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Alcoholism: A multi-systemic molecular insult to organ damage.

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Abstract

Alcohol abuse can result in detrimental multisystem effects. Chronic alcohol abuse is known to be associated with pathophysiological changes in multiple organs often resulting in life threatening clinical outcomes e.g. breast and colon cancer, pancreatic disease, cirrhosis of the liver, diabetes, osteoporosis, arthritis, kidney disease, immune system dysfunction, hypertension, coronary artery disease, alcohol-induced cardiomyopathy and heart failure as well as central nervous system disorders. In this review article, we will discuss the multisystemic effects of alcohol abuse and explore in greater detail alcohol's impact on two main systems that result in pathophysiological changes i.e. the cardiovascular and central nervous systems.

Introduction

According to the Center for Disease Control (CDC), each day 28 people in the United States die in a motor vehicle accident that involves an alcohol-impaired driver. One person dies every 53 minutes in an alcohol use related accident compared to one every 33 minutes for heart disease. Alcohol is responsible for about 88,000 deaths in the U.S each year according to Center for Disease Control.As reported by the Department of Transportation (US), in 2014 drivers with blood alcohol concentration (BAC) levels of 0.08% or higher involved in fatal crashes was thirty percent for adults between 21 and 24 years of age. Fatal crashes for adults 25 to 34 years of age was thirty-nine percent and for people 35 to 44 years of age it was twenty-four percent. Motorcyclists 40-44 years of age have the highest death toll with BACs of 0.08% or greater (40% in 2013). Alcohol-related crashes account for an estimated 18% of $103 billion in annual U.S auto insurance payments (Funk et Wagnalls 2017). According to a recent report by Allstate

insurance company, alcohol impaired drivers are estimated to cost American taxpayers $21 -$24 billion per year.

Despite motor vehicle deaths associated with alcohol intake there is importantly a more chronic life threatening impact of alcohol abuse on public health. Alcoholism is a pathology resulting from high alcohol intake (Peck RS. et. al, 2008). Alcoholism is classified as an “Alcohol Use Disorder" under which there are several sub-categories such as alcohol abuse which refers to a pattern of drinking which causes one to fail to meet everyday life obligations, interferes with the ability to make decisions or operate machinery, and engenders trouble legally and domestically (Gebers MA et.al,2008). Another alcohol use disorder is alcohol dependence, which is diagnosed when there are clinically significant impairments.Criteria for such a diagnosis include (but are not limited) high level sof tolerance, the presence of symptoms upon withdrawal, rate of success in quitting, time spent both drinking and recovering from its effects, and failure to quit drinking for the sake of a separate physical or mental issue that is worsened by alcohol use.

With alcoholism, the behavior does not necessarily initiate abruptly. Alcoholism progresses from light drinking with little to no consequences to excessive uncontrollable drinking which most often affects a person’s behavior. When a person becomes an alcoholic, they most often lose the ability to regulate drinking habits. Individuals who are struggling with alcohol abuse often feel they cannot function normally or reach their full potential without drinking alcohol. As a result, they often depend on it for psychological support. With time, chronic alcohol abuse can cause physical side effects and resultin severe systemic complications.

Alcoholism is arranged into three categories i.e. moderate, binge, or severe. Moderate alcohol consumption is defined as one drink per day for women while two drinks per day is considered mild for men. The National Institute on Alcohol Abuse and Alcoholism defines binge drinking as 4 drinks for women and 5 drinks for men within a 2-hour period which brings blood alcohol concentration to 0.08 grams. According to the substance Abuse and Mental Health Services Administration, severe alcohol use is 5 or more days in a month of binge drinking.

Despite the high incidence of alcohol use associated vehicular deaths, alcohol is also associated with more insidious disease processes that can impact multiple organ systems including the cardiovascular and central nervous system. Although the effects of alcohol on the development of systemic disease can differ depending on the person, severe complications of chronic drinking are often dependent on a person's genetics, state of health, gender, body mass, and age as well as the presence or absence of other co-morbidities. Therefore, chronic alcohol abuse can lead to multi-systemic disease similar to what is experienced by diabetic patients.

As shown in Figure 1 alcohol abuse is known to be associated with known pathophysiological changes (IARC Monogr Eval Carcinog Risks Hum., 2010) in most organs e.g. the incidence of breast cancer in women (Hamajima H. et. al, 2002), colon cancer (Na H-K et. al, 2017), pancreatic disease (Korsten M.A. et. al,1990), cirrhosis of the liver (Korsten M.A. Et. al, 1987), diabetes (Babor T. et. at, 2012), osteoporosis (Abukhadir S. et. al, 2013), arthritis (Wang K-S. et. al, 2014), kidney disease (Varga Z. et. al, 2017), immune system dysfunction (Curtis B.J et. al, 2013), hypertension (Pan X-Q et. al, 2010), coronary artery disease (Dai J. et. al, 2015), alcohol-induced cardiomyopathy (Maisch B, 2016), and heart failure (Larsson S.C.

