cue-reactivity procedure as measured by psychophysical and subjective data in response to slides depicting cocaine and cocaine use (LaRowe *et al*, 2007). Additionally, recent data indicate that repeated administration (4 days) of NAC (1200–2400 mg/day) to cocaine-dependent participants reduced craving following an experimenter-delivered IV injection of cocaine (Amen *et al*, 2011).

Although there are no approved medications for cocaine or other psychostimulant addictions, converging lines of research fully support the clinical utility of NAC for treatment of cocaine addiction. First, behavioral pharmacology studies demonstrate that NAC persistently decreases both conditioned cue-induced and drug-primed reinstatement to cocaine seeking. Second, clinical findings report reduced cocaine craving in humans. And third, the neurobiological mechanisms by which NAC exerts its lasting effects on glutamate function have been identified. Further characterization of these mechanisms in appropriate animal models and clinical laboratories will lead to improved medications for the treatment of multiple forms of addiction.

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DISCLOSURE
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Methamphetamine-Induced Oxidation of Proteins and Alterations in Protein Processing

Methamphetamine (METH) is a CNS stimulant with high potential for abuse.