

N-acetylcysteine in addiction management: current knowledge and future perspectives

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ABSTRACT

Drug abuse disorders and addictive behaviors are serious public health problems and major contributors to the global burden of disease. Previous studies show that N-acetylcysteine (NAC) may be involved in neurodevelopment adult brain. The potential neuroprotective effect of NAC is associated with modulate several neurological pathways, including prevention of oxidative stress or inflammation damage to nervous tissue and glutamate dysregulation, NAC is being explored as an adjunctive therapy for drug addiction and addiction management. We here review the role of NAC in the addiction, such as cannabis abuse, methamphetamine abuse, cocaine addiction, nicotine dependency, and gambling. Adequate administration of NAC seems to be crucial in terms of addiction management. NAC is safe and well tolerated when administered orally but has documented risks with intravenous administration. An evidence study supports its use as an adjunctive therapy clinically for drug addiction, administered concomitantly with existing medications. The aim of this review is to assess the current knowledge related to the role of NAC administration on drug addiction and addiction management.

Key words: N-acetylcysteine (NAC), drug addiction, addiction management

INTRODUCTION

Substance abuse and drug addiction are a chronically relapsing disturbance that has been characterized by the compulsive use of addictive substances despite side effects consequences to the community and common people(1). Drug addiction represents a significant and pressing public health concern; also, lost productivity and drug-related crime total about \$621 billion per year in US(2). Drug abuse is a major social and public health difficulty and one of the top ranking risk factors for other health conditions in Iran(3). Opioid abuse disturbance were the most common form of illicit drug use disorder in Iran. The types of opioids used by subjects with a diagnosis of opioid abuse disorder were opioid (82.3%), smoked opium ashes ("shireh") (27.8%), methadone (not medical usages) (16.6%), heroin/crack of heroin (16.1%), and morphine (2.6%). The percentages add up to more than 100% because some individuals used more than one type of opioid. Cannabis and amphetamine-type stimulants abuse disorders were less common than

opioid abuse. The use of hallucinogens and cocaine was rare(4). Opioid markets increase illegal careers and negatively affect the resources available in legal economies. Illegal opioid markets are also linked to rises in crime and social insecurity(5). Addiction to alcohol, drugs and cigarette smoking is now regarded as a major public health problem. Other forms of addiction including gambling, computer games, food and sex also have severe consequences on the health of the subjects and to society(6). The National Institute of Health and Clinical Excellence (NICE) recommends both methadone and buprenorphine as a first line treatment for both medically assisted withdrawal syndrome from types of opiates and for maintenance treatment purposes, with due consideration given to service user preference. Guidelines protocols for management of opioid abuse adopt similar recommendations, that is, both methadone and buprenorphine as pharmacotherapy(7). Despite methadone maintenance treatment (MMT) and buprenorphine maintenance treatment (BMT) programs being one of

the most important treatment strategies for reducing individual and public harms associated with opioid use, a large proportion of Iranian patients refuse to participate in such treatment programs(8). MMT and BMT are the most frequently used opioid therapy. It is readily available for patients seeking opioid treatment in many countries. Evidence studies has demonstrated that MMT and BMT has the capacity to reduce the need to drug abuse, reduced the adverse health effects of opioid use, such as fatal and nonfatal drug overdoses, and keep patients in maintenance treatment and decrease the risk of relapse and withdrawal syndrome to drug use. Also, MMT and BMT seems to improve HIV outcomes, decrease hepatitis and HIV transmission, control disturbance behaviors, and suppress criminal activities such as drug dealing(7-10). Generally, MMT and BMT improve social functioning and quality of life(11). However, despite the extensive and successful implementation of the MMT, many challenges and obstacles remain. Recent evidence demonstrated that NAC is vital for mental health and central nervous system function. Grant et al.(12), showed NAC plus naltrexone intake for 8-week in subjects with metamphetamine addiction was associated with a significant improved in craving and withdrawal syndrome. In addition, results of a systematic review reported that supplementation with NAC had beneficial impact on treatment of addiction, especially of cocaine and cannabis dependence(13). Studies that have evaluated the role of NAC on drug addiction are common. The aim of this review is to assess the current knowledge related to the role of NAC on addiction management.

