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Review Article

Implications of Substance Use in Patients with Cystic Fibrosis: A Review

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Abstract

Substance use and substance use disorders are very common, with high personal and societal costs. With increases in life expectancy, substance use has become more commonly identified in individuals with cystic fibrosis (CF). Problem substance use has special implications for those with CF, including effects on the respiratory system, decreased adherence to medical treatments, and perhaps increased mortality. In the present review, we discuss commonly used substances including alcohol, tobacco, marijuana, opioids and benzodiazepines. We also discuss developmental considerations for substance use in adolescents and young adults with CF as well as special considerations for those undergoing transplantation.

Keywords: Substance use; Cystic fibrosis; Adolescence

Introduction

Substance use has reached epidemic proportions. It is estimated that, in 2016, 1 in 10 individuals aged 12 or older in the United States used illicit drugs in the past month, approximately 20.1 million people aged 12 or older had a substance use disorder (SUD) related to their use of alcohol or illicit drugs in the past year [1]. Cystic Fibrosis (CF) is the most common inherited, life-shortening chronic disease in the United States. Although CF remains a chronic, life-shortening illness, significant advances in treatment have extended median survival age, with many individuals with CF living well into their 40s and beyond [2]. Thus, more than half of the individuals with CF in the US are adults. It is therefore inevitable that cystic fibrosis (CF) Care Centers and providers will need to manage and treat the adverse effects associated with substance misuse. The rates of co-occurrence of substance use in CF are not well established, and a better understanding of the impact of substance use in this population could improve prevention and treatment. Additionally, many of these agents

affect the respiratory system and there are several potential pulmonary complications of substance use. These complications vary depending on the specific substance and the route of administration.

The impact of substance use is far-reaching, including poor medical adherence. Cystic fibrosis treatment regimens are time intensive and complex, requiring administration of medications and airway clearance treatments in a certain order with attention to proper technique. Daily adherence to treatments is the single largest factor under patient control which affects the trajectory of their disease; non-adherence in CF is associated with significant increases in morbidity and mortality (Modi & Quittner, 2006). Forgetting and not having enough time have been identified as significant barriers to adherence in youth with CF [3]. Given that those with substance use disorders typically spend large amounts of time obtaining, using and recovering from the effects of substances, in addition to the neurocognitive effects associated with substance use/substance use disorders (e.g. changes in memory and executive functioning associated with marijuana and alcohol use), it is likely that significant substance use would lead to decreased adherence. In the present review, we will discuss implications of commonly used substances for individuals with CF.

Alcohol

Alcohol is one of the most commonly used substances in the United States, and is the most commonly used substance by adolescents [4]. In 2016, over 136 million Americans reported current use of alcohol [1], with most drinkers staying within the current guidelines for moderate alcohol consumption -- up to 1 drink per day for women and up to 2 drinks per day for men. However, a significant number of adults report some problem drinking. In 2015, there were a reported 65.3 million binge alcohol drinkers, defined as when males consume 5 or more drinks on an occasion and females consume 4 or more drinks on an occasion, and 16.3 million heavy alcohol drinkers, defined as binge drinking on 5 or more days in the past 30 days based on the above thresholds [1].

There have been relatively few studies examining alcohol use by individuals with CF and no compelling data to suggest that we can afford to ignore examination of alcohol consumption in this population. [5] Reported that levels of alcohol use in their sample of individuals with CF were similar to rates of population-representative cohorts. A study by [6] found that 83% of their sample of individuals with CF consumed alcohol, and 13% of their sample consumed alcohol at levels above recommended guidelines. That percentage is similar to a national sample that reported heavy alcohol use by 11.9% of a United States population sample [1].

