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“DANGEROUS RELATIONSHIPS”: ASTHMA AND SUBSTANCE ABUSE

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Commonly abused drug are cocaine, marijuana, cigarettes, heroin, and alcohol. The review emphasizes the importance for clinicians to be alert to the possibility of this substance as a precipitating factor for acute asthma. Substance use disorders to characterize illnesses associated with drug use. The use of drugs of abuse increases risk of developing more severe symptoms, higher frequency of exacerbations and having and significant effect on care resources due to clinicians visits and frequent hospital admissions. Abused drug has been shown to accelerate the decline in lung function and to increase numbers of life-threatening asthma attacks, and greater asthma mortality.

KEYWORDS. Addiction, substance use disorders, asthma, mental health

INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders (DSM) uses the term *substance use disorders* to characterize illnesses associated with drug use.¹ Commonly abused drug are cocaine, marijuana, cigarettes, heroin, and alcohol. Substance use disorders are prevalent in approximately 9% of the U.S. population, but only 10% of those individuals access addiction treatment and interference from pressing medical conditions may thus contribute to perceived unimportance of addiction treatment among the 94% of people deemed in need but who reported they did not need it.² The incidence of many chronic medical diseases (including asthma) is higher, and for some disorders more than double, among people with substance use disorders.³

Asthma remains a significant source of morbidity and mortality in the United States. Recent reports from the Centers for Disease Control and Prevention estimate that 7.7% of Americans currently have asthma and that 11.2% will experience asthma at some point during their lifetimes. In 2004, a total of 1.8 million emergency department visits, 14.7 million outpatient visits, and 497,000 hospitalizations were attributed to asthma.⁴ More than 4,000 people in the United States die from asthma each year.⁴ Asthma and other medical conditions are found at higher rates among patients with substance-related disorders^{5,6} and to enhance care of both asthma and substance abuse, it is important to better understand their relationships. This article presents a review of current knowledge of relationships between asthma and substance abuse.

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COCAINE AND ASTHMA

Cocaine is a short-acting stimulant that can lead abusers to binge (to take the drug many times in a single session). Cocaine abuse can lead to severe medical consequences related to the heart and the respiratory, nervous, and digestive systems. In the last century, cocaine was used as an ingredient in tonics used for curing asthma.⁷ Cocaine was first temporally associated with the development of an acute asthma exacerbation in 1932 in a young girl treated with nasal cocaine for anesthesia.⁸ Cases of cocaine-precipitated bronchospasm, including severe or life-threatening exacerbations of bronchospasm, have been described in the literature.^{9,10} These effects are more commonly seen in cocaine use in the form of free-base or crack. Crack cocaine results in quicker absorption and euphoria than nasal insufflation or snorting and avoids the use of needles required for intravenous injection, which also provides instantaneous euphoria. Free-base is a cocaine alkaloid that melts at 98°C, vaporizes at higher temperatures, and is heat stable, thus allowing the drug to be smoked.¹¹ Free-base is usually prepared by mixing cocaine hydrochloride and baking soda, which is then boiled in water and cooled. The precipitate is either filtered or extracted by adding a solvent such as ether or alcohol. The cocaine remains dissolved in the solvent, which can be evaporated, leaving the relatively pure base as a residue. The simpler crack method allows the alkaloidal cocaine to precipitate without a solvent extraction method. Cocaine may then be smoked using various methods, such as in a glass or regular pipe or by mixing it with tobacco or marijuana in cigarette form.¹¹ This method of use is the most irritating to the bronchial epithelium and bronchospasm may be a result of inflammation of the respiratory epithelium by either cocaine or adulterants. In a study comparing the acute effects of inhaled vs. IV cocaine on airway dynamics, it was demonstrated that smoked cocaine base caused bronchoconstriction, whereas a similar intoxicating intravenous injection of cocaine did not.¹² Asthmatic patients who smoke

cocaine may be at high risk for developing severe exacerbations of their asthma, depending on the degree of airways hyperresponsiveness, the dose of inhaled cocaine, and the nature of the contaminants inhaled during crack smoking.¹²