Neurological status in substance abuse

Drug addiction can be described as a disturbance which involves the neurological pathways of the structure and neuronal brain. Evidence studies have demonstrated that addiction can be alter the neural circuitries that are involved in psychological parameters (depression, anxiety, sleep, and sexual function), decision making, cognitive function, reward pathways, and memory. These regions are important in reward related processes and drug abuse, including anterior cingulate gyrus, orbitofrontal cortex, mesocortical systems, ventral tegmental area, nucleus accumbens, and cortex(14-16). In human imaging studies, decreases in dopaminergic function have been identified as a key common element of addiction, lending support to what became a strong program on the role of dopamine in addiction(17). In addition, to the mesocorticolimbic dopamine system, specific components of the basal forebrain have more recently been identified with the hedonic neuroadaptations to acute drug reward. As the neural circuits for the reinforcing effects of drug abuse have evolved, the role of neurotransmitters also has evolved including GABA, serotonin, opioid peptide, and mesolimbic dopamine(18-20). Also,

changes in neurotransmitters and neurochemical level occur in drug addiction include decreased GABAergic, increased NMDA and glutamatergic transmission, decreases in dopaminergic and serotonergic transmission, increased sensitivity of opioid receptor transduction during alcohol and opiate withdrawal(20, 21). Reported studies from brain imaging have shown an enhanced in opioid receptors density in patients with alcohol, opioids, and cocaine dependence(22-24). Evidence studies have also demonstrated that the corticostriatal glutamate pathway may be important in the initiation and expression of a number of addictive behaviors including conditioned place preference (CPP), drug seeking and locomotor sensitization(25). In other hand, the roles neuropeptides in drug abuse related behaviors have been demonstrated; and for the most part, neuropeptides including endogenous opioids, signaling molecules like substance P, and neuropeptide Y have been studied extensively as possible therapeutic targets for addiction management(14). The overall, although a number of neuropeptides, neurotransmitters and neuromodulators are involved in the reinforcing impacts of addictive drugs; the dopaminergic reward systems are central to the reinforcing properties of drug abuse and the initiation of addiction(14, 26, 27). However, other mediators are believed to exert their influence via dopamine pathway modulation.

N-acetylcysteine (NAC)

NAC, as a safe and inexpensive medication, is commercially accessible since long-time ago. NAC is a metabolite of the sulphur containing amino acid cysteine. It has the molecular formula $\text{HSCH}_2\text{CH}(\text{NHCOCH}_3)\text{CO}_2\text{H}$ and formula weight 163.19(28, 29). NAC exerts survival-promoting effects in several cellular systems(30). Cysteine is transported mainly by the ASC system, a ubiquitous system of Na^+ dependent neutral amino acid transport in a variety of cells(31). However, NAC is a membrane-permeable cysteine precursor that does not require active transport. After free NAC enters a cell, it is rapidly hydrolyzed to release cysteine, a precursor of GSH(32). The mechanism of action of NAC and consequently its dosing varies with indication(28). Nausea, vomiting and diarrhea have been demonstrated as dose-dependent adverse effects of oral NAC(33). Oral bioavailability of NAC is estimated at 6 – 10%, due to extensive first-pass metabolism, with T_{max} at 1 – 2 h. The volume of distribution ranges from 0.33 to 0.47 l/kg(34, 35). Taking NAC has been demonstrated to increase available GSH. After free NAC enters a cell, it is rapidly hydrolyzed to release cysteine, a precursor of GSH. GSH is synthesized by the coactions of γ -glutamylcysteine synthetase and GSH synthetase(36-38). GSH participates enzymatically and non-enzymatically in protection against oxidative stress damage caused by Reactive Oxygen Species. In addition, GSH peroxidase catalyzes the destruction of