The adverse consequences of alcohol misuse are well established and include negative effects to the brain and heart, as well as increased risk of cancer, diabetes, sexual assault, suicide, school failure, and accidents [7]. Individuals with CF face additional concerns related to alcohol-related risks with potential negative interactions with medication, negative impact on nutrition, poor sleep quality, and problems with treatment adherence and self-care. In one study, alcohol use was associated with decreased adherence to medications in a heterogeneous group of adolescents with chronic illnesses including CF [5]. No relationship between marijuana use and medication adherence was found in this study; however, adherence to airway clearance was not included and there was low power to detect an association between marijuana use in adolescents with CF. Perhaps most importantly, individuals with CF have particular concerns related to the adverse effects of alcohol misuse on the lungs, liver, pancreas, and immune system.

There are a number of pulmonary complications associated with alcohol use including: lower lung function, increased risk of acute lung injury, higher risk of infections, complications and pneumonia, and impairment in mucociliary clearance, and specific to individuals with CF, impaired expression and localization of the cystic fibrosis transmembrane conductance regulator (CFTR) (See Table 1).The well-established negative effects of alcohol on the liver and pancreas represents additional concern to individuals with CF, as alcohol misuse can exacerbate liver damage to pancreatic insufficient patients or patients who may have CF related liver disease. Additionally, the well-established relationship between alcohol misuse and diabetes presents an additional problem for individuals with CF, as diabetes is a common CF comorbidity. In terms of immune response, excess alcohol is shown to suppress a wide range of immune

responses predisposing the user to various infections, and in particular lower respiratory infections (See Table 1).

In summary, alcohol is commonly used by individuals with CF in numbers that mirror the general population. However, the adverse effects of alcohol misuse can have a significant impact on health problems common to individuals with CF.

Tobacco

The negative consequences of smoking tobacco in the general population are well known, with significant increases in morbidity and mortality. For individuals with CF, smoking is an even riskier behavior associated with greater negative health consequences. In particular, there are a number of pulmonary complications associated with tobacco use including: decreased pulmonary function, rapid progression of lung disease, and increased risk of infection (see Table 1). Smoking also impacts functioning of CFTR; one study showed that cigarette smoking decreases the activity of the CFTR function by 60 percent [8]. There is evidence that exposure to nicotine during adolescence affects neural development and may increase sensitivity to nicotine, which persisted after smoking cessation in animal studies. Additionally, there is evidence that parents of children with CF smoke at higher rates than the general population [9].

Electronic cigarettes (e-cigarettes) deliver aerosolized nicotine to the user in a process known as vaping. E-cigarettes are not regulated by the FDA, and thus, the safety of this nicotine delivery system has not been rigorously studied and there is considerable speculation and controversy over the long-term health effects e-cigarettes. Pulmonary complications associated with the use of e-cigarettes include increased inflammation in airways, which may lead to increased risk of infection, increased progression of lung disease and increased risk of lung cancer (see Table 1).
Nicotine is highly addictive, and another risk of e-cigarette use is progression to combustible cigarettes, particularly among adolescents [10]. There is also evidence that nicotine sensitizes the reward circuitry of the brain, leading to increased experience of rewarding effects from other drugs of abuse such as cocaine, acting as a gateway drug [11].

It is well known that users of tobacco have a significantly increased risk of cancer. Individuals with CF also have more instances of gastrointestinal cancer than the general public. There may be additional increases in gastrointestinal cancers for individuals with CF who use tobacco, although this is not documented in the literature.

Marijuana

Marijuana may be used recreationally or for medical purposes, each with benefits and potential hazards. Potential hazards differ based on method of use. For example, oral ingestion does not carry the pulmonary risks of smoking. Due to the potential for worsening lung function, it is recommended that individuals with CF avoid smoking any substances.Cigarette smoking has long been unequivocally associated with harmful respiratory effects; however the effects of smoking marijuana on lung health has been poorly understood [12]. Although short-term effects of smoking marijuana include a bronchodilation effect, which results in improved airflow, heavy long-term use (consistent with marijuana use disorders) is associated with increased respiratory symptoms. Pulmonary symptoms associated with marijuana use include: increased cough, sputum, and wheeze, as well as the potential for bullous disease, spontaneous pneumothorax, aspergillus infection, and pulmonary infections (See Table 1). Additionally, marijuana use is associated with neurocognitive effects including decreased memory, which could potentially affect treatment adherence [12].