The Office of National Drug Control Policy estimates the number of chronic cocaine users to be 3.6 million.¹³ Approximately 40% of cocaine users use cocaine in the form of crack (National Household Survey on Drug Abuse data).¹³ It is the leading cause of illicit drug-related visits to emergency departments in the United States.¹³ In a prospective study by McNagny et al.,¹³ the prevalence of cocaine use in young men presenting to an inner-city walk-in clinic was determined to be 39% by urine testing; 72% of those testing positive denied illicit drug use in the prior 3 days. In a study by Rome et al.,¹⁴ only 3 of 13 patients who tested positive for cocaine actually admitted to its use. In a study by McNagny et al.,¹³ consent was not obtained for drug screening. The results of the aforementioned study emphasize the magnitude of the cocaine epidemic and indicate the unreliability of self-reporting of illicit drug use. In another study, patients in the emergency department who reported new-onset bronchospasm were tested for cocaine metabolites, with 21 (36%) of 59 patients having positive results.¹⁵ This was compared with a control group of randomly selected, age- and sex-matched individuals without a history of respiratory disease, in which 15% tested positive for cocaine.¹⁵ This finding indicates an association between cocaine use and new-onset bronchospasm or recrudescence of asthma. In a similar study by Gaeta and Hammock,¹⁶ 44 of 100 (44%) patients with asthma admitted to or tested positive for illicit drugs, compared with 20 of 100 (20%) control patients.

It is likely that cocaine-induced asthma will primarily be observed in patients who smoke the substance because this route is associated with the most direct damage and inflammation of the bronchial epithelium.¹⁷ Support for this theory has come from a study by Tashkin et al.¹² who examined airway dynamics in patients who consumed cocaine via various

routes. They observed that smoking but not injecting cocaine produced acute bronchoconstriction. Moreover, it should be noted that the insufflation of cocaine has also been linked to near-fatal status asthmaticus.¹⁸ The increase in the prevalence of cocaine use in the United States may be an important factor responsible for increasing asthma severity and mortality, particularly in the young age group, despite major advances in treatment modalities. Several studies reported a relatively high prevalence of cocaine use among patients with asthma exacerbation that possibly contributes to the increase in asthma morbidity.^{15,16,19}

Levine et al.¹⁶ reported a 42.8% prevalence rate of cocaine or heroin use among adult patients who had been admitted to an inner-city Chicago hospital for acute asthma exacerbations. They also found that cocaine use was associated with higher intubation rates and with longer lengths of stay and a higher likelihood of being admitted to the intensive care unit.¹⁶ Levenson et al.²⁰ examined asthma deaths in Cook County, Illinois. They reported that 31.5% of asthma deaths were confounded by substance abuse or alcohol ingestion. Cocaine was the most frequently identified drug found on toxicologic analysis in this study.²⁰ An important implication of the current review is to emphasize the importance for physicians to be alert to the possibility of cocaine as a precipitating factor for acute asthma, and patients who have been admitted to the hospital with acute asthma exacerbations in areas where illicit drug use is prevalent should be screened for the use of cocaine.

SMOKING MARIJUANA AND TOBACCO AND ASTHMA

Marijuana

Marijuana is derived from the cannabis plant and is intended for use as a psychoactive drug. It is smoked in the form of cigarettes or a pipe to filter out particulate matter. Marijuana is the most commonly abused illicit substance.¹ This drug impairs short-term memory and learning, the ability to focus, and coordination. It also increases the heart rate, can harm the lungs, and

may increase the risk of psychosis in vulnerable individuals. Marijuana smoke contains similar levels of tar as tobacco smoke and up to 50% more carcinogens.²¹ Marijuana users smoke unfiltered material, inhale the smoke more deeply, and hold the smoke longer than tobacco smokers, resulting in substantially greater tar deposits in the lungs than tobacco smokers.^{22–25}

Reports from clinical samples suggest that marijuana smokers exhibit a range of chronic respiratory symptoms.²⁶ In addition, marijuana users have greater utilization of outpatient medical services for respiratory and other illnesses.²⁷ In view of such a high prevalence of marijuana use and the association of greater medical service utilization by its users, it is imperative to review marijuana's short- and long-term consequences. Several studies showed an association between marijuana smoking, worsening asthma symptoms,²⁸ and acute exacerbations of bronchial asthma.¹⁶ Smoking marijuana may also give rise to symptoms highly suggestive of bronchial asthma, including cough and sputum production.^{29,30}

Given the rampant abuse of marijuana and the burden on health care it may produce through the development of emphysema, barotrauma, inflammation, and infection, physicians should question their patients carefully about marijuana use. Efforts to prevent and reduce the use of marijuana, such as advising patients to quit and providing referrals for support and assistance may have substantial public health benefits.

