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David M. Guidot
Ashish J. Mehta *Editors*

Alcohol Use Disorders and the Lung

A Clinical and Pathophysiological Approach

Humana Press

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David M. Guidot • Ashish J. Mehta
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Editors
David M. Guidot, M.D.
Division of Pulmonary, Allergy
and Critical Care Medicine
Emory University School of Medicine
and the Atlanta VA Medical Center
Atlanta, GA, USA

Ashish J. Mehta, M.D., M.Sc.
Division of Pulmonary, Allergy
and Critical Care Medicine
Emory University School of Medicine
and the Atlanta VA Medical Center
Decatur, GA, USA

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Preface

Lung health is a precious commodity and is essential for human productivity as well as the quality of our individual lives. Unfortunately, there is a worldwide increase in mortality from lung diseases of various types that stands in sharp contradistinction to the declines in cardiovascular disease mortality. A progressively modernized world with ready access to tobacco products and constant exposure to air pollution in our larger and evermore industrialized cities is certainly a major cause. However, a major risk factor for acute and chronic lung diseases is rarely cited in textbooks and reviews of the global pandemic in lung diseases. Specifically, alcohol use and in particular excessive alcohol use and abuse contribute to millions of deaths per year worldwide from pneumonia and acute lung injury. However, its role in lung disease has frequently been overlooked and in the case of acute lung injury was unrecognized altogether until less than two decades ago. Although alcohol abuse was identified as a major risk factor for pneumonia more than two centuries ago, its diverse and devastating impact on overall lung health in a variety of forms and contexts is now being appreciated. There has been an explosion in laboratory research and clinical studies that are elucidating the remarkably diverse mechanisms by which this simple two-carbon compound impacts the delicate functions of the lung, from the upper airways to the resident immune cells in the alveoli and essentially every cell type and function in between. Therefore, we hope this textbook will be of interest to our colleagues but also a resource for them as the global pandemic of alcohol-related lung disease is recognized and, tragically, continues to grow. Although the great majority of this volume is focused on the epidemiology and pathophysiology of what we have termed "alcoholic lung," we hope that there will be an optimistic note as well in the discussions of evolving therapies. In this context, the exciting research discoveries made in the past two decades are already laying the foundation for the identification and testing of therapies designed to enhance lung health in those individuals who struggle with alcohol abuse and dependence and decrease the morbidity and mortality of alcohol-related lung diseases. Further, we are optimistic that such therapeutic approaches will have salutary effects on other organs such as the liver and brain. In fact, in many important instances the basic

research discoveries of the mechanisms by which excessive alcohol ingestion renders individuals susceptible to acute lung injury and pneumonia were guided by prior and/or parallel investigations of the effects of alcohol on other organs such as the liver, pancreas, and brain. Therefore, there is every reason to anticipate new treatment options to mitigate the pathological effects of alcohol in those who are at greatest risk. Although the ideal "solution" would be a society in which alcohol use is always moderate and in a safe context, the history of human societies and our current social challenges make it clear that no such "ideal solution" is imminent. Until such a lofty goal is achieved, it is imperative that we dissect the specific mechanisms by which alcohol perturbs health and identify biological interventions that can complement the important efforts in cognitive and behavioral therapy that are the focus of alcohol treatment programs.

Atlanta, GA, USA David M. Guidot, M.D.
Decatur, GA, USA Ashish J. Mehta, M.D., M.Sc.

Contents

Contributors

Gregory J. Bagby, Ph.D. Departments of Physiology and Internal Medicine, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Lou Ann S. Brown, Ph.D. Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Emory University, Emory+Children's Healthcare of Atlanta Center for Developmental Lung Biology, Atlanta, GA, USA

Ellen L. Burnham, M.D., M.S. Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Denver, Aurora, CO, USA

Katharina Chalk, M.D. Department of Anesthesiology and Intensive Care Medicine Mitte and Campus Virchow Klinikum, Charité – Universitätsmedizin Berlin, Berlin, Germany

Brendan J. Clark, M.D. Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Denver, Aurora, CO, USA

Sushma K. Cribbs, M.D. Division of Pulmonary, Allergy and Critical Care Medicine, Emory University School of Medicine, Atlanta, GA, USA

Karen Drexler, M.D. Department of Psychiatry and Director of the Substance Abuse Treatment Center, Atlanta VA Medical Center, Decatur, GA, USA

Theresa W. Gauthier, M.D. Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Emory University, Atlanta, GA, USA

Danielle Giliberti, M.D., Ph.D. Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Emory University, Atlanta, GA, USA

