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An open-label trial of *N*-acetylcysteine for the treatment of cocaine dependence: A pilot study

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Abstract

Recent preclinical studies implicate *N*-acetylcysteine (NAC), a cysteine prodrug, as a potential medication for preventing relapse to cocaine use; however, little is known about the safety and tolerability of NAC in cocaine-dependent subjects in an outpatient setting. This pilot study examines the safety and tolerability of 3 doses of NAC for the treatment of cocaine dependence. Twenty three treatment-seeking cocaine-dependent patients participated in a 4-week medication trial and received NAC at doses of 1200 mg/day, 2400 mg/day or 3600 mg/day. Results suggested that the three doses were well tolerated. Overall, the retention rates appeared to favor higher doses of NAC (2400 mg/day and 3600 mg/day). The majority of subjects who completed the study ($n=16$) either terminated use of cocaine completely or significantly reduced their use of cocaine during treatment. Overall the findings suggest that it is feasible to treat cocaine-dependent treatment seekers with *N*-acetylcysteine on an outpatient basis.

Keywords: Cocaine dependence; *N*-acetylcysteine; Open-label trial; Pilot study

1. Introduction

Although overall rates of cocaine use and the number of individuals seeking treatment for cocaine dependence have declined over the last decade, cocaine is still abused by about 14 million people worldwide and is second only to heroin in terms of treatment demand (United Nations, Office of Drugs and Crime, 2003). Cocaine abuse is associated with serious physical, psychiatric and social problems. Acute cocaine use can result in serious vascular adverse events (Brust and Richter, 1977; Schwartz and Cohen, 1984; Cregler and Mark, 1986). Cocaine use is associated with substance-induced mood and psychotic disorders and expression of suicidal ideation (Garlow et al., 2005). There is a strong association with cocaine use and criminal activity (Conaboy, 1995). While some medications have shown promise in the treatment of cocaine dependence, including Disulfiram (Caroll et al., 1998), Baclofen (Shoptaw et al., 2003), Topiramate (Kampman et al., 2004), and Modafinil (Dackis et al., 2005), none have received FDA approval. The identification of a pharmacological treatment that can effectively complement psychosocial treatment for cocaine dependence would constitute major public health advancement.

Recent preclinical work has indicated that basal levels of glutamate within the nucleus accumbens are lower in rats treated chronically with cocaine (Pierce et al., 1996; Baker et al., 2003; McFarland et al., 2003). The lower levels of basal glutamate in the accumbens are associated with the ability of cocaine to reinstate cocaine-seeking behavior (i.e. restore lever pressing) long after such behavior has been extinguished (Baker

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et al., 2003; McFarland et al., 2003). Cysteine prodrugs, such as *N*-acetylcysteine (NAC), restore basal levels of glutamate within the accumbens by introducing extracellular cystine, which is "exchanged" for intracellular glutamate (Baker et al., 2003) via cystine/glutamate antiporters. The restoration of glutamate levels that results from this exchange produces a reduction of reinstatement of cocaine-seeking behavior (Baker et al., 2003). These findings suggest that NAC may be a useful pharmacological treatment for cocaine dependence.

Worldwide, NAC is available in intravenous, oral, and nebulizer forms. In the United States, NAC is available as a prescription product in a liquid form for nebulizer use in cystic fibrosis, and is frequently used in other chronic pulmonary conditions (Grandjean et al., 2000). It is also available in oral and intravenous forms to treat acetaminophen overdose (Smilkstein et al., 1988; Mucomyst, 2005). Finally, *N*-acetylcysteine is sold orally as an over-the-counter product in health food stores, usually promoted as improving overall mental function.

In general, NAC appears to be safe and well tolerated, even at relatively high doses. Used intravenously (IV), a patient undergoing treatment for acetaminophen overdose typically receives a loading dose of NAC that ranges between 140–150 mg/kg, or 9800–10,500 mg for a typical 70 kg adult (Mucomyst, 2005). Patients receiving oral NAC for acetaminophen overdose receive a loading dose comparable to NAC administered IV (~10,000 mg). Overall, side effects have a fairly low prevalence rate, with mild symptoms (e.g. headache, lethargy, fever, skin rash) occurring approximately 1–5% of the time, and moderate symptoms (e.g. increased blood pressure, chest pain, hypertension, rectal bleeding, respiratory distress) occurring less than 1% (Miller and Rumack, 1983).