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et. al, 2017) as well as central nervous system disorders (Kuehn D. et. al, 2012). In this review article, we will discuss the multisystemic effects of alcohol abuse and explore in greater detail two main systems that develop pathophysiological effects from alcohol abuse i.e. the cardiovascular and central nervous systems.

Breast Cancer and Colon Cancer, Liver , Bone ,and Kidney Disease, Diabetes, and the Immune System: Effects of Alcohol

Many studies show drinking alcohol increases the risk of breast cancer. The risk of breast cancer increases by almost 7% for each alcohol drink consumed per day. Drinking 2-3 alcoholic beverages a day has a 20% greater risk for breast cancer in women who drink (Hamajima H. et. al, 2002). It is known that estrogen levels in women can promote or control breast cancer. High estrogen levels have been reported to be associated with a risk for breast cancer, and one of the factors that increases estrogen levels is excessive alcohol consumption (Hamajima H. et. al, 2002). The World Health Organization International Agency for research on cancer care have concluded that for breast cancer there is an increased risk with increasing alcohol beverage consumption regardless of beverage type.

Similarly, alcohol use has been linked with a high risk of cancer of the colon and rectum. Meta-analyses of large cohort studies as well as experimental studies suggest that chronic alcohol consumption increases the risk of gastric and colon cancer (Na H-K et. al, 2017). Ethanol is metabolized by alcohol dehydrogenases, catalase, or cytochrome to acetaldehyde, which is further oxidized to acetate by aldehyde dehydrogenase. Acetaldehyde is classified by the International Agency for Research on cancer as a group 1 carcinogen to humans. The World

Cancer Research fund and American Institute for cancer research have reported that consumption of more than 30g/day of ethanol can be a cause of colorectal cancer.

As the body takes in alcohol the liver metabolizes it. When too much alcohol is consumed, it is not properly metabolized and toxic metabolites accumulate then circulate within the body. The liver is the primary site for alcohol metabolism. Alcohol is detoxified and removed from the blood through a process called oxidation (DiMartini A. et. al, 2015). Oxidation prevents alcohol from accumulating in cells and organs causing cell death. Women have less of the detoxifying enzymes, which is why alcohol passes into their bloodstream quicker than in men.

There is an entire subcategory of diseases called alcohol-related liver disease (ALD). The liver's detoxifying abilities are used in part for toxic substances and can change toxins from harmful to beneficial effects or eliminate them entirely from the body. According to the Germany Institute for Quality and Efficiency in Health Care, when alcohol is consumed in excess, liver cells die and are replaced by scar tissue. This phenomenon results in cirrhosis and is generally detected through blood tests, biopsy, or MRI or ultrasound. Liver scarring as a result of cirrhosis makes it difficult for the liver to perform detoxification, leaving patients susceptible to inflammation and infection. In the case of manypatients suffering from cirrhosis , abstinence may ameliorate many of the associated clinical conditions. However, some individuals with severe liver cirrhosis will likely require a liver transplant (DiMartini A. et. al, 2015).

The skeletal system performs vital functions including locomotion and biomechanical function, blood cell production, endocrine and immune regulation and calcium storage (Jang H-D, et. al, 2017). Osteoporosis, a condition in which one's bones become weakened due to tissue

loss or vitamin D and calcium deficiencies and often manifests with alcohol related liver disease (ALD). When alcohol is consumed excessively, it can inevitably lead to nutrient deficiency and bone loss. In a study done by the Korean National Health and Nutrition Examination Survey in which participants self-reported their weekly alcohol intake and consented to tests for bone mineral density (BMD) by dual energy x-ray absorptiometry, the results showed that there was an inversely proportional relationship between alcohol intake and BMD. This finding corroborates the initial belief that alcohol intake destroys bones and puts drinkers at a significantly greater risk of osteoporosis.

All studies attempting to elucidate a direct link between alcohol abuse and kidney disease have been mostly inconclusive; there are some studies that confirm other means by which alcohol abuse can engender kidney dysfunction (Varga Z.et. al, 2017). One likely mechanism is through oxidative stress; as excessive consumption of alcohol causes an increased production of reactive oxygen species. The excess of free radicals causes tissue injury, apoptosis, and inflammation, all of which have the capacity to cause tissue damage as well as cell death. In addition, the proven deteriorating effects of alcohol on other organs can contribute to damage of the kidneys. (Varga Z. et. al, 2017).