There are no clear standards on medical marijuana use for individuals with CF. However, some researchers have suggested that although use is controversial, cannabinoids would likely have beneficial effects in cystic fibrosis patients, including appetite stimulation, antiemetic, bronchodilating, anti-inflammatory and hypoalgesic effects [13]. Further, [13] suggests that anti-inflammatory effects of cannabinoids may slow decline in lung functioning. Providers should also be aware of the potential for drug-drug interactions [14].

Opioids

Opiate misuse can develop within the confines of medical management, secondary to recreational use or may occur in conjunction with mental health disorders such as anxiety and depression that are known to be more frequent in individuals with CF. Opiate use and misuse in individuals with CF is a complicated matter with potentially lethal con-

sequences. For instance, a history of opiate misuse or substance abuse disorder may compromise candidacy for lung transplantation [15]. Patients with CF patients may deal with chronic pain issues, dyspnea and end-of-life decisions more commonly than their age-matched cohorts. Thus, they may be more likely to come into contact with opioid medications, which may increase risk for opioid misuse. However, the rate of opioid misuse in individuals with CF is unknown, making comparisons to the general population impossible.

Opiate use is associated with central nervous system suppression of respiration, and opiate misuse may pose special risks to individuals with CF secondary to decreased respiratory reserve and need for cough to clear secretions, decreased cough, and decrease in cough-related chest wall pain (See Table 1). Although this effect can be helpful in palliating symptoms in conjunction with end-of-life care, suppression of respiration and cough inhibit lung clearance and can accelerate pulmonary decline or increase the risk of respiratory failure in individuals with CF. As with the general population, individuals with CF may not fully appreciate these risks.

Opiates have anticholinergic effects such as dry mouth, decreased sweating, difficulty urinating and constipation. Constipation is a well-known side effect of opiate use, which does not resolve even when tolerance develops with chronic use. As individuals with CF are already predisposed to constipation, this side effect is particularly problematic and has potential to progress to the more serious complication of bowel obstruction. There is also evidence that opioids can affect the immune cell function of the lungs, increasing histamine release, which may trigger bronchospasm, vasoconstriction and hypersensitivity reactions (see Table 1).

A review on pain and CF indicated a high incidence of pain reported in this population, but little standardization of CF pain measures [16]. Chest and abdominal pain are the most commonly reported symptoms. The clinical decision of how and when to institute pain management for individuals with CF is beyond the scope of this document, but at a minimum, practitioners should be aware of the potential risks of opiate use or misuse and utilize recommended screening and monitoring practices. For instance, [17] created a resource for universal precautions when prescribing opiates. Urine toxicology screening is a recommended tool when prescribing opioids as well in cases of suspicion for misuse or diversion. However, clinicians need to be aware that false positives may be present on preliminary screening and a confirmatory test is needed for any positive test. For example, antibiotics commonly used in the treatment of CF such as fluoroquinolones can trigger a false positive preliminary screening test for opiates and the confirmatory test may take several days or weeks to resolve [18]. False positive preliminary results can lead to dilemmas relative to patient management and assessing immediate risk, pending the final result.

Even with appropriate management of chronic opioid prescribing, there is a risk for development of misuse. A review by [19] found that individuals with chronic pain have substance use disorders (SUD) ranging from 8% to 12%. Adolescents are at increased risk secondary to the adolescent stages of brain development [20]. Developing brains have increased neuroplasticity and underdevelopment of the frontal cortex, which is involved in self-control [19, 20]. This is particularly relevant given the young age of some individuals with CF presenting with significant pulmonary compromise and related complaints. A multidisciplinary approach, optimizing nonnarcotic medications and limiting opiate duration as possible is recommended [19,20] and if narcotics are prescribed, patients should be advised of the risk for a SUD, global risks of opioid use as well as risks particular to CF, and this discussion should be documented. Of note, the Cystic Fibrosis Foundation is developing palliative care resources that may assist clinicians in making these decisions.