hydroperoxides and H₂O₂(36). Therefore, supplementation with NAC is an antioxidant and a free-radical scavenging agent that increases GSH, and prevention from oxidative stress(39). Also, NAC has been demonstrated to have anti-inflammatory properties. In addition, NAC is inhibited induction of the pro-inflammatory transcription factors NF- κ B and AP-1. These transcription factors have been found to be induced in response to oxidative stress, supporting the argument that the anti-inflammatory properties of NAC are due to its mechanism of action as an antioxidant(40). Treatment with NAC has been shown for several illnesses including acetaminophen poisoning(41), pulmonary diseases(42), addictive behaviors(43, 44), psychiatric illnesses(45, 46), neurological diseases(47, 48), and infectious diseases(49, 50). The current evidence supporting NAC for treating substance use disorders(51). Dosages of NAC suggested for the treatment of stimulation disorder including cocaine, range from 1,200 to 3,600 mg/d, with higher retention rates noted in subjects who received 2,400 or 3,600 mg/d(52). NAC is to act as an anti-relapse agent, rather than an agent that can help someone who is actively using stimulants to stop. Also, NAC will likely be most helpful for individuals who are motivated to quit and are abstinent when they start consuming NAC (51).

NAC and methamphetamine abuse

Methamphetamine (MA) abuse is a growing social problem all over the world. MA abuse is a new health concern in the Iranian population(53). MA first appeared in 2005, initially and illegally imported from South-east Asia. The prevalence of MA dependence is less than one percent in the general population of Iran. Research findings demonstrated that recent years, the MA abuse increased from 3.9% to 89.5% among women and 60.3% among men in Iran(54). Also, studies indicated that the prevalence of MA in Iran during recent years has risen among patients under MMT(54, 55). The psychiatric effects of MA use are problems such as increased craving, cognitive impairment, depression and anxiety symptoms and sleep disturbances, and withdrawal syndrome accompany acute withdrawal from MA(56-63). Recently, various psychosocial interventions including technology-based treatments, matrix model and cognitive-behavioural therapy have been employed in the treatment of patients with MA dependence(64-66). Chronic and severe MA abuse is associated with deep alterations in brain circuits, which results in severe craving for the substance. Thus, the use of an effective pharmacotherapy that could reduce craving is an important goal of treatment of addiction. Pharmacotherapy might provide some benefit, but there is disagreement about the potential benefits of various pharmacologic agents for the treatment of drug abuse. The beneficial effect of NAC for the treatment of drug abuse has been demonstrated in patients

with MA dependence. Previous studies demonstrated that NAC may have the beneficial effects on craving and withdrawal. In the study by Mousavi et al.(67), it was documented that consuming 600 mg/day to a maximum of 1200 mg/day NAC for two four-week in patients with MA dependence disorders had favorable effects on craving scale. In commentary studies demonstrated that administration of NAC may be helpful in managing signs of dependence that develop with heavy MA use including craving and relapse(68). In addition, in a meta-analysis conducted by Duailibi et al.(69), NAC intakes were linked into craving reduction in substance use disorders including MA abuse. However, in another study NAC supplementation showed no significant effect on craving symptoms or MA use in MA-dependent(12). NAC, a cysteine pro-drug, is involved in restoring glutamate concentrations (enhancing activation of the mGluR2/3 receptors) in the nucleus accumbens, which would be linked to craving signs, and relapse(70-73). In addition, effects of NAC intake might mediated by antioxidant effects. NAC serves as a source of cysteine, which can promote glutamate exchange through the cysteine glutamate in glial cells. Cysteine would then enhance cellular production of GSH, which is an intracellular antioxidant, preventing cellular damage from ROS(69, 74).