Two important hormones produced by the pancreas are glucagon and insulin (Korsten M.A. et. al,1990). It is estimated that a person must engage in 10 to 15 years of heavy drinking (of at least 60 to 80 grams of alcohol per day or about six to eight drinks per day, usually more), before alcoholic pancreatitis becomes clinically apparent. The pancreas of an alcoholic often shows fibrosis, calcium deposits, loss of functioning enzyme and hormone producing cells which may lead to poor digestion of food and loss of control over blood sugar levels. Other serious complications associated with alcoholic pancreatitis are kidney failure, jaundice, and formation

of pancreatitis pseudocysts. These cysts are harmful because when they become too large, they may rupture in the abdominal cavity or cause hemorrhage by eroding into a large adjacent abdominal blood vessel (Varga Z. et. al, 2017).

Chronic complications of alcoholic pancreatitis arise as a result of inadequate pancreatic production of certain digestive enzymes and hormones. This is referred to as pancreatic insufficiency. The most common clinical outcomes are weight loss, steatorrhea, and diabetes mellitus. Diabetes mellitus results from the lack of insulin production by the pancreas. Its development denotes extensive loss of insulin-secreting cells within the atrophied pancreas. In addition, people consuming excessive amounts of alcohol can also suffer acute alcoholic pancreatitis (Korsten, M.A. et. al,1990).

The immune system is yet another system affected by alcohol abuse. The immune system consists of a group of organs, cells, and tissues in the body that serve the function of fighting infection, illness, and disease. When people consume alcohol in excess, inflammation occurs at a cellular level which oftenb activates the immune system. As a result the body can become immuno-deficient (Barr T. et. al, 2016). Additionally, heavy drinking is associated with declining numbers of lymphocytes resulting in a higher susceptibly to bacterial and viral infections (Barr T.et. al, 2016).

Cardiovascular System: Effects of Alcohol

Chronic alcohol consumption is known to contribute to the occurrence of cardiovascular disease by negatively impacting not only the vasculature of the heart and peripheral vasculature, but also has direct negative effects on the myocardium (Figure 2). It is known that alcohol abuse

can lead to coronary artery related heart disease (Dai J.et. al, 2015), hypertension (Pan X-Q et. al, 2010), myocardial infarction (Larsson S.C. et. al, 2017) and alcohol induced cardiomyopathy which often results in heart failure (Maisch B, 2016) as well as cerebral stroke (Hillbom J. et. al,1999) (see Figures 1and 2). Not only does the abuse of alcohol result in pathophysiological changes in structure, but also functional changes in the heart and vasculature. Chronic alcohol consumption can result in heart failure and cardiomyopathy, which is a structural enlargement of the heart, as well as atrial fibrillation (an electrical dysrhythmia). An estimated 2.7-6.1 million people in the United States have atrial fibrillation (AF). With the aging of the U.S. population, this number is expected to increase. Atrial fibrillation often requires either surgical ablation and/or medical management with anti-arrhythmic drugs, anti-coagulants, and rate/rhythm control medications e.g. beta-blockers. Atrial fibrillation can result in emboli and lead to cerebral strokes (Tolstrup J. et. al, 2016).

Alcohol consumption has been directly linked to the occurrence of atrial fibrillation. In a study done on the risk of atrial fibrillation associated with alcohol consumption, 88,782 men and women were studied during 2003-2010 were used (Tolstrup J. et. al,2016). Information on incident cases of atrial fibrillation was obtained from a validated nationwide registry. The result proved that high alcohol consumption was associated with the risk of atrial fibrillation among men, but not as much among women. Among the men who drank 28-35 and 35 plus drinks/week, the hazards ratio was 1.40 and the confidence interval was 1.62 compared with men who consumed 1 drink/week. The study concluded that alcohol consumption was associated with a higher risk of atrial fibrillation in men.

There are also reports of the beneficial effects of alcohol consumption on the cardiovascular system (Agarwal D.P, 2002). According to one study, drinkers consuming less

than 30 grams of alcohol/day without ever engaging in heavy drinking had the lowest risk of developing coronary artery disease relative to those who did not drink at all (Dai J. et. al, 2015). Additionally, it was advised that women drink less than men as the effects of drinking became more detrimental to the health of women before it did for men because of body composition and tolerance levels. A meta-analysis in the British Medical Journal comparing varying levels of alcohol consumption and specific cardiovascular conditions found that light to moderate alcohol intake was associated with a 25%-35% decline a person's risk for coronary heart disease. However, the cardioprotective effects of alcohol consumption were found to be dose dependent, with 2.5g-14g/day of alcohol being beneficial and >60g/day significantly increasing the risk of stroke . (Ronksley P. et al, 2011).