David M. Guidot, M.D. Division of Pulmonary, Allergy and Critical Care Medicine, Emory University School of Medicine and the Atlanta VA Medical Center, Atlanta, GA, USA

Kyle I. Happel, M.D. Section of Pulmonary and Critical Care, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Juna Konomi, B.A. Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Emory University, Atlanta, GA, USA

Michael Koval, Ph.D. Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Emory Center for Alcohol and Lung Biology, Emory University School of Medicine, Atlanta, GA, USA

Kevin L. Legge, Ph.D. Department of Pathology, University of Iowa, Iowa City, IA, USA

Yan Liang, Ph.D. Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Emory University, Emory+Children's Healthcare of Atlanta Center for Developmental Lung Biology, Atlanta, GA, USA

Ashish J. Mehta, M.D., M.Sc. Division of Pulmonary, Allergy and Critical Care Medicine, Emory University School of Medicine and the Atlanta VA Medical Center, Decatur, GA, USA

J. Nicholas Melvan, M.D., Ph.D. Departments of Physiology, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Sowmya S. Mohan, M.D. Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Emory University, Atlanta, GA, USA

Samuel A. Molina, Ph.D. Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Emory Center for Alcohol and Lung Biology, Emory University School of Medicine, Atlanta, GA, USA

David Rimland, M.D. Infectious Diseases, Atlanta VA Medical Center, Emory University School of Medicine, Atlanta, GA, USA

Joseph H. Sisson, M.D. Division of Pulmonary, Critical Care, Sleep & Allergy, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, USA

Claudia Spies, M.D. Department of Anesthesiology and Intensive Care Medicine Mitte and Campus Virchow Klinikum, Charité – Universitätsmedizin Berlin, Berlin, Germany

Thomas J. Waldschmidt, Ph.D. Department of Pathology, University of Iowa, Iowa City, IA, USA

Todd A. Wyatt, Ph.D. Department of Environmental, Agricultural & Occupational Health, University of Nebraska Medical Center, Omaha, NE, USA

Samantha M. Yeligar, M.S., Ph.D. Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Emory University, Emory+Children's Healthcare of Atlanta Center for Developmental Lung Biology, Atlanta, GA, USA

Department of Medicine, Atlanta Veterans' Affairs and Emory University Medical Centers, Decatur, GA, USA

Part I
The Epidemiology of Alcohol Use and Lung Health

Chapter 1
A Brief History of Alcohol Use and Abuse in Human History

David M. Guidot and Ashish J. Mehta

Abstract There is clear archaeological evidence that dates the production and consumption of alcoholic beverages back ~20,000 years. Over the millennia the techniques of fermenting various organic materials have been gradually refined, and now there are thousands of different alcohol beverages that are produced, both commercially and noncommercially, throughout the world. Mankind's relationship with alcohol has been decidedly mixed, with its use associated both with celebration and with despair. The perceived salutary effects of alcohol in human culture have been celebrated in song and prose. In contrast, the negative effects of alcohol on behavior have led to its prohibition by various societies and religions since its use first became widespread in human culture many thousands of years ago. Independently of the arguments for and against the ingestion of alcoholic beverages, it is clear that its prohibition in free societies is not only impossible but in fact may also have unintended consequences such as the growth in organized crime and tragic side effects of consuming unsafe homemade products. Therefore, even with a growing public awareness of the adverse consequences of alcohol use and a justifiable tightening of laws that regulate its sale and distribution and punish dangerous alcohol-related activities such as driving while under the influence, it is clear that alcohol consumption will remain common throughout the world for the foreseeable future.

Keywords Alcohol • Alcoholism • Prohibition • Temperance

D.M. Guidot, M.D. (✉)
Division of Pulmonary, Allergy and Critical Care Medicine, Emory University School of Medicine and the Atlanta VA Medical Center, 615 Michael Street, Suite 205, Atlanta, GA 30322, USA
e-mail: dguidot@emory.edu

A.J. Mehta, M.D., M.Sc.
Division of Pulmonary, Allergy and Critical Care Medicine, Emory University School of Medicine and the Atlanta VA Medical Center, 1670 Clairmont Road, Decatur, GA 30033, USA

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Chapter Body

Alcoholic beverages of various kinds have been used, and abused, by humans for thousands of years. There is archaeological evidence that the fermentation of grains into beer dates back ~20,000 years and that similar fermentation of grape juice into wine is almost as ancient a custom. It is almost certain that the discovery of alcoholic beverages was accidental. For example, long before the domestication of grains and the development of farming there was evidence of the consumption of alcoholic beverages. Although we will never know for sure where the first alcoholic beverage was discovered, it appears that one of the first alcoholic drinks was fermented mare's milk in ancient Siberia, which likely was identified by trial and error when "spoiled" milk was found to have stimulant properties. In fact, a version of this alcoholic beverage, known as *kumis*, is still consumed in some parts of Russia.