Tobacco

Smoking is associated with a higher incidence of asthma and is strongly predictive of the development of new onset asthma in allergic adults.³¹ Compared with nonsmoking asthmatics, smoking asthmatics are at risk of developing more severe symptoms and having a worse asthma-specific quality of life with a significant effect on health care resources due to unscheduled doctor visits and frequent hospital admissions.³² Moreover, cigarette smoking in asthma is associated with higher frequency of exacerbations, increased numbers of life-threatening asthma attacks, and greater asthma mortality. Asthma

severity is higher and asthma control is worse in asthmatics who smoke, the strongest association with more severe disease being observed in those who smoked more than 20 pack-years.³³ In most studies, smoking has been shown to accelerate the decline in lung function and increase the severity of airflow obstruction in asthma.³⁴ It is worth noting that lung function changes can be reversed with smoking cessation.³⁵

Smoking asthmatics appear to be less sensitive to the beneficial effects of inhaled corticosteroids compared with nonsmoking asthmatics. Although inhaled corticosteroids dosage may relieve unresponsiveness, loss of responsiveness to inhaled corticosteroids continues to be present despite the length of treatment, steroid molecule, and type of formulation (inhaled vs. oral).³⁶ Few clinical trials studied reversibility of corticosteroid unresponsiveness in smoking asthmatics. A non-controlled study demonstrated that a low-dose theophylline in addition to inhaled beclomethasone improved both lung function and asthma symptoms in 68 smoking asthmatics.³⁷ A randomized clinical trial suggested that leukotriene antagonists may have a beneficial effect in smokers with mild asthma,³⁸ but this study has not yet been replicated. To the best of our knowledge, only one study has examined the role of smoking cessation on corticosteroid responsiveness. Progressive improvement in Forced Expiratory Volume in One Second (FEV1) and restored corticosteroid responsiveness has been reported after 6 weeks of smoking cessation in 21 individuals compared with 11 smoking controls.³⁵

The above findings highlight the importance of smoking cessation in improving many clinical and functional outcomes of asthma. Physicians have the responsibility both to alert their patients with asthma about the additional risks of smoking and also to engage in smoking cessation interventions.³⁹

HEROIN AND ASTHMA

Heroin is a powerful opiate that produces euphoria and feelings of relaxation. It slows respiration and can increase the risk of serious

infectious diseases, especially when taken intravenously. Other opioid drugs include morphine, oxycodone, acetaminophen and hydrocodone, and aspirin and oxycodone, which have legitimate medical uses; however, their nonmedical use or abuse can result in the same harmful consequences as heroin abuse.

During much of the 1990s, heroin use in the United States increased steadily.⁴⁰ The current epidemic is characterized by new, young users, who increasingly report insufflation (snorting), rather than injection, as their sole method of use. In Chicago, New York City, Newark, and Detroit, insufflation is the most commonly reported means of heroin administration for those entering drug treatment programs. This shift toward insufflation has occurred in association with an increasing availability of heroin of higher purity.⁴¹ Numerous reports have associated injection of heroin and inhalation of morphine or heroin with asthma exacerbations.^{42–46}

Hughes and Caverly⁴⁷ reported three patients requiring mechanical ventilation after inhaling heroin, one of whom commonly developed acute wheezing after heroin use. In the context of the current heroin epidemic, five patients with status asthmaticus associated with heroin inhalation (four from insufflation, one from smoking) were reported in Chicago.⁴² These cases were characterized by preexisting asthma, the sudden onset of symptoms, relatively prolonged intubation, and eosinophilia. Krantz et al.⁴⁸ examined the prevalence of drug use in asthmatic patients who had been admitted to the ICU and compared the pattern of drug use in these patients to patients in the ICU who had been admitted for diabetic ketoacidosis. The authors observed that asthmatic patients in the ICU were more likely to have used heroin than were the diabetic ketoacidosis patients in the ICU.⁴⁸ Levine et al.¹⁶ reported a surprisingly high prevalence of heroin use among adults who were admitted to an inner-city hospital for asthma exacerbation. Heroin appeared to be a risk factor for intubation. It is probable that the high prevalence of drug use in inner-city populations contributes to the high rates of asthma exacerbations in patients in inner-city settings. Patients who have been admitted to

the hospital with acute asthma exacerbations in areas where illicit drug use is prevalent should be screened for the use of heroin.