Benzodiazepines

Benzodiazepines are commonly prescribed psychotropic medications and are used clinically for the treatment of multiple medical conditions including anxiety, insomnia, alcohol withdrawal, and seizures. Benzodiazepines, particularly those with a rapid onset, are commonly misused due to their widespread availability, anxiolytic and relaxation/euphoric effects. Benzodiazepines are not typically recommended for ongoing use in individuals with CF due their depressant effects on the respiratory centers and potential to decrease respiratory muscle strength. When prescribed,

duration of use should be as short as possible. For instance, single-dose use of benzodiazepines for procedural anxiety (e.g. placement of PICC lines) is widely accepted.

Although studies specific to CF are limited, physiology studies and animal studies suggest benzodiazepines cause adverse respiratory effects through multiple mechanisms, such as increased risk of infection and increased risk of and mortality from pneumonia (See Table 1). They depress the central respiratory drive and chemoreceptor responsiveness to hypercapnia. Animal studies found that benzodiazepines could be a risk factor for pneumonia likely through direct suppression of innate immunity, and another possible explanation for the increased risk of pneumonia associated with benzodiazepines is sedation leading to an increasing risk for aspiration (See Table 1). A national prospective study found benzodiazepines were associated with increased mortality, with a dose response trend in patients with severe respiratory disease (See Table 1).

Other undesirable side effects include drowsiness, dependence, and memory impairment. Therefore, the potential for adverse effects needs to be taken into consideration when prescribing benzodiazepines for individuals with CF, particularly when misuse or its potential is suspected.

Special considerations

Developmental considerations

Adolescence (ages 10-25) is a developmental stage characterized by rapid biological, social and cognitive changes and an associated increase in risky behavior, including the initiation and escalation of substance use [4]. Adolescent substance use is associated with a range of well-known negative consequences, including driving after drinking, risky sexual behavior, and poor school performance. For youth with CF, there are additional risks of substance use, including decreased treatment adherence which may alter the trajectory of their disease [5]. Substance use is common during adolescence and early initiation and escalation in substance use is associated with increased risk of problem substance use and substance use disorders, yet substance use is infrequently discussed by physicians caring for adolescents with CF, both pediatricians and those at specialty CF Care Centers [21].

Despite advances in care resulting in significant increases in expected lifespan, CF remains a life-limiting disease. One normative developmental task of adolescence is identity development, which includes a search for meaning in life in the broader social and global context. During adolescence, youth with CF begin to explore the meaning of having CF in a more complex way as they develop cognitively (e.g. abstract reasoning), and may experience associated existential distress [22]. Adolescents and young adults often begin trying to understand their prognosis and life expectancy, and may experience increased awareness of death and the probability of a shortened life span leading to fear and distress. Substance use may be a means of self-medication: short-term reduction of distress associated with awareness of death and other significant stressors associated with cystic fibrosis (e.g. a negative reinforcement mechanism; [23]. Late diagnosis is particularly stressful, and those diagnosed with CF during adolescence may be particularly vulnerable to using substances to cope with the negative affect and existential distress associated with a late diagnosis [24]. Alternatively, substance use during adolescence may be part of a "live hard, die young" mentality. If an adolescent does not expect to live past young adulthood, long-term risks of substance use will have little weight [25]. Other adolescents may use substances in attempt to avoid or deny that they have cystic fibrosis. For instance, young adult patients at our CF care center have endorsed smoking cigarettes during middle and late adolescence as a form of magical thinking (e.g. *There was part of me that thought maybe I didn't have CF... I was proving to myself and my friends that I didn't have CF by smoking*).