In many cultures, both ancient and modern, the consumption of beer, wine, and spirits is a part of religious ceremonies, social events, and simple daily living. Although many religious and social groups have proscribed its use and temperance movements have arisen at various times in virtually every society, alcohol ingestion has proven to be an enduring human custom. Unfortunately, a significant proportion of individuals who consume alcohol on a regular basis develop patterns of alcohol abuse or even frank physical dependence, and the long-term health consequences of excessive alcohol use can be devastating.

Long before the negative consequences of alcohol abuse on physical health such as cirrhosis and dementia were recognized, its adverse effects on behavior and productivity were recognized. These social effects led to various forms of alcohol prohibition even in ancient cultures. Several major religions, including Islam and Mormonism, have clear bans on all alcohol ingestion, and in some countries such as Saudi Arabia the production, sale, and ingestion of alcohol are all prohibited by law because it violates religious doctrine. In the United States, a growing temperance movement in the nineteenth century that was driven largely by religious beliefs eventually led to the passage of the 18th Amendment to the Constitution in 1919, which imposed a complete prohibition on the production, sale, and consumption of alcoholic beverages within the United States. The "Prohibition Era" was marked by widespread disobedience and was in fact largely responsible for the rapid growth of organized crime in this country as the black market for alcoholic beverages was enormous. In parallel, the unregulated production of "homemade" liquors at times was associated with significant side effects from contaminants including methanol and lead. The 18th Amendment was repealed in 1933, and the unintended negative consequences of this attempt to eliminate alcohol from American society effectively ended the temperance movement as a meaningful political force. However, the prohibition of alcohol use by some religions and their influence on local laws remain evident in current times, as reflected best by the so-called dry counties in various states.

Whether or not one endorses or condemns the ingestion of alcohol on moral, religious, or social grounds, there can be no refuting that excessive alcohol use can have devastating health consequences and is directly or indirectly causative in millions of deaths worldwide each year.

Worldwide, alcohol is the most frequently abused drug [1]. In the United States, half of the general population regularly consumes alcohol, and 15–20 million individuals are alcoholics [2, 3]. According to the 2008 National Survey on Drug Use and Health, more than 50 % of the adult population in the United States consumes alcohol, which would roughly translate into more than 125 million people. In this same survey, almost 7 % reported heavy drinking [Substance Abuse and Mental Health Services Administration. (2009). *Results from the 2008 National Survey on Drug Use and Health*: *National Findings* (Office of Applied Studies, NSDUH Series H-36, HHS Publication No. SMA 09-4434). Rockville, MD]. Data from the 2001 National Epidemiologic Survey on Alcohol and Related Conditions reported that the lifetime prevalence of alcohol abuse was about 18 %, making alcohol the most widely used and abused among all drugs [4, 5]. While average alcohol intake has decreased over time, more recent data suggest that the incidence of alcohol use disorders has not changed [6]. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has estimated that alcohol-related problems cost our society more than $185 billion per year [7]. Among persons admitted to general hospitals, 20–40 % have alcohol-related problems [8]. A more recent report published by the Centers for Disease Control and Prevention conservatively estimated that in the year 2001, there were ~76,000 alcohol-attributable deaths and more than 2.3 million years of potential life lost due to alcohol abuse in the United States alone [9]. The majority of these deaths were attributed to chronic conditions such as cirrhosis and to alcohol-related acute trauma, particularly automobile accidents. However, as we shall discuss in the context of acute lung injury, these estimates failed to include a large number of cases in which a causative role for alcohol abuse was unrecognized.

Perhaps most tragically, the prevalence of unsafe alcohol consumption in the so-called underage segment of our society (those under the age of 21) is rising dramatically. The NIAAA estimates that in 2009 ~10.4 million people in the United States between the ages of 12 and 20 had some degree of significant alcohol intake (http://www.niaaa.nih.gov/alcohol-health/special-populations-co-occurring-disorders/underage-drinking). Further, although people in this age group drink less often on average than their adult counterparts, they are far more likely to binge drink, defined as five or more drinks in one setting. Sadly, the NIAAA also estimates that ~5,000 people under the age of 21 die every year in the United States from alcohol-related injuries such as automobile accidents, burns, and drowning. Ironically, there is now anecdotal evidence that increasing the legal drinking age from 18 to 21 across the country by the National Minimal Age Drinking Act in 1984 may have actually increased the incidence of binge drinking, particularly among college students.