Pathophysiologically, there are several reasons why heroin use might induce an acute asthma exacerbation. Direct thermal injury can occur following the inhalation of heroin. The bronchoconstrictive effects of morphine, which is a metabolite of heroin, have been known since the early 1900s.⁴⁹ It is now known that bronchoconstriction after heroin use is likely because of the ability of heroin to directly cause the degranulation of the mast cells, with the subsequent release of preformed inflammatory mediators such as histamines.⁵⁰ Furthermore, under normal circumstances, asthmatic patients will increase their respiratory rate in an effort to compensate for the relative hypoxemia caused by bronchoconstriction. Because opioids cause respiratory depression, it is possible that the heroin induced respiratory depression at least partly thwarts the ability of the body to adequately compensate, exacerbating the severity of an asthma attack.

ALCOHOL AND ASTHMA

Alcohol consumption can damage the brain, the liver, and most body organs. Areas of the brain that are especially vulnerable to alcohol-related damage are the cerebral cortex, the hippocampus, and the cerebellum. Alcohol has been used as a treatment for asthma since antiquity. The earliest indication of alcohol as a treatment for asthma appears on Egyptian papyri ca. 2000 BC.⁵¹ In ancient Greece, Hippocrates popularized alcohol as treatment for a variety of ailments and suggested that wine reduces sputum production, a problem that plagues asthmatics having exacerbations.⁵² In the 19th century, Hyde Salter⁵³ reported self-administration of high amounts of oral alcohol by three of his patients with severe asthma exacerbations and noted improvement of their symptoms. Indeed, the use of alcohol as a treatment for asthma was widespread by physicians in the United States well into the early 20th century until prohibition, when its use was officially renounced by the American Medical Association. Following

the repeal of prohibition in 1933, more rigorous studies using alcohol as a treatment for asthma began to appear.

In 1963, Herxheimer measured lung vital capacity (VC) in normal patients and patients with asthma following the ingestion of brandy, vodka, or pure ethanol.⁵⁴ Alcohol ingestion did not change vital capacity in normal patients but increased vital capacity between 6% and 38% in most of the patients with asthma and was accompanied by subjective improvement in their asthma symptoms. The vital capacity improvement began about 10 minutes after alcohol ingestion, peaked by 30 minutes, and returned to baseline by 2 hours. The authors concluded that alcohol had a clear anti-asthmatic effect, confirming the findings of Salter from a century before.

Soon thereafter, a small but important clinical study by Ayres et al.⁵⁵ examined the effects of drinking alcohol on asthma. Changes in airflow were measured following the ingestion of different concentrations of pure ethanol (diluted in water) in five patients without and five patients with asthma.⁵⁵ Two of the patients without asthma and three patients with asthma had a slight decrease in specific airways conductance with 20% alcohol within 5 minutes of quickly swallowing the whole drink. Higher concentrations of alcohol (60%), when sipped slowly over 5 minutes, resulted in significant increases in airway conductance in four of five of the patients with asthma.⁵⁵ This study suggests that although alcohol can immediately trigger an initial small upper airway irritant response, a separate slow bronchodilator effect can be observed in asthmatics.

The first reported use of intravenous alcohol for the treatment of asthma appeared in 1947 when Brown⁵⁶ infused 5% ethanol into children with severe asthma attacks who were unresponsive to conventional asthma therapy. Five of the six patients improved with the alcohol infusion and no adverse reactions were reported.⁵⁶ The implication that a pure alcohol infusion acted as a bronchodilator and did not worsen asthma was important because some atopic patients report bronchospasm following ingestion of alcoholic beverages. This point was

made in a study by Breslin et al.⁵⁷ in which 11 patients with asthma reported worsening of their asthma symptoms following the ingestion of an alcoholic beverage. The authors were able to provoke bronchospasm in the laboratory in 6 of the 11 patients challenged with the offending alcoholic beverage precipitating a $\geq 15\%$ reduction in the forced expiratory flow in the first second (FEV1) on spirometry. Importantly, in three of these patients, drink-precipitated bronchospasm was not triggered by an oral ingestion of an equivalent amount of pure alcohol in water implicating the non-alcohol components of the beverage as the likely asthma trigger.⁵⁷ Indeed, treatment with disodium cromoglycate, a drug that inhibits mast cell granule release and used in the treatment of asthma, prevented bronchospasm to the offending alcoholic beverage.⁵⁷ Similar findings were obtained in another study that implicated the sulfur dioxide content in red wine as a likely trigger for bronchospasm in asthmatics rather than the alcohol itself.⁵⁸ These studies indicate that the purity (pure ethanol vs. an alcoholic beverage) and the delivery route (oral vs. intravenous) are factors that may determine how alcohol might modify airway function. (An excellent review of alcoholic drinks as triggers for asthma was published by Vally et al.⁵⁹)