A large case-control study combined observations from 52 countries reported an association between alcohol consumption and the risk of myocardial infarction (Lippi G. et al, 2010). The study found that heavy drinking (6 drinks or more) might increase the risk of acute myocardial infarction in the following 24 hours after alcohol consumption, especially for the elderly. However, according to subsequent studies, patients who survive an MI might benefit from moderate alcohol consumption due to decreased risks of all-cause and cardiovascular mortality (Agarwal D.P., 2002). In the case of stroke, studies showed a decreased risk of stroke with mild alcohol exposure (<15g/day) while moderate drinkers showed no difference (Agarwal D.P., 2002) as compared to non-drinkers. Furthermore, it was reported that in older patients heavy alcohol increases their risk for heart failure and hypertension, whereas moderate alcohol drinking did not show negative effects on cardiovascular function (Kalla A. and Figueredo VM, 2017).

The heart has not only electrical components that can be impacted by alcohol consumption e.g. AF and other dysrhythmias of the heart, but also has a mechanical function. The pumping of the heart (excitation-contraction coupling) is responsible for the force generated to “pump blood". When cardiomyocytes of the heart develop impaired contraction (systolic) and relaxation (diastolic) function because of chronic alcohol abuse, the condition results in cardiac enlargement, reduced ejection fraction and is referred to as alcoholic cardiomyopathy. Alcohol has been shown to be involved in about 33% of all cases of dilated cardiomyopathy(Maisch B 2002). (Figure 2).

We have reported that the observed detrimental effects of acute alcohol exposure on the heart are mediated through modulation of the survival pathway known as the PI3K/Akt signaling (Umoh N.A, 2014). In particular, acute exposure to low alcohol, such as in casual drinking, decreases Akt activity due to reduced oxidative cellular stress. On the other hand, acute exposure to high alcohol, such as in binge drinking, led to the activation of Akt due to increased cellular oxidative stress. This latter effect can inhibit AMPK leading to the manifested contractile dysfunction. Accordingly, we have shown that acute low alcohol improves cardiac function *in vivo* through enhanced contractility and stroke volume, while acute high alcohol levels induce the opposite effect in a PI3K/Akt-dependent manner.

Interestingly, we have found that the beneficial cardioprotective effect of chronic alcohol intake were PI3K/Akt-independent. The enhanced contractility was instead associated with the activation of Nrf-2 survival pathway (Walker R.K., 2013). However, the reduced contractility and compliance of hearts chronically exposed to high levels of alcohol was mediated by reduction in the PI3K/Akt activity and a simultaneous increase in oxidative stress.

Along this line, a recent meta-analysis concluded that high level of alcohol exposure is associated with elevated risk for atrial fibrillation (AF) while no risk was found with low alcohol intake (Gallagher C. et. al, 2017). This heightened AF occurrence with elevated alcohol intake could be due to an increase in triggered atrial calcium waves induced by L-type calcium channels (Shiferaw Y et al, 2017). Thus, improper calcium channel expression and activity may contribute to alcohol-induced cardiomyopathy. In thid regard, it was suggested that dysregulation in protein synthesis and autophagy contribute to the reduced contractility seen with high alcohol exposure (Steiner JL et al, 2017).

The prevalence of the alcohol-induced cardiomyopathy is most likely underreported as autopsy findings commonly reveal pathologic characteristics of the heart that yield no clinical symptoms or diagnostic clues other than family reporting (Maisch B, 2002). The most effective treatment for alcohol-induced cardiomyopathy is the cessation of alcohol intake. Although high amounts of alcohol consumption can be detrimental to the heart, when used in moderation alcohol can help the user avoid coronary artery disease (CAD), a condition in which plaque builds up in the arteries. Eight hundred and forty-three male twins age 42-55 years old who were casual drinkers without coronary artery disease were observed over a period of years (Dai J. et. al, 2015). Their alcohol use was recorded and over the years, 129 of the men died from CAD and 219 had died from other cardiovascular conditions. The results found that in a majority of cases, the twin who had suffered from CAD had consumed less alcohol. The study concluded that moderate alcohol consumption is associated with a lower CAD mortality risk. The belief is that alcohol slows the process by which plaques form in the coronary arteries (Dai J. et. al, 2015). Furthermore, moderate alcohol intake has been shown to impact cholesterol levels i.e.

HDL and LDL. Alcohol intake may increase plasma HDL levels either by altering the synthesis or clearance of HDL (Agarwal D.P., 2002).