Both decreased adherence and substance use may be part of a pattern of rebellion against parental control. One of the developmental tasks of adolescence is increased separation and independence from parents and chronic illness may interfere with this process [22]. Due to fear about long-term consequences of non-adherence, some parents are reluctant to cede control over treatments to their adolescent in a developmentally appropriate manner, a pattern known as miscarried helping [26]. Predictably, this over-control often backfires as patients assert their autonomy by decreasing adherence and sometimes engaging in other defiant behaviors such as substance use [22].

Transplant

The International Society for Heart and Lung Transplantation guidelines include current substance use as an absolute contraindication for lung transplantation because of the significant risk of perioperative morbidity and mortality [15]. Further, for those with a history of a substance use disorder they recommend "convincing evidence of risk reduction behaviors, such as meaningful and/or long-term participation in therapy," together with serial blood and urine testing to verify abstinence before offering lung transplantation [15]. For individuals with CF and severe disease, they may not have time to age out of problem use, as many emerging adults do, or to participate in long-term treatments before needing transplant. This suggests the need for more preventative approaches and early detection. There are significant concerns around the risk for relapse post-transplantation, especially in light of associations between post-transplant alcohol or other substance misuse and poor adherence to medications, which increases the rate of rejection [27].

One study that included over 100 pre-lung transplant individuals with CF found 16% had a history of smoking cigarettes and 80% had a history of alcohol use, with 33% currently consuming alcohol [28]. That same study assessed post-transplant use and found 100% of transplant recipients reported total abstinence from cigarette smoking, with 30% consuming alcohol after transplantation [28]. In a more recent study of post lung transplant patients (n=331, of whom 67 had CF), 12% reported smoking cigarettes; however, this was a heterogeneous group with highest rates in the emphysema group and overall low rates in the group with CF [29]. Post-lung transplant smoking has been associated with an increased risk of infections, increased risk of developing cancer [29, 30] and together with immunosuppressant therapies, increased cardiovascular events and mortality [30].

Post-transplant alcohol use, combined with many medications prescribed after transplantation (such as calcineurin inhibitors), increases the risk of liver damage. Among post-transplant patients, chronic opioid use was followed by increased mortality and decreased lung function [31].

As described above, marijuana has recreational and medical use each with benefits and potential hazards. There are no clear standards on medical marijuana use and many centers may reject individuals who regularly smoke medical marijuana given the potential hazards. Additionally, marijuana use is associated with cognitive side effects including impairing the ability to make-decisions, plan, organize, and remember [12], which could potentially affect adherence to the complex medical regimen after transplantation.

Illicit substances such as cocaine, heroin, amphetamines, hallucinogens, non-prescribed opioids and other controlled substances are a contraindication to transplantation due to risks associated with use on a primary and secondary (e.g. decreased adherence) level. IV drug use post-transplant is also associated with increased risk of infections [27].

Conclusion

In summary, substance use is widespread across society, including individuals with CF. Substance use and SUDs pose particular risks for those with CF, given a wide range of specific effects on body systems, cross-substance effects on adherence, and contraindication for transtransplantation. There is evidence that commonly used substances (e.g. alcohol, tobacco) impair CFTR functioning. The impact of substance use on individuals with CF is likely underestimated by those with CF as well as their CF care centers. Areas for future research include current prevalence rates of substance use and SUDs, associations between substances and adherence, associations between substances and common complications of CF and mortality, and best practices for screening and early intervention in this population. Both adult and pediatric CF programs should consider implementing a screening tool to assess for problem substance use. If a SUD is identified, information should be readily available to patients and family for linking with local treatment programs and other community resources such as naloxone (Narcan) administration training. Substance use can greatly impact the physical and emotional health of individuals with CF, and as such it is an important target for screening, prevention and early intervention within pediatric and adult CF centers.

Table 1: Pulmonary Complications.