Summary

Alcohol is the most widely used and abused drug worldwide, and its production and ingestion have been woven into human cultures for thousands of years. Although the balance between the social benefits of alcohol and its negative consequences has been hotly debated for centuries and many societies have attempted to curb or even eliminate its use, the drinking of alcohol is inextricably connected to our modern society. Therefore, it is imperative to understand how excessive alcohol ingestion impairs human health and identify strategies to mitigate its impact as its complete prohibition is not feasible.

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Chapter 2
Overview of the Evolving Recognition of the Health Effects of Excessive Alcohol Use Over the Past Two Centuries Including the Classic Citations

David M. Guidot and Ashish J. Mehta

Abstract The negative behavioral and social consequences of alcohol ingestion, particularly when done so in excess, have been recognized for thousands of years and have led to various types of prohibition imposed on religious, moral, or social grounds in nearly every society at one time or another. However, the relatively modern era of medicine has only more recently documented and investigated the adverse health effects of excessive alcohol consumption. Although the pathophysiological effects of alcohol on the liver and the brain are more widely recognized and have attracted much of the attention by physicians and scientists, alcohol abuse has a myriad of systemic targets including the lung. In fact, it has been recognized for more than two centuries that alcohol abuse is a major risk factor for pneumonia. More recently, clinical observations have identified that alcoholics are at risk for much poorer outcomes if they develop certain pneumonias such as from *Streptococcus pneumoniae*. Further, even more recent epidemiological studies have identified that alcohol abuse significantly increases the risk of acute lung injury following acute insults such as sepsis or trauma. This chapter highlights some of the classic observations and discoveries of the relationship between alcohol use and lung disease over the past two centuries and sets the stage for the more detailed analyses and accounts of the current state of our knowledge of specific facets of this relationship in subsequent chapters.

Keywords Alcohol • Alcohol abuse • Pneumonia • Acute lung injury • ARDS

D.M. Guidot, M.D. (✉)
Division of Pulmonary, Allergy and Critical Care Medicine, Emory University School of Medicine and the Atlanta VA Medical Center, 615 Michael Street, Suite 205, Atlanta, GA 30322, USA
e-mail: dguidot@emory.edu

A.J. Mehta, M.D., M.Sc.
Division of Pulmonary, Allergy and Critical Care Medicine, Emory University School of Medicine and the Atlanta VA Medical Center, 1670 Clairmont Road, Decatur, GA 30033, USA

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Chapter Body

This chapter provides an overview of the relatively modern history of medical observations and investigations of the untoward effects of alcohol ingestion on respiratory health and highlights some of the seminal events in this history. Subsequent chapters in this book will focus on specific aspects of how excessive alcohol ingestion impairs airway and lung health in far greater depth and detail.

Unfortunately, a significant proportion of individuals who consume alcohol on a regular basis develop patterns of alcohol abuse or even frank physical dependence, and the long-term health consequences of excessive alcohol use can be devastating. Many of the medical complications of alcohol abuse, including hepatitis, cirrhosis, pancreatitis, cardiomyopathy, peripheral neuropathy, and dementia, are well known to both the general public and to the medical community [1]. By contrast, the ravages of alcohol abuse have been viewed as relatively sparing the lung. For example, an "alcoholic pneumopathy" or an "alcoholic pneumonitis" analogous to the aforementioned complications of chronic alcohol abuse has not been described. The notable exception is the long recognized link between alcohol abuse and pneumonia.

More than two centuries ago the first Surgeon General of the United States, Benjamin Rush, noted that pneumonia and tuberculosis were infectious complications more commonly encountered in people who drank alcohol, and, a century later, William Osler cited alcohol abuse as the major risk factor for pneumonia [2]. However, this risk has largely been attributed to alterations in immune function and/or structural/functional defects in the upper airway such as colonization of the oropharynx with gram-negative bacteria and the obvious risk of aspiration during inebriation. In fact, until relatively recently it had been generally assumed that chronic alcohol abuse had no effect on the lung parenchyma itself as there is no epidemiological evidence to implicate it as an independent risk factor for common pulmonary disorders such as bronchogenic carcinoma, asthma, emphysema, or interstitial lung disease.

Our understanding of the effects of alcohol abuse on the lung itself was changed when a novel epidemiological finding published in 1996 revealed for the first time that alcohol abuse independently increased the risk for developing a severe form of lung injury known as the acute respiratory distress syndrome (ARDS) in critically ill individuals [3]. Specifically, an otherwise healthy individual with an alcohol use disorder (i.e., "alcohol abuse" or "alcohol dependence") who suffers a critical illness such as pneumonia, sepsis, or trauma has a two- to fourfold increased risk of developing ARDS than nonalcoholics. Remarkably, this association and its impact had been missed even though independent risk factors for ARDS had been vigorously sought, and even two decades later they are not recognized routinely by the medical community.