Wine consumption has similarly been shown to be cardio-protective (Lippi G. et. al, 2010). The term French paradox describes the relatively low incidence of cardiovascular disease in the French population and the benefits of consuming red wine. After nearly 20 years, several studies have investigated the positive biological and clinical association of red wine consumption with cardiovascular disease and mortality. Light to moderate intake of red wine produces a kaleidoscope of potentially beneficial effects that target all phases of the atherosclerotic process, from atherogenesis to vessel occlusion (flow-mediate dilation, thrombosis). Red wine components, especially resveratrol, and other polyphenolic compounds may decrease oxidative stress, enhance cholesterol efflux from vessel walls (by increasing levels of high-density lipoprotein cholesterol) and inhibit lipoproteins oxidation. Light to moderate red wine consumption is also associated with a favorable genetic modulation of fibrinolytic proteins, ultimately increasing the surface-localized endothelial cell fibrinolysis. Conversely, chronic heavy alcohol consumption and binge drinking are associated with increased risk of cardiovascular events.

Central Nervous System: Effects of Alcohol

The forebrain, the midbrain, and the hindbrain (Figure 3). can be affected by high chronic alcohol consumption. However, all divisions of the brain can be affected differently by alcohol abuse. Alcohol abuse has well recognized neurological as well as psychological side effects (Figure 3). Neonatal alcohol syndrome, seen in infants born to chronic alcohol abusers results in impaired neonatal brain development as well as physical and mental disorders.

Alcohol is known to not only result in brain damage, but also mental disorders as well. Neuropsychological consequences of brain damage resulting from chronic alcohol abuse include a change in behavior, memory loss (especially short term), amnesia and atrophy (shrinkage of the cerebral cortex) (Oscar-Berman M, 1992). The areas of the brain most susceptible to alcohol-induced damage are the limbic lobe, the diencephalon, and the basal forebrain.

Alcoholism is thought to contribute to premature mental aging. According to the right hemisphere hypothesis, the right hemisphere of the brain is more susceptible to damage,which explains the disproportionate impact of alcohol on nonverbal and visuospatial functions as well as emotional dysfunctions all of which are thought to be governed by the right hemisphere (Oscar-Berman M, 1992). In one study, alcoholics, average drinkers, and non-drinkers were given images to describe and analyze in order to gauge their emotional intelligence and competence. According to the results, the alcoholic groups reported emotions that were more intense than non-alcoholics, which suggested that alcohol disrupts emotional competence and emotional intelligence. Additionally, although the alcoholics were significantly more depressed than non-drinkers, this was not a significant factor in the differences in performance of the two groups.

Estimates of the incidence of Parkinson's disease range from 7.9 to 19 per 1,000,000 person-years and a prevalence of 57 to 230 per 100,000 populations (Nussbaum R.L. et. al, 2003). Although genetics and environmental exposures are recognized as being contributors to Parkinson's disease, researchers have also begun to investigate the relationship between alcohol consumption and the occurrence of Parkinson's disease (Nussbaum R.L. et. al, 2003). According to a review article on alcohol consumption and Parkinson's disease, a prospective study conducted in Finland found that persons who consumed more than 5 grams of alcohol per day

had an increased risk of developing Parkinson's disease compared to non-drinkers. Another study from the U.S.A. found an increased risk for the development of Parkinson's Disease among men who consumed 10 to 19. 9 grams of alcohol per day and women who consumed 10 to 14.9 grams of alcohol per day (Huang W. et. al, 2016). The study also revealed that heavy alcohol consumption, defined as having at least two drinks per day, was associated with an increased risk for Parkinson's Disease while low to moderate alcohol consumption, i.e. beer drinking, of less than one drink a day was associated with a decreased incidence for the development of Parkinson's Disease.

Drinking more than the recommended limit of alcohol has also been shown to increase a person's risk of developing common types of dementia such as Alzheimer's disease and vascular dementia (Huang W. et. al, 2016). The recommended maximum limits of alcohol as mentioned previously are reported to be 14 units each week for men and women spread over three or more days.

Alzheimer's disease is caused by a concentrated deposition of amyloid-β (Aβ) protein in the brain, memory failure, and dementia (Langballe E. et. al, 2015). Preventative measures have encouraged low consumption of alcohol. Studies have reported that moderate consumption of ethanol may protect against the buildup of Aβ protein, though this advice is dangerous because "low to moderate" are poorly defined ubiquitously. Like with Alzheimer's, studies have found that greater intake of alcohol is associated with higher risk of dementia, which is marked by the decline in cognitive function severe enough to interfere with daily life (Langballe E. et. al,2015). However, light to moderate consumption of alcohol can reduce one's chances of developing dementia 25-28%. However, with Alzheimer's, the amount of alcohol being endorsed is vague

and the lack of specificity makes it difficult to practically apply the information within this finding.

The most common form of alcohol-related brain damage is alcoholic dementia which is also called alcohol-related dementia. This clinical syndrome includes Korsakoff's syndrome called Korsakoff's psychosis. Korsakoff syndrome is a chronic memory disorder caused by severe deficiency of thiamine (vitamin B-1). The most common cause of Korsakoff syndrome is alcohol misuse, but AIDS and poor nutrition can also be associated. Since thiamine (vitamin B1) helps brain cells produce energy, when thiamine levels fall too low, the brain cannot generate enough energy to function properly. An overwhelming 80% of alcoholics are vitamin B1 deficient.