While the bulk of the data suggest that NAC is generally well tolerated and safe, there are reports of (albeit rare) severe reactions (Death after *N*-acetylcysteine, 1984; Hershkovitz et al., 1996) that necessitate an investigation of the safety and tolerability of NAC in cocaine-dependent individuals before large-scale treatment studies are conducted.

Recently, we completed a double-blind placebo controlled crossover inpatient safety and tolerability study with thirteen non-treatment seeking cocaine-dependent individuals. Subjects were hospitalized and received 600 mg oral NAC, twice daily (an average daily dosage of 1200 mg) over two days (4 doses total) or placebo. Subjects completed a second stay that was identical except they were crossed over to receive the opposite medication condition. Subjects were evaluated for side effects, tolerability, self-reported craving, and symptoms associated with cocaine abstinence (LaRowe et al., 2006). Results suggested that NAC was safe and well tolerated. The number of side effects reported in the NAC condition did not differ significantly from placebo (20 v. 13), and side effects were mild (e.g. pruritus, headache, diarrhea, abdominal cramps). Most importantly, no serious or unexpected side effects were noted. Throughout the course of the 3-day study, approximately every 12 h, subjects rated their on-going cravings for cocaine, and there was a trend for reduced craving in the NAC condition. In addition, ratings of cocaine-related abstinence symptoms were collected before and after each hospital stay, and there was evidence for a reduction of these symptoms within the NAC condition, but not within placebo.

While the initial safety and tolerability results were encouraging, the study was limited by a small sample size ($n=13$) and investigated only one dose (1200 mg/day). Further, because the earlier trial was performed on an inpatient basis, it could not be determined from the inpatient results whether treatment-seeking patients taking NAC would be willing and able to follow a treatment regimen involving multiple daily doses for several weeks on an outpatient basis. Given the encouraging initial inpatient results, combined with the extensively documented safety record of NAC, it was determined that an outpatient open-label safety trial would be a suitable approach for addressing these issues.

The current study was a four-week, open-label pilot study that assessed patients taking the following three doses of NAC: 1200 mg/day (600 mg BID), 2400 mg/day (1200 mg BID) and 3600 mg/day (1200 mg TID). The primary outcome measures of interest were overall tolerability and safety of medication, retention and compliance. Secondary outcome measures included self-reported cocaine use (as verified by urine drug screens), and self-reported cocaine abstinence symptoms.

2. Method

2.1. Subjects

Subjects were required to be treatment-seeking males and females (18 to 60 years) who met DSM-IV criteria for cocaine dependence (APA, 1994). Subjects were excluded if they met dependence criteria for any substance other than cocaine, alcohol, nicotine, or marijuana. Alcohol-dependent subjects requiring medical detoxification were excluded as well. Other exclusionary criteria included: serious medical conditions, major axis I psychiatric disorders that would impair ability to participate safely in the study, or a past medical history of asthma or seizures. Subjects who had recently used medications (<14 days) felt to be hazardous if taken with NAC (e.g. carbamazepine, nitroglycerin) were excluded, as were females who were pregnant or nursing.

2.2. Design and procedures

The study was an open-label pilot study using three doses of NAC. For each subject, baseline data was collected followed by a 4-week treatment program (i.e. the medication phase). During the medication phase, the first 8 subjects were given one 600 mg capsule of NAC twice daily (1200 mg/day total). After these 8 subjects demonstrated sufficient tolerance for this dose of medication, the next 9 subjects were given two 600 mg capsules of NAC twice daily (2400 mg/day total). Once these 9 subjects demonstrated tolerance at this dose, the final 6 subjects were given NAC 1200 mg two capsules three times daily (3600 mg/day total).

After providing written and oral informed consent approved by the University Institutional Review Board, each subject received a complete medical history and physical, an electrocardiogram, and