Pulmonary Complications of Alcohol	
Complications	*Citations*
Lower lung function compared to individuals with the same lung diseases that do not misuse alcohol in obstructive lung disease (asthma and COPD) and fibrotic lung disease.	Cuddy, R., & Li, G. (2001). The role of alcohol in asthma: a review of clinical and experimental studies. *The American journal of emergency medicine*, *19*(6), 501-503. Frantz, S., Wollmer, P., Dencker, M., Engström, G., & Nihlén, U. (2014). Associations between lung function and alcohol consumption–Assessed by both a questionnaire and a blood marker. *Respiratory medicine*, *108*(1), 114-121. Zureik, M., Liard, R., Kauffmann, F., Henry, C., & Neukirch, F. (1996). Alcohol Consumption, Gamma-Glutamyl Transpeptidase (GGT), and Pulmonary Function: A Cross-Sectional and Longitudinal Study in Working Men. Alcoholism: Clinical and Experimental Research, 20(9), 1507-1511.
Increased risk of acute lung injury.	Moss, M., Bucher, B., Moore, F. A., Moore, E. E., & Parsons, P. E. (1996). The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. *JAMA-Journal of the American Medical Association-US Edition*, *275*(1), 50-54.
Higher risk of infectious complications and pneumonia.	Jong, G. M., Hsiue, T. R., Chen, C. R., Chang, H. Y., & Chen, C. W. (1995). Rapidly fatal outcome of bacteremic Klebsiella pneumoniae pneumonia in alcoholics. *Chest*, *107*(1), 214-217.
Prolonged and heavy exposure impairs mucociliary clearance.	Sisson, J. (2007). Alcohol and airways function in health and disease. *Alcohol*, *41*(5), 293–307. Simet SM, Sisson JH. (2015) Alcohol's Effects on Lung Health and Immunity. Alcohol Res, 37(2):199-208.
Excess alcohol is shown to suppress a wide range of immune responses predisposing the individual to various infections, and in particular pulmonary infections.	Diaz, L. E., Montero, A., Gonzalez-Gross, M., Vallejo, A. I., Romeo, J., & Marcos, A. (2002). Influence of alcohol consumption on immunological status: a review. *European journal of clinical nutrition*, *56*(S3), S50. Mehta AJ, Guidot DM. (2017) Alcohol and the Lung. Alcohol Res, 38(2):243-254. Zahs, A., Cook, R. T., Waldschimdt, T. J., Choudhry, M. A., Kovacs, E. J., & Bird, M. D. (2012). Alcohol and inflammation and infection: clinical and experimental systems—summary of the 2010 Alcohol and Immunology Research Interest Group Meeting. *Alcohol*, *46*(2), 147-153.