This initial epidemiological observation inspired experimental and clinical studies that have led to an explosive growth in our understanding of the relationship between chronic alcohol abuse and pulmonary disease. The ensuing chapters in this

book will focus on the key aspects of research of the past decade on alcohol abuse and acute lung injury and synthesize the novel findings in this area with previous and ongoing studies of alcohol abuse and pulmonary host defense. Specifically, it is becoming increasingly clear that alcohol abuse, even in otherwise healthy individuals, causes significant oxidant stress within the alveolar space and impairs both alveolar epithelial and alveolar macrophage function via common pathophysiological mechanisms. Therefore, this textbook will integrate the parallel but often independent findings on immune dysfunction and susceptibility to acute lung injury in the "alcoholic lung" into a common pathophysiological scheme. In addition to in-depth analyses of the impact of underlying alcohol-use disorders on health outcomes in a variety of clinical contexts, the mechanisms by which alcohol impairs airway function and in particular lung immunity will be reviewed. Finally, we will discuss recent experimental findings that raise the possibility that novel therapies, targeted at the airway epithelial and macrophage dysfunction in alcoholic individuals, could limit the incidence and/or severity of lung infections as well as modify their dramatically increased risk of acute lung injury in the setting of serious lung infections and/or other critical illnesses. However, before we delve deeply into detailed analyses of the "alcoholic lung," it is worth remembering that alcohol abuse is in fact a systemic illness and that its devastating biological consequences do not spare any organ system.

Alcohol abuse causes a myriad of serious health consequences. Perhaps for obvious reasons, much of the medical attention has focused on alcohol-mediated pathophysiology within the gastrointestinal system. Following ingestion, alcohol is rapidly absorbed by the gastric and small intestinal mucosa and is metabolized primarily in the liver by alcohol dehydrogenase, a cytosolic enzyme with multiple isoforms that vary in their affinities for alcohol binding [4, 5]. Only the liver and the gastric mucosa have the high-affinity isoform, and therefore alcohol metabolism by alcohol dehydrogenase in tissues other than the liver and the stomach is limited [4, 5]. Alcohol can also be metabolized in microsomes via the cytochrome p450 component CYP2E1 [5]. This enzyme complex has a lower affinity for alcohol than the hepatic alcohol dehydrogenase enzyme and therefore may not contribute significantly to overall alcohol metabolism following occasional use. However, in the context of chronic use, the CYP2E1 enzyme metabolizes a significant percentage of ingested alcohol. Alcohol metabolism in the liver forms acetaldehyde and free radicals that have been implicated as direct causes of hepatocyte injury [4, 5]. As many as 35 % of heavy drinkers develop alcoholic hepatitis, and half of these individuals develop frank cirrhosis [4, 5]. Another prominent target of alcohol abuse within the gastrointestinal tract is the pancreas. An association between alcohol abuse and pancreatic injury was reported as early as 1878 [6], and alcoholic pancreatitis has become a well-recognized clinical entity since then that, although less common than alcoholic hepatitis, can cause significant morbidity and mortality in affected individuals. Alcohol consumption has diverse deleterious effects elsewhere throughout the gastrointestinal tract including gastroesophageal reflux, damage to the gastric mucosa, and malabsorption of nutrients in the small intestine [7].

Beyond the gastrointestinal system, alcohol abuse has diverse targets. For example, it impacts the endocrine system by disrupting the actions of hormones such as cortisol, testosterone, growth hormone, and prolactin, and it interferes with glucose and lipid metabolism [8]. Although much attention in recent years has been paid to the salutary effects of moderate alcohol consumption on the cardiovascular system, alcohol abuse can lead to significant morbidity and mortality from cardiomyopathy and vascular disease [9]. Further, alcohol abuse is clearly associated with certain cancers, such as esophageal and gastric carcinoma, and causes osteoporosis, myopathy, dementia, and peripheral neuropathy [1]. Therefore, one could argue that alcohol abuse is a truly systemic disorder in which the clinical manifestations may vary depending on the individual affected. As this textbook will focus on the effects of alcohol abuse on the lung, readers are directed to several excellent reviews of the medical complications of alcohol abuse that have been only briefly mentioned here [1, 10].