NAC and cannabis abuse

Marijuana is the most commonly used illicit substance in the world. Consumed by an estimated 2.5% of the world's population and rates of abuse continue to enhance(75). Cannabis abuse has become increasingly popular in Iranian cities according to various reports(76, 77). Cannabis is used in Iran in both the form of grass (marijuana) and hashish. Whereas the public perception of risks is diminishing; cannabis abuse is linked to substantial health-related impacts and disturbance(78, 79). Evidence studies demonstrated lifetime history of cannabis abuse at 0.2% in secondary school boys aged 12-14 and 8.2% for high school boys aged 15-17. The Zanjan study showed a 2.8% lifetime use of cannabis in high school students. The rate was 5.7% among boys, and none of girls had history of cannabis use(80). There is evidence that substance abuse in Iran and other countries have greater psychological dysfunction(81, 82). Depending on age of onset, frequency, duration, and other variables, cannabis use can be associated with a broad spectrum of medical consequences, the range of which mirrors the physiological ubiquity and versatility of the endo-cannabinoid system(83). Experimental evidence has shown dys-regulation in glutamatergic pathway within a prefrontal cortex-nucleus accumbens following periods of self-administration and withdrawal syndrome across multiple drug abuse(25, 84, 85). These reported demonstrated that glutamate plays a key role in substance abuse and reinstatement models,

suggesting that glutamate is a promising neurochemical target for medication development to treat drug abuse(86, 87). Also, an evidence study suggests that cannabinoid intake disrupts normal glutamate functioning, and disinhibits dopamine transmission(88-90). Among glutamate-targeted pharmacotherapies for illicit drug, NAC has emerged as a particularly strong candidate(86, 87). Therefore, supplementation of NAC can be the favorable effects on cannabis abuse. In the study by McClure et al.(91), it was documented that 1200 mg/twice-daily orally-administered NAC for 12-week among cannabis users in any age group had favorable effects on increased odds of abstinence. Also, after NAC intake for 8 weeks, compared to placebo more than doubled the odds of abstinence during treatment, reflected in negative weekly urine cannabinoid tests in adolescents ages with cannabis abuse(92). However, in another study by Gray et al.(93), there is no evidence that NAC 1200 mg/twice-daily plus contingency management is differentially efficacious for cannabis use disorder in adults when compared to placebo plus contingency management. NAC is pro-drug and stimulates cystine-glutamate and increasing non-synaptic glial release of glutamate(94). So, NAC has also been demonstrated to decrease the reinstatement of drug-seeking in animal evidence across mix-users substances (94-97).

NAC and cocaine addiction

Cocaine is a tropane ester alkaloid found in leaves of the *Erythroxylum coca* plant, a bush that grows in the Andes Mountain region of South America. Cocaine abuse can lead to addiction and side effects, such as cardiac arrest and stroke(98). The rate reported by the United Nations Office on Drugs and Crime in the year of 2017 for the whole world population was of 0.35%(99). In Iran abuse of cocaine, hallucinogens and inhalants was rare(4). Several mechanisms have been demonstrated for cocaine neuro-toxicity, including oxidative stress alterations. NF- κ B, considered a sensor of inflammation and oxidative stress, is involved in drug abuse and addiction. NF- κ B is a key mediator for immune responses that induces microglial/macrophage activation under inflammatory parameters and neuronal injury/degeneration. Cocaine exposure linked to up-regulation of pro-inflammatory mediators such as cytokines and chemokines, or astroglia/microglia activation(100-103). In addition, evidence studies has demonstrated that following chronic cocaine abuse, basal extracellular glutamate status within the nucleus accumbens are decreased, which linked to the reinstatement of cocaine-seeking behaviors in animal models of relapse(71, 104). NAC, a cysteine pro-drug and amino acid, appears to restore basal status of glutamate in the accumbens, leading to a marked decreased in cocaine-seeking behavior after a cocaine challenge(105). In clinical trials

