The prevalence and impact of drug addiction on society are staggering. The abuse of alcohol, tobacco, and illicit drugs accounts for approximately 10% of the global burden of disease, and for the United States, it is estimated that substance use disorders affect 20.4 million individuals. Despite the deleterious economic and social consequences of drug use, approved medications to treat substance use disorders are few or absent depending on the drug. We and others have explored the possibility that dysregulation in prefrontal and allocortical (amygdala and hippocampus) glutamatergic inputs to the basal ganglia may be a mechanism responsible for relapse that is shared between classes of addictive drugs, as well as other disorders characterized by maladaptive compulsive behavior. Herein, we describe the bench-to-bedside chronology of preclinical discovery and clinical trials that led to the cysteine prodrug N-acetylcysteine being evaluated for the treatment of substance abuse and compulsive disorders.

Drug addiction is a chronic brain disorder characterized by compulsive drug use that occurs at the expense of other biologically adaptive activities. The transition from casual to compulsive drug use and the enduring propensity to relapse is maintained by long-lasting neuroadaptations in specific brain circuits. For example, it is well established that all drugs of abuse enhance dopaminergic neurotransmission to reinforce and establish drug-seeking behavior. Although less thoroughly studied, we and others have shown that the enduring vulnerability to relapse to drug use involves the recruitment of glutamatergic projections to the ventral striatum, in particular the nucleus accumbens, and is associated with enduring changes in glutamatergic synaptic transmission. Glutamatergic inputs from the amygdala, hippocampus, and prefrontal cortex to the accumbens regulate adaptive behavioral responses by integrating environmental stimuli with memories of relatable experiences. Thus, by producing enduring changes in glutamatergic synapses in the accumbens, long-term use of addictive drugs impairs the ability of an individual to inhibit drug seeking and use, ultimately producing the persistent relapsing disorder that characterizes drug addiction.

Animal models of drug addiction have shown that drug seeking is associated with increased glutamate release from prefrontal projections into the nucleus accumbens. When large amounts of glutamate are released, the excess spills out of the synaptic cleft and activates extrasynaptic glutamate receptors (Figure). Demonstrating spillover of synaptically released glutamate in animals trained to self-administer cocaine, heroin, nicotine, or alcohol was an important indication that alterations in glutamatergic synapses might be responsible for initiating relapse. Two lines of research evolved from this insight. The first was to examine proteins contributing to glutamatergic transmission and determine if these proteins were altered and could serve as targets for treating drug relapse. The second strategy was based on the hypothesis that long-term drug use may induce persistent changes in how glutamatergic synapses adapt to changing input. The process of synaptic adaptation is termed synaptic plasticity and is the molecular basis for learning and memory. Thus, impairments in synaptic plasticity could contribute to a cardinal characteristic of addiction disorders: the persistence of relapse even though the addict is aware of the negative consequences of continued drug use.

Supporting a role for synaptic glutamate release in relapse, blocking AMPA glutamate receptors in the nucleus accumbens inhibits relapse in rats trained to self-administer cocaine. Buttressing an important role for synaptic glutamate spillover in particular, a number of studies have found that metabotropic glutamate receptors (mGluRs) located outside of the synaptic cleft can regulate drug seeking. Genetic deletion of mGluR5 or administering mGluR5 antagonists prevents relapse to many addictive drugs, implying that glutamate overflow from the synapse to stimulate these receptors during relapse is a causal event. Similarly, N-methyl-D-aspartate glutamate receptors containing the GluN2B subunit are thought to be located primarily outside of the synaptic cleft, and either reducing GluN2B synthesis or selective blockade of GluN2B-containing N-methyl-D-aspartate receptors inhibits heroin and nicotine relapse.