Summary

Alcohol abuse is common worldwide and has been a major cause of health problems for thousands of years. The effects of alcohol on the body are remarkably protean, with devastating consequences on the brain, liver, musculoskeletal system, and other organ systems. Although the association between alcohol abuse and pneumonia has been recognized for more than two centuries, it is only relatively recently that a link between alcohol and acute lung injury was identified. This textbook will detail the remarkable epidemiological and experimental findings that elucidate the mechanisms by which alcohol abuse renders the even otherwise healthy people susceptible to lung disease and will preview the novel therapies that have the promise of improving lung health in these vulnerable individuals.

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Chapter 3
Current Definitions of Alcohol Use Disorders and the Use of Validated Questionnaires in Clinical Practice and Research

Karen Drexler

Abstract Alcohol use among people varies widely from abstinence to high-risk alcohol use to addiction. Diagnostic criteria have varied somewhat over time and across the globe, but the essential features of severe alcohol use disorder, also known as alcohol dependence or alcohol addiction, share common elements. A variety of validated questionnaires have been developed to assist clinicians and researchers in screening for at-risk alcohol use and/or severe alcohol use disorders. This chapter provides a brief overview of the definitions and cardinal features of alcohol use disorders and the alcohol use questionnaires that have been developed and validated in clinical studies.

Keywords Alcohol abuse • Alcohol dependence • Alcoholism • Alcohol use disorders • Diagnosis • Screening

Introduction

Alcohol is one of the most widely used and is the most abused psychoactive substance worldwide. Initial mild intoxication causes euphoria, a feeling of relaxation and of warmth (as capillaries dilate), and increased energy. With higher amounts of alcohol ingestion, people experience a loss of inhibition, poor judgment, unsteady gait, lack of coordination, slurred speech, slowed reaction time, and drowsiness [1]. At higher blood alcohol levels, stupor, coma, and respiratory arrest can occur.

With prolonged intoxication on a daily basis over weeks to months, biological tolerance to the intoxicating effects of alcohol develops and one is able to maintain

K. Drexler, M.D. (✉)
Department of Psychiatry and Director of the Substance Abuse Treatment Center, Atlanta VA Medical Center, Decatur, GA 30033, USA
e-mail: karen.drexler@va.gov

D.M. Guidot and A.J. Mehta (eds.), *Alcohol Use Disorders and the Lung: A Clinical and Pathophysiological Approach*, Respiratory Medicine 14,
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alertness and show diminished signs of intoxication at relatively high blood alcohol levels. When an individual has developed tolerance, signs of withdrawal often occur upon abrupt session or reduction of alcohol use. Withdrawal symptoms include anxious and irritable mood, insomnia, nausea, hand tremor, diaphoresis, tachycardia, and hypertension. More severe withdrawal can include vomiting, visual and auditory illusions or hallucinations, confusion, and withdrawal seizures. Severe alcohol withdrawal, classically termed "delirium tremens," can be life threatening due to cardiac arrhythmias and generalized tonic, clonic seizures [2].

Physiologic tolerance and withdrawal symptoms are together known as "physiologic dependence" [1, 3], which occurs when an individual has become addicted to alcohol. The biological factors that render an individual addicted to alcohol remain incompletely understood and some individuals with severe alcohol use disorders (particularly those with episodic alcohol dependence) do not manifest physiologic dependence.

Alcohol use disorders have been characterized along a spectrum from low-risk alcohol use to high-risk use to hazardous use (or mild alcohol use disorder) to alcohol dependence (or alcoholism, addiction, or severe alcohol use disorder). The majority of alcohol drinkers consume low to moderate amounts of alcohol without experiencing alcohol-related problems. These individuals are called "low-risk drinkers." According to the National Institute of Alcohol Abuse and Alcoholism (NIAAA), 72 % of adults in the USA never exceed the daily or weekly recommended limits. Other individuals (approximately 18 % of US adults) consume high amounts of alcohol without experiencing significant alcohol-related problems. These individuals are referred to as "high-risk" or "at-risk" drinkers. Unfortunately, a high percentage of heavy alcohol users experience significant alcohol-related problems. Those whose use is problematic but not compulsive are designated as "hazardous drinkers" by criteria in the 10th version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) from the World Health Organization (WHO) [3, 4] or diagnosed with alcohol abuse or a mild alcohol use disorder by the criteria published in the 4th version of the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-IV) [5]. Some heavy drinkers become addicted to alcohol when their use becomes compulsive such that they are not able to control their drinking and continue to use alcohol despite knowing that alcohol is causing significant medical, psychiatric, or other problems. By the WHO's ICD-10 guidelines and the American Psychiatric Association's DSM-IV criteria, these individuals are diagnosed with Alcohol Dependence and per DSM-V criteria the diagnosis would be further classified as a severe alcohol use disorder. The WHO diagnostic guidelines for Alcohol Dependence are illustrated in Table 3.1.