demonstrated that subjects NAC supplementation decreased cocaine abuse for one month. Importantly, clinical studies thus far have found NAC to be safe and well-tolerated among cocaine-dependent subjects(52, 106). A previous systematic review of NAC was superior to placebo for craving reduction in substance use disorders including methamphetamine, cannabis, cocaine, and nicotine(69). LaRowe et al.(107), showed that administration NAC at a dosage of 1200 mg and 2400 mg/daily for 8 weeks had beneficial effects on reduces cocaine use in cocaine-dependent subjects actively using. Also, taking NAC supplementation for three-day by cocaine-dependent humans had beneficial effects on reduces cocaine-related withdrawal symptoms and craving(106). However, there is a growing body of evidence indicating that NAC is not only potentially useful as a treatment for cocaine dependence(43, 108). So, further clinical trials for assessing the efficacy of NAC on cocaine dependence are warranted. The accurate mechanism of effect of NAC on craving reduction is not completely understood. Importantly, NAC have been found to have beneficial effects on enhance in glutamate status, stimulating inhibitory presynaptic mGluR2/3 receptors, and stimulating excitatory postsynaptic mGluR5 receptors (109-112).

NAC and nicotine abuse

There are 1.1 billion people smokers in the world, almost 80% of who reside in developing countries. With 26 countries now considered to be in active conflict or in the post-conflict setting(113), some 1.5 billion people are living in high exposure risk worldwide(114). In Iraq, smoking prevalence estimates are estimated to be 31% and 4% for males and females, respectively(115). Iran still has good tobacco control measures in place and prevalence has remained fairly stable, with 20% of males and 2–3% of females smoking daily(116, 117). WHO reported the prevalence of cigarette consumption in Iran to be 22 % among adult men and 1% among women in 2010. Furthermore, they estimated that these figures would reach 19% among men and 10% among women in 2025. Nine percent of the total population in Iran was anticipated to be smokers in 2025(118, 119). WHO also estimates that smoking (cigarette and smoke) is currently responsible for death of 6 million people worldwide, of which many are premature deaths(119). And a third of all cancer deaths are associated with smoking(120, 121). Most cigarette smokers try to quit smoking without professional assistance, though there is evidence studies that pharmacologically supported interventions are effective in the prevention of relapse and withdrawal symptoms including bupropion or varenicline(122, 123). Nicotine stimulates nicotine acetylcholine receptors in the CNS, which in turn elevate the release of several neurotransmitters (i.e., glutamate, dopamine, serotonin and GABA). Treatment strategies have focused on ACh receptors

or blocking the reuptake of noradrenaline and dopamine including bupropion or varenicline(124-129). Despite the relative effectiveness of current first-line medications for promoting smoking abstinence, most quit attempts result in relapse. Recently, the role of glutamate transmission in drug abuse dependence has been more extensively investigated. Preclinical evidence studies have emerged for the involvement of glutamate in relapse and withdrawal symptom(73, 130). In animal studies, chronic nicotine exposure is demonstrated to disturb functioning of the glial glutamate transporter (GLT-1) in the nucleus accumbens. Disturbance GLT-1 function reduce the rate of glutamate elimination, thereby augmenting the spillover of synaptically-released glutamate during reinstated drug seeking(70, 131, 132). Also, synaptic glutamate transmission mediates the primary reinforcing effects of nicotine in animal models: stimulating mGluR2/3 receptors, inhibits synaptic glutamate release, and decrease the rewarding effects of nicotine. However, enhancing extracellular glutamate attenuates symptoms linked to nicotine withdrawal(133, 134). NAC, a cysteine pro-drug that regulates cellular glutamate, holds promise as a medication to normalize frontostriatal function or prevent relapse and withdrawal symptom. NAC exerts antioxidant properties with activation of the cystine-glutamate exchanger(135, 136). Few studies have assessed the effects of NAC administration on nicotine dependence. Schmalet al.(137), showed that administration NAC at a dosage of 3600 mg/day for 4 days had beneficial effects on withdrawal symptoms in patients with nicotine dependence, but there was no significant effect on craving. The results of this pilot study are suggested that NAC may be a promising new treatment option for relapse prevention in nicotine dependence. In an animal and human study by Knackstedt et al.(97), it was seen observed that the administration of NAC reduced xCT expression in the nucleus accumbens and VTA, and decreased GLT-1 expression in the nucleus accumbens rats. Also, in this study reported a reduction in cigarettes smoked, and there was no effect on estimates of CO levels, craving, or withdrawal in human smokers. In addition, taking NAC supplementation may positively affect potentially dys regulated corticostriatal connectivity, help to maintain abstinence immediately and restructure reward processing(138). However, more clinical trial studies are needed to evaluate its potential clinical effect in cigarette smoking. NAC activates system xc- and enhances intracellular glutathione synthesis and releases glutamate. Also, supplementation with NAC is increasing system xc- activity in smokers. Such a restoration of xc- activity may underlie the improved success by the NAC treated individuals in resisting cigarette smoking (71, 94, 96).