The cerebrum controls mental processes such as memory, movement, and sensory perception (Figure 3). According to the 2nd edition of the Dictionary of Nursing, when there is thiamine deficiency, it can result in confusion and memory loss. This is associated with Wernicke–Korsakoff syndrome (WKS) which is a disease that has two separate syndromes: (1) Wernicke's encephalopathy which is considered the acute phase with a shorter duration and more serious symptoms and (2) Korsakoff's psychosis, a long-lasting and chronic condition that psychologically and socially debilitates the patient.

Korsakoff's psychosis has been shown to be clearly associated with thiamine deficiency and is defined by severe retrograde and anterograde amnesia, meaning the patient loses old memories and lacks an ability to form new ones (Brokate B. et. al, 2003). In addition to thiamine deficiency, the cortical atrophy caused by alcohol intoxication causes frontal lobe dysfunction which worsens the effects of this condition (Brokate B. et. al, 2003). It is important to note that length of drinking plays a more significant role in the manifestation of Korsakoff's psychosis as

opposed to the quantity of drinking. People who have been drinking for a long period of time experience worse effects than those who have consumed significant amounts over a short period of time.

The pathological lesion associated with Wernicke's encephalopathy is also located in the cerebrum. The encephalopathy results in extreme mental confusion and forgetfulness. Someone suffering from this component of WKS may have extreme difficulty doing something as common as exiting a room because of the disruption in brain function making it virtually impossible to comprehend the idea of a door or exiting. Treatment is recommended in early stages of WKS and consists of administering vitamin B1. Patients that are unable to reverse their condition during later stages require custodial care and mental support. An article on "Alcoholic Brain Damage about Alcohol Research and Health" states that 25% of cases of WKS develop to a point where custodial care becomes necessary.

. People who consume excessive amounts of alcohol may not walk properly, demonstrate poor coordination, and have impaired balance (Mariën P et. al, 2005). This is due to the effects of alcohol on the cerebellum. Like the cerebrum, the cerebellum is sensitive to excessive alcohol and its malfunction is also associated with the psychosis associated with WKS. About 80% to 90% of alcoholics who develop Wernicke's encephalopathy also develop Korsakoff's psychosis (Brokate B. et. al, 2003). Similar to alcoholics with encephalopathy, patients in this state are confused and have learning and memory problems. The difference, however, is that the psychosis often comes with physical debilitation, as it affects the cerebellum which controls the body's movements.

Although long-term abuse of alcohol is related to the development of the Wernicke-Korsakoff's syndrome or related dementias, light to moderate alcohol intake have been

suggested to reduce the risk of dementia and Alzheimer's disease (Letenneur L, 2004). A population based prospective study done in Bordeaux, France found that for subjects drinking 3 to 4 standard glasses of wine per day, categorized as moderate drinkers, the odds ratio was 0.18 for incident dementia and 0.25 for Alzheimer's disease. After adjusting for age, sex, education, occupation, baseline cognitive performances and other possible confounders, the odds ratio was respectively 0.19 and 0.28. In the 922 mild drinkers (1 to 2 glasses per day) there was a negative association only with Alzheimer's disease after adjustment. The inverse relationship between moderate wine drinking and the incidence of dementia was explained neither by known predictors of dementia nor by medical, psychological, or socio-familial factors. Light-to-moderate drinking (one to three drinks per day) was significantly associated with a lower risk of dementia.

Alcohol is known to behave as a depressant on the central nervous system (Kuehn D. et. al, 2012) thereby affecting a person's ability to behave appropriately in response to environmental stimuli. Alcohol can affect the frontal lobe of the brain, which can make an individual act without thinking and makes it difficult to control emotion. The frontal lobe, thalamus, middle cerebellar peduncle have been demonstrated to be more vulnerable to the effects of acute alcohol consumption (Kong L.M. et. al, 2012). The frontal lobe is responsible for decision making, planning, learning, and using self-control. Gamma Aminobutyric Acid (GABA) is the brain's primary inhibitory neurotransmitter that acts to slow neuronal signals along pathways in the brain to produce a natural calming effect (Allan A. M. et al, 1986). When alcohol is present, the activity of the GABA receptor increases. It inhibits neuronal signals longer and allows the GABA receptor to act to a greater extent than in the absence of alcohol.

Alcoholism can alter the cognitive process. Some of the effects are memory loss, difficulty with learning, and emotional disturbances. An insight from neuroimaging studies shows that acute alcohol administration affects brain structures implicated in motivation and behavior control and chronic intoxication is correlated with structural and functional abnormalities (Bjork J.M. et al, 2014). The cerebral cortex, which is responsible for thinking, senses and controls the ability to make good judgments or to think clearly is often impaired by alcohol.