The WHO definition of psychoactive substance dependence is as follows:

> A cluster of physiological, behavioral, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviors that once had greater value. A central descriptive characteristic of the depen-

Table 3.1 WHO diagnostic guidelines for psychoactive substance dependence

A definite diagnosis of dependence should usually be made only if three or more of the following have been present together at some time during the previous year
(a) A strong desire or sense of compulsion to take the substance
(b) Difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use
(c) A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms
(d) Evidence of tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users)
(e) Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects
(f) Persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm

> dence syndrome is the desire (often strong, sometimes overpowering) to take psychoactive drugs (which may or may not have been medically prescribed), alcohol, or tobacco. There may be evidence that return to substance use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with nondependent individuals.

The terms "alcohol dependence" and "alcoholism" are synonymous with addiction to alcohol. The WHO has preferred the term "dependence"; however, the American Psychiatric Association (APA) prefers the term "substance use disorders." By comparison, the American Society of Addiction Medicine (ASAM) uses the term "addiction." ASAM issued a position statement in 2011 [6] updating their short definition of addiction as follows:

> Addiction is a primary, chronic disease of brain reward, motivation, memory, and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected by an individual pathologically pursuing reward and/or relief by substance use and other behaviors.
>
> Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished ability to recognize problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery related activities, addiction is progressive and can result in disability or premature death.

The ASAM definition of addiction is similar to that of the WHO and the APA, but adds information about the pathophysiology of the disorder, specifically dysfunction in brain circuits that mediate reward, motivation, memory, and inhibition. Discussion

of the neurobiology of reward and addiction is beyond the scope of this chapter, and interested readers are referred to an excellent review by Drs. Volkow and Li [7].

Low- and High-Risk Alcohol Use

The NIAAA has established guidelines for low-risk alcohol consumption [8], and these differ for men and women, and for men of different ages. For men between the ages of 21 and 64 years, the recommended amount is no more than 14 standard drinks per week and no more than 4 standard drinks on any occasion. For women of any age and for men 65 years and over, the recommendation is no more than 7 standard drinks per week and no more than 3 per occasion. What is a standard drink? A standard drink contains 14 g of pure ethanol and is equivalent to 1.5 oz of 80 proof spirits, 5 oz of table wine, 9 oz of malt liquor, or 12 oz of beer. Individuals whose alcohol consumption remains within these guidelines have less than a 1 % risk of developing an alcohol use disorder. However, those who exceed both the daily and weekly limits have about a 50 % chance of developing an alcohol use disorder at some time in their lives [8].

Many individuals suffering from a severe alcohol use disorder need medication and/or specialty care in an addiction treatment program in order to successfully abstain from alcohol use. However, selected high-risk drinkers respond well to brief interventions in primary care and other medical care settings [9, 10]. For this reason, the NIAAA and the Department of Veterans Affairs in the USA, along with the National Institute for Health and Clinical Excellence (NICE) in the UK, have recommended that general practitioners routinely screen for high-risk alcohol use.

Screening and Diagnostic Instruments

Even the most forthright individuals have difficulty quantifying their alcohol use based on the amount of alcohol (i.e., ethanol) they consume. Although the "standard drink" is defined above, in reality the preparation and consumption of alcoholic drinks, and particularly so-called "mixed drinks," makes it virtually impossible for someone to quantify their consumption based on recall alone. Therefore, a variety of questionnaires have been developed that can be used to routinely screen for high-risk alcohol use and alcohol use disorders. The NIAAA recommends a single-item screen, as follows [8]: The practitioner asks a prescreening question, "Do you sometimes enjoy beer, wine, or other alcoholic beverages?" Explicitly asking about beer and wine is important because some regard only spirits as "alcoholic beverages." If the patient answers affirmatively, then the follow-up screening question is asked: "How often in the last year did you have 5 or more drinks (for a man; 4 or more drinks for a woman) on one occasion?" If the answer to this follow-up screening question is anything other than "zero," then the screen is positive. Further questions

are needed to determine whether the person is an at-risk drinker or whether he or she may have an alcohol use disorder. If the person answers that they have not exceeded the daily limits within the past year, then the screen is negative and the practitioner is advised to remind the patient of recommended low-risk limits for alcohol use and commend the patient for healthy alcohol use.

The WHO and NICE recommend using the ten-question Alcohol Use Disorders Identification Test (AUDIT) when screening for alcohol use disorders [4, 11]. This instrument contains three questions about alcohol consumption and seven questions about symptoms of an alcohol use disorder, and each item is scored 0–4 points. The AUDIT can be self-administered on paper or on computer, and computerized versions can calculate the score and provide feedback on the individual's risk for alcohol use disorders and medical consequences. A score of 8 or more is considered positive on the ten-question AUDIT [12].