Other studies directly assessed the involvement of glutamate spillover in animal models of relapse by manipulating glutamate uptake. There are several glutamate transporters expressed in the brain, but glutamate transporter 1 (GLT1) is strategically expressed near the synaptic cleft to minimize spillover of glutamate into the nonsynaptic extracellular space (Figure). This transporter is downregulated in the accumbens by long-term administration of addictive drugs. Downregulation of GLT1 decreases the elimination of synaptically released glutamate, thereby causing larger amounts of glutamate to spill over and stimulate extrasynaptic glutamate receptors (Figure). Increasing the expression of GLT1 with the antibiotic ceftriaxone sodium or increasing GLT1 activity with the cysteine prodrug N-acetylcysteine inhibits relapse in animal models. In addition to downregulating GLT1, glutamate spillover is facilitated by long-term drug use downregulating the capacity of presynaptic mGluR2 autoreceptors to inhibit glutamate release, thereby increasing the probability of synaptic glutamate release (Figure). Thus, stimulating glutamate release from the synaptic cleft appears to be a common molecular event in relapse.
Based on the preclinical data outlined earlier showing that N-acetylcysteine inhibits relapse by restoring drug-induced glutamatergic dysregulation at nucleus accumbens synapses, this compound is being tested as an antirelapse medication in human addicts. Surprisingly, the first clinical study to examine this possibility was conducted in a nondrug addictive disorder, gambling. Daily N-acetylcysteine (1800 mg) administered to 27 pathological gamblers in an open 8-week trial significantly reduced symptoms of gambling, and a subsequent 6-week, randomized, double-blind trial of 13 subjects who had responded to treatment revealed that at the end of the treatment phase, only 28% in the placebo group were still categorized as responding to treatment, compared with 83% of those treated with N-acetylcysteine.7 The first double-blind, placebo-controlled clinical trial for drug addiction involved 15 inpatient cocaine addicts who received N-acetylcysteine (1200 mg) for 3 days. When they were exposed to slides of cocaine-associated cues, N-acetylcysteine reduced the time spent viewing cocaine slides without affecting viewing time for pleasant, neutral, or unpleasant slides.5 The N-acetylcysteine–induced reduction in interest in cocaine was replicated in a study where N-acetylcysteine inhibited drug desire induced by a cocaine injection.8 A larger double-blind, randomized, 8-week study with daily N-acetylcysteine administration (1200 or 2400 mg) did not find a significant effect on cocaine use, but further analysis of subjects, who were abstinent (negative urine test results) the week prior to beginning N-acetylcysteine or placebo treatments, revealed a marked reduction in relapse in both N-acetylcysteine groups compared with the placebo group.9 Supporting involvement of glutamate in the potential efficacy of N-acetylcysteine in treating cocaine abuse, magnetic resonance spectroscopic measures of glutamate reveal that the increased glutamate levels observed in the anterior cingulate cortex of cocaine addicts are reduced by a single administration of N-acetylcysteine.10 N-acetylcysteine has also proven effective at reducing the use of marijuana and cigarettes, as well as in treating compulsive behavioral disorders such as gambling and trichotillomania. Much of this clinical literature has been recently reviewed elsewhere.11

The discovery of a persistent disruption of glutamatergic neurotransmission in animal models of cocaine, heroin, alcohol, and nicotine relapse led to studies showing that N-acetylcysteine reverses drug-induced synaptic pathology and reduces relapse in animal models. In these studies, N-acetylcysteine diminished drug-seeking behavior by normalizing synaptic plasticity at glutamatergic inputs to the basal ganglia. Early clinical trials with cocaine, nicotine, and marijuana addiction support this view. Moreover, successful clinical trials examining N-acetylcysteine in other compulsive behavioral disorders, including gambling and trichotillomania, support a general action by N-acetylcysteine on a shared corticostriatal neuropathology that diminishes an individual’s capacity to inhibit maladaptive, compulsive behaviors. While the bench-to-bedside history of N-acetylcysteine is promising and internally consistent, large clinical trials are necessary to determine definitively its utility as a treatment for drug addiction and other compulsive behavioral disorders.