When affected by alcohol, the hippocampus, which controls memory, can result in blackouts or memory loss. The hypothalamus coordinates important activities in the pituitary gland, the autonomic nervous system (see figure), and controls body temperature, hunger, thirst, and other homeostatic systems. After drinking too much alcohol, hunger, thirst, blood pressure and the urge to urinate increase while body temperature decreases.

The medulla oblongata is also affected by alcoholism (Oscar-Berman M, 1992). The medulla is responsible for involuntary functions such as body temperature regulation and breathing. When the medulla is affected, it causes the body temperature to drop and can depress respiration.

Drugs: Effects of Alcohol

Consuming alcohol with other drugs whether simultaneously or sequentially can have a tragic effect. According to a Consumer Health News (English) article on “Opioids and Alcohol a Dangerous Cocktail”, when alcohol is consumed with opiates or "painkillers", such as oxycodone, severe respiratory depression can occur. In one study, 12 young volunteers between

age 21 to 28 and 12 older volunteers between age 66 and 77 were observed as they consumed alcohol and opioids. None of the volunteers had taken opioids before. The study found that the consumption of only one oxycodone tablet with a "modest" volume of alcohol is sufficient to increase the risk of respiratory depression. The older individuals were more susceptible to the side effects. Likewise, when taken with sedatives, alcohol, which is a depressant, works along with the sedative to slow the user's heart rate and breathing. Due to alcohol's damaging effects on the central nervous system, especially the parts of the brain that impact mood and behavior when taken with sedatives or antidepressants there is a worsening of behavioral and mental side effects through worsening of symptoms making depression harder to treat.

Epidemiology of Alcohol Abuse: Psychological and Societal Effects

In addition to pathophysiological systemic and cellular effects, people suffering from alcoholism may also experience psychological and social effects. A societal impact of alcoholic mothers has been reported. According to the British Medical Journal, it was estimated that in every 67 women who consumed alcohol during pregnancy, they will deliver a child with Fetal alcohol syndrome (FAS), which translates to about 119,000 children born with FAS in the world every year (Nathanson V, et al 2008).

Psychological effects of alcohol can include severe depression, suicidal thoughts and tendencies, anxiety, violence, and unexplained mood swings. Persons afflicted with alcoholism often suffer from isolation and separation from family, loved ones, and friends. Alcoholics tend to socialize with individuals sharing a similar addiction. Alcoholism, therefore, not only poses

physical and physiological effects, but also is often associated with negative psychological and social outcomes.

As children transition to young adults, many attend college away from home and use the extended freedom to engage in social drinking. “Drinking games”, or competitions in which individuals perform difficult tasks for alcohol as either the punishment for losing or the reward for winning, encourage partygoers to drink more than they otherwise would. This can result in college atmospheres being especially dangerous for people prone to addiction and alcoholic behavior. The implication is that college environments can be a risk factor and contributor to the growing problem of alcohol abuse. A study in the Journal of Adolescent Health found that students believed alcohol was “very easy to obtain” on campuses as prices are intentionally kept very low. The unmonitored college atmosphere provides a setting for experimentation that is potentially harmful.

Similar to many chronic diseases, alcoholism develops over time. Early symptoms include stress, which is associated with availability of alcohol, a sudden gravitation to social groups that actively encourage drinking and a reliance on drinking to achieve a specific psychological state (Zhou Y, et. al, 2016). Typically, the individual will begin to exhibit a heightened tolerance to alcohol, consuming more and showing noticeably less effects than other

people. In addition, a person's ability to manage their drinking will decline, as they are unaware of how much they will drink.

Conclusions

Despite beneficial effects having been reported for mild alcohol consumption, there are, nevertheless, there can be negative life threatening effects on multiple organs especially the cardiovascular and central nervous system. The beneficial effects of alcohol appear to be dependent on multiple factors including age, gender, co-morbidities as well as the frequency and amount of alcohol consumed (Stockley C.S., 2012). The benefits of moderate alcohol consumption have been reported to include a reduction in the risk of developing coronary heart disease, congestive heart failure, intermittent claudication, and myocardial infarction. Furhter, study is needed on the effects of alcohol not only from a health perspective, but also from a societal outcome.

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REFERENCES

1. Peck R.C., Gebers M.A., Voas R.B., Romano E. The relationship between blood alcohol concentration (BAC), age, and crash risk. Journal of Safety Research. May 2008; 39(3): 311-319.

2. Blincoe L. J., Miller T. R.,Zaloshnja,E., Lawrence,B. A. The economic and societal impact of motor vehicle crashes, 2010(Revised). Washington, DC:National Highway TrafficSafety Administration.May 2015; (Report No. DOT HS 812 013).