Although the ten-item AUDIT provides the information needed to screen for high-risk alcohol use and to make an alcohol use disorder diagnosis, it may be too lengthy for a busy medical practice. Therefore, the first three questions from the AUDIT about alcohol consumption have also been shown to provide an effective and valid screen for at-risk alcohol use and alcohol use disorders. The Department of Veterans Affairs Healthcare system screens enrolled veterans annually using this abbreviated version called the AUDIT-C where C' stands for "consumption." A score of 3 or more for a woman, or 4 or more for a man, is considered a positive screen on the AUDIT-C [13]. The clinician can then proceed with the full AUDIT or with a clinical interview to determine the presence of an alcohol use disorder.

Although there have been many different models for brief intervention for at-risk drinking, most have a few common elements. First, the screening and follow-up questions must be asked in a matter-of-fact and nonjudgmental manner as part of routine health screening. Because of the stigma associated with alcoholism, some patients may need reassurance that these questions are an important part of a general health screen. Secondly, if the screen is positive the clinician should determine whether an alcohol use disorder is present. If an alcohol use disorder is not present but the individual is at risk based on their consumption habits then the practitioner can recommend reducing drinking to within NIAAA guidelines or abstaining from alcohol completely, whichever is most appropriate. The NIAAA Clinician's Guide for Helping Patients Who Drink Too Much provides helpful patient education materials with strategies for cutting down or abstaining from alcohol and is a valuable tool for healthcare practitioners [8]. If an individual meets criteria for an alcohol use disorder then abstinence is recommended. Thirdly, if the patient is not willing to follow advice the clinician should reiterate their concern and encourage the patient to reflect on his or her reasons to continue drinking versus their reasons to quit, and express willingness to help whenever he or she is ready. If the individual's chief complaint or other pertinent medical conditions are exacerbated by alcohol use, the clinician should make the connection explicitly between their medical condition and their alcohol use and emphasize the importance of reducing or abstaining for health reasons. If the individual is willing to cut down or quit, the clinician should

assist them in setting a goal and provide support materials. Finally, the clinician should then follow up with questions about their alcohol use at subsequent visits. It is important to praise them for any approximations they have made toward achieving the drinking recommendations and offer to help with medication or referral to specialty addiction treatment as appropriate.

In addition to the AUDIT and AUDIT-C there are other clinician-administered and self-report questionnaires that have been used to screen for alcohol use disorders. The Michigan Alcoholism Screening Test (MAST) was the first such validated instrument [14]. There are several alternate versions of the MAST including the Short-MAST [15]. Both instruments have good reliability in men but may not be as reliable in women. They target severe alcohol use disorders and may not be sensitive to at-risk drinking.

The "CAGE" questionnaire has also been used successfully in inpatient hospital settings and trauma care settings to screen for alcohol dependence [16]. "CAGE" is an acronym for the four screening questions:

1. Have you ever felt the need to *Cut* down on your alcohol use?
2. Have you ever felt *Annoyed* by others concerns about your drinking?
3. Have you ever felt *Guilty* about your drinking?
4. Have you ever needed an *Eye-opener* first thing in the morning to treat the shakes or a hangover?

The CAGE questionnaire has the advantage of being easy to commit to memory and easy to score. A positive response to each question scores one point and even one positive answer should trigger more questions to elicit symptoms of an alcohol use disorder. Two positive responses is less sensitive, but highly specific for an alcohol use disorder. The disadvantage to the CAGE for screening is that it is unlikely to be positive for at-risk drinkers whose consumption is problematic and may be most responsive to brief interventions.

For research purposes, the Structure Clinical Interview for DSM (SCID) has been used to diagnose alcohol use disorders by DSM criteria [17–19]. It has good reliability and validity and is most often used in clinical trials to document the diagnosis of an alcohol use disorder [17, 20]. This clinician-administered questionnaire has modules for each of the major categories of mental disorders, as well as patient and non-patient versions. The entire SCID can be administered to determine substance use disorders and coexistent mental illness, or the alcohol use disorder module can be administered in isolation depending on the aims of the study. However, SCID administration requires 45–90 min for a complete evaluation, making it impractical for most clinical practices.

Summary

Alcohol use disorders span a spectrum from high-risk use to alcohol dependence or addiction. There are a variety of valid and reliable instruments available for screening for high-risk use or severe alcohol use disorders in clinical practice and research. Within clinical practice it is essential to screen everyone for underlying (and often