Alcohol disrupts expression and localization of the Cystic Fibrosis Transmembrane Conductance Regular (CFTR). This can contribute to the development of pancreatitis.	Maléth, J., Balázs, A., Pallagi, P., Balla, Z., Kui, B., Katona, M., . . . Rakonczay Jr, Z. (2015). Alcohol disrupts levels and function of the cystic fibrosis transmembrane conductance regulator to promote development of pancreatitis. *Gastroenterology, 148*(2), 427-439. e416.
Pulmonary Complications of Tobacco	
Complications	*Citations*
Smoking irritates mucosal lining which leads to decreased pulmonary functioning and more rapid progression of lung disease. Passive smoking is associated with decreased pulmonary functioning and increased risk of infection.	Feldman, C., & Anderson, R. (2013). Cigarette smoking and mechanisms of susceptibility to infections of the respiratory tract and other organ systems. *Journal of Infection*, *67*(3), 169-184. Verma, A., Clough, D., McKenna, D., Dodd, M., & Webb, A. K. (2001). Smoking and cystic fibrosis. *Journal of the Royal Society of Medicine*, *94*(40_suppl), 29-34.
E-cigarettes can increase inflammation in airways, which may lead to increased risk of infection, increased progression of lung disease and increased risk of lung cancer.	Chun, L. F., Moazed, F., Calfee, C. S., Matthay, M. A., & Gotts, J. E. (2017). Pulmonary toxicity of e-cigarettes. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, *313*(2), L193-L206. Rowell, T. R., & Tarran, R. (2015). Will chronic e-cigarette use cause lung disease? *American Journal of Physiology-Lung Cellular and Molecular Physiology*, *309*(12), L1398-L1409.
Pulmonary Complications of Marijuana	
Complications	*Citations*
Cough, phlegm and wheeze, which suggest obstructive lung disease in patients without CF.	Tetrault, J. M., Crothers, K., Moore, B. A., Mehra, R., Concato, J., & Fiellin, D. A. (2007). Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. *Archives of internal medicine*, *167*(3), 221-228.
Potential for bullous disease and spontaneous pneumothorax, and pulmonary infections.	Lutchmansingh, D., Pawar, L., & Savici, D. (2014). Legalizing cannabis: a physician's primer on the pulmonary effects of marijuana. *Current respiratory care reports*, *3*(4), 200-205.
Aspergillus infection related to use of marijuana contaminated with mold (in CF patients and non-CF patients).	Franquet, T., Müller, N. L., Giménez, A., Guembe, P., de la Torre, J., & Bagué, S. (2001). Spectrum of pulmonary aspergillosis: histologic, clinical, and radiologic findings. *Radiographics*, *21*(4), 825-837.

Short-term effects of smoking marijuana include a bronchodilation. Heavy long-term use is associated with increased respiratory symptoms.	Chabi, M., Goracci, A., Roche, N., Paugam, A., Lupo, A., & Revel, M. (2015). Pulmonary aspergillosis. *Diagnostic and interventional imaging, 96*(5), 435-442.
Pulmonary Complications of Opiates	
Opioids can affect the immune cell function of the lungs, increasing histamine release, which may trigger bronchospasm, vasoconstriction and hypersensitivity reactions.	Yamanaka, T., & Sadikot, R. T. (2013). Opioid effect on lungs. *Respirology*, *18*(2), 255-262.
Central nervous system suppression of respiration. Decreased cough and decrease in cough-related chest wall pain.	Radke, J. B., Owen, K. P., Sutter, M. E., Ford, J. B., & Albertson, T. E. (2014). The effects of opioids on the lung. *Clinical reviews in allergy & immunology*, *46*(1), 54-64.
Pulmonary Complications of Benzodiazepines	
Increased risk of infection in chronically ill patients.	Riker, R. R., Shehabi, Y., Bokesch, P. M., Ceraso, D., Wisemandle, W., Koura, F., ... & Rocha, M. G. (2009). Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *Jama*, *301*(5), 489-499.
Increased risk of and mortality from pneumonia in community samples.	Obiora, E., Hubbard, R., Sanders, R. D., & Myles, P. R. (2013). The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. *Thorax*, *68*(2), 163-170. Sanders, R. D., Godlee, A., Fujimori, T., Goulding, J., Xin, G., Salek-Ardakani, S., ... & Hussell, T. (2013). Benzodiazepine augmented γ-amino-butyric acid signaling increases mortality from pneumonia in mice. *Critical care medicine*, *41*(7), 1627. Taipale, H., Tolppanen, A. M., Koponen, M., Tanskanen, A., Lavikainen, P., Sund, R., ... & Hartikainen, S. (2017). Risk of pneumonia associated with incident benzodiazepine use among community-dwelling adults with Alzheimer disease. *Canadian Medical Association Journal*, *189*(14), E519-E529.
Increased mortality, with a dose response trend in patients with severe respiratory disease.	Ekström, M. P., Bornefalk-Hermansson, A., Abernethy, A. P., & Currow, D. C. (2014). Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *Bmj*, *348*, g445.

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