NAC and pathological gambling

Worldwide, concern has grown over the expansion of gambling among adolescents, who have an enhanced likelihood of developing risk-taking behaviors(139). Past-year adult prevalence rates for pathological gambling are estimated at 1%. Although pathological gambling occurs frequently in primary care, it often goes unrecognized and untreated. Because untreated pathological gambling can disturbance function in multiple domains, validated treatments are needed to optimize mental health care(140-142). Gambling practices and opportunities have evolved to the point where they are widely available and viewed as a socially acceptable form of entertainment, while becoming increasingly attractive to young people including mobile gambling, online gambling, social casino gambling, gambling within online video games, and simulated gambling within other forms of entertainment(143-145). The severe gambling problems may meet criteria for pathological gambling, a diagnostic entity introduced in the Diagnostic and Statistical Manual. Several neurochemical systems have been implicated in gambling. Adrenergic systems have been linked to excitement, serotonin to impulse control, dopamine to rewarding and reinforcing aspects, opioids to euphoria, cortisol to stress responsiveness, and glutamate to cognitive functioning. In addition, many neurotransmitter systems including norepinephrine, serotonin, dopamine, opioid and glutamate and brain regions such as ventral striatum, ventromedial prefrontal cortex, insula, have been implicated in gambling(146-148). Furthermore, pathological gambling is linked to elevated nicotine dependence, and tobacco smoking in pathological gamblers has been associated with enhanced problem-gambling severity(149). Evidence of pre-clinical studies has demonstrated that status of glutamate within the nucleus accumbens mediate reward seeking behavior(72, 73, 150, 151). NAC has demonstrated the beneficial benefit of on reducing the reward-seeking behavior, by enhanced status of glutamate, stimulate inhibitory metabotropic glutamate receptors, and reduce synaptic release of glutamate(70). The results of the study showed that Grant et al.(149), a significant benefit of NAC treatment on nicotine dependence total scores. Also, during the 3-month follow-up, there was a significant benefit for NAC versus placebo on measures of problem-gambling severity. So, NAC treatment during therapy facilitates long-term application of behavioral therapy techniques once individuals are in the community after therapy has been completed. In addition, Grant et al.(44), showed that 600mg/day and increased to 1200 mg/day NAC supplementation for 8 weeks was linked into a significant improve in reward-seeking addictive behaviors such as gambling. NAC seems to enhanced the activity of cysteine-glutamate antiporters in the nucleus accumbens and abolishes

the reward-seeking behavior(72, 73). Therefore, the studies longer, and placebo-controlled double-blind studies are needed.

Conclusion

The supplementation of NAC has been studied in several drug abuse disorders and seems to be a novel treatment approach. Data is still limited, but overall the effect trends in a positive direction for many drug abuse including cannabis abuse, methamphetamine abuse, cocaine addiction, nicotine dependency, and gambling. NAC supplementation appears effective, affordable, safe, and tolerable. Long-term interventions and larger clinical trials are needed for addiction management. Prospective studies are needed to evaluate the eligibility of NAC in addiction management and drug abuse.

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