Acetaldehyde is produced by the metabolism of ethanol through the action of alcohol dehydrogenases. Acetaldehyde has long been recognized as a trigger for asthma in Asians and is referred to as alcohol-induced bronchial asthma.⁶⁰ The most susceptible individuals are Asians, who have a greatly reduced function of the enzyme aldehyde dehydrogenase isoform 2 (ALDH2) and can be identified through genetic testing and/or ethanol challenge testing.⁶¹ Approximately half of Japanese have inadequate ALDH2 activity and cannot effectively metabolize acetaldehyde. Bronchospasm following alcohol ingestion is well described in asthmatics of Japanese descent⁶² and is closely linked to the ALDH2 genotype.⁶⁰ The mechanism for acetaldehyde-triggered bronchospasm in these individuals is thought to occur through a non-cholinergic pathway related to degranulation of mast cells triggered by high blood acetaldehyde

levels that result in the release of histamine and other bronchoconstricting mediators.⁶¹

Interestingly, Myou et al.⁶³ found that inhaled ethanol did not trigger bronchospasm in Japanese patients with alcohol-induced asthma. Indeed, inhaled ethanol attenuated methacholine-induced bronchospasm in these asthmatics.⁶³ This is likely due to the inability of the airway epithelium to significantly metabolize ethanol into acetaldehyde. This study is consistent with the hypothesis that alcohol, in the absence of acetaldehyde or congeners, does not trigger asthma even in susceptible individuals with impaired ALDH2 function. This hypothesis is further supported by an animal study that determined that aerosolized acetaldehyde but not ethanol induced histamine-mediated bronchoconstriction in guinea pigs.⁶⁴

Pure ethanol is a moderately effective and transient bronchodilator and likely relaxes airway smooth muscle tone. The mechanisms responsible for alcohol-induced relaxation of airways are poorly understood and may include receptor- and nonreceptor-mediated signal transduction pathways involving calcium or nitric oxide as second messengers. Many non-alcohol components of alcoholic beverages likely act as triggers for asthma in sensitized individuals and as such are not different from other asthma triggers. Acetaldehyde, the primary metabolite of ethanol, can trigger bronchoconstriction in asthmatics with genetically reduced ALDH2 activity and represents a significant trigger for asthma in certain Asian populations.

ASTHMA CARE IN PATIENTS WITH SUBSTANCE ABUSE DISORDERS

Asthma and other medical conditions are found at higher rates among patients with substance-related disorders.^{5,6} There is a growing body of evidence that patients with substance-related disorders may receive lower quality care for some medical conditions.⁶⁵⁻⁶⁸ In 2004, a total of 1.8 million emergency department visits, 14.7 million outpatient visits, and 497,000 hospitalizations were attributed to asthma. More than 4,000 people in the United States die from asthma each year.⁴ Government health

agencies have devoted a great deal of attention to improving the quality of asthma care over the past two decades.^{69–71} Substance-related disorders may influence rates at which patients achieve standardized asthma care quality measures. Several studies have shown that patients who abuse drugs may be at increased risk of severe asthma exacerbations or asthma death.^{14,15,19,20,48}

Baxter et al.⁷² demonstrated that patients with substance-related disorders and persistent asthma fill prescriptions for controller medications at lower rates than patients without substance-related disorders. Although the authors cannot say whether these differences are due to differential access to care, decreased compliance with treatment recommendations, or the receipt of substandard care, these findings still may partially explain the disparities in asthma outcomes observed for these patients. Decreased use of outpatient asthma care may also be a factor contributing to the decreased quality of asthma care for patients with substance-related disorders because efforts to improve asthma care have largely focused on improving monitoring and prescribing practices in outpatient settings.^{69,70,73} In another analysis conducted by Baxter et al.,⁷⁴ the authors showed that patients with substance-related disorders were half as likely as patients without these disorders to receive asthma care in outpatient settings, and therefore they may be less likely to benefit from outpatient-based quality improvement efforts. An integrated approach could lead to effective treatment for these conditions.

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