3. National Center for Statistics and Analysis. Alcohol impaired driving: 2014 data. Washington, DC:National Highway Traffic Safety Administration. December 2015;(Traffic Safety Facts. DOT HS 812 231).

4. Alcoholism. Funk & Wagnalls New World Encyclopedia [serial online]. 2016;1p. 1. Available from: Funk & Wagnalls New World Encyclopedia, Ipswich, MA. Accessed May 5, 2017.

5. Substance Abuse and Mental Health Services Administration (SAMHSA). 2015 National Survey on Drug Use and Health (NSDUH). Table 2.83B—Alcohol Use, Binge Alcohol Use, and Heavy Alcohol Use in Past Month among Persons Aged 12 to 20, by Demographic Characteristics: Percentages, 2014 and 2015.

6. International Agency for Research on Cancer Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol consumption and ethyl carbamate. IARC Monogr Eval Carcinog Risks Hum 2010;96:3–1383.

7. Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer – collaborative reanalysis of individual data from 53 epidemiological studies, including 58515 women with breast cancer and 95067 women without the disease. British Journal of Cancer. November 2002; 87(11):1234-1245.

8. Na H-K, Lee JY. Molecular Basis of Alcohol-Related Gastric and Colon Cancer. Ferguson L, Parslow VR, eds. International Journal of Molecular Sciences. June 2017;18(6):1116.

9. Korsten M.A., Wilson J.S., Lieber C.S. Interactive effects of dietary protein and ethanol on rat pancreas. Protein synthesis and enzyme secretion. Gastroenterology. July 1990; 99(1): 229–236.

10. Korsten M.A., Klapholz M.B., Leaf M.A., Lieber C.S. Use of the triolein breath test in alcoholics with liver damage. Journal of Laboratory and Clinical Medicine. February 1987; 109(1):62-66.

11. Babor T., Rehm J., Jernigan D., Vaeth P., Monteiro M., Lehman, H. (n.d). Alcohol, diabetes, and public health in the Americas. Revista Panamericana De Salud Publica-Pan American Journal Of Public Health. August 2012; 32(2): 151-155.

12. Abukhadir S. S., Mohamed N., Mohamed N. (n.d). Pathogenesis of Alcohol-Induced Osteoporosis and its Treatment: A Review. Current Drug Targets. December 2013; 14(13): 1601-1610

13. Wang K-S, Liu X., Wang L. (n.d). Associations of alcohol consumption and mental health with the prevalence of arthritis among US adults: data from the 2012 National Health Interview Survey. Rheumatology International. September 2014; 34(9): 1241-1249.

14. Di Giuseppe D., Alfredsson L., Bottai M. Long term alcohol intake and risk of rheumatoid arthritis in women: a population based cohort study. The British Medical Journal. July 2012; 345: e4230.

15. Varga Z, Matyas C, Paloczi J, Pacher P. Alcohol Misuse, and Kidney Injury: Epidemiological Evidence and Potential Mechanisms. Alcohol Research: Current Reviews. April 2017;38(2):e-1-e-6.

16. Curtis BJ, Zahs A, Kovacs EJ. Epigenetic Targets for Reversing Immune Defects Caused by Alcohol Exposure. Alcohol Research : Current Reviews. Spring 2013;35(1):97-113.

17. Pan X-Q, Zhang Y-H, Liu Y-Y, Tong W-J. Interaction between the C(-344)T polymorphism of CYP11B2 and alcohol consumption on the risk of essential hypertension in a Chinese Mongolian population. European Journal Of Epidemiology. November 2010;25(11): 813-821.

18. Dai J, Mukamal K, Krasnow R, Swan G, Reed T. Higher usual alcohol consumption was associated with a lower 41-y mortality risk from coronary artery disease in men independent of genetic and common environmental factors: the prospective NHLBI Twin Study. American Journal Of Clinical Nutrition. July 2015; 102(1):31-39.

19. Maisch B. Alcoholic cardiomyopathy: The result of dosage and individual predisposition. Herz. September 2016;41(6):484-493.

20. Larsson S.C, Wallin A, Wolk A. Alcohol Consumption and risk of heart failure: Meta-analysis of 13 prospective studies. Clinical Nutrition. May 2017; pii: S0261-5614(17)30168-1.

21. Kuehn D, Aros S, Cassorla F, et. al. A Prospective Cohort Study of the Prevalence of Growth, Facial, and Central Nervous System Abnormalities in Children with Heavy Prenatal Alcohol Exposure. Alcohol Clinical & Experimental Research. October 2012; 36(10):1811–1819.

22. DiMartini A, Neuberger J. Alcohol Abuse And Liver Disease. Chichester, West Sussex: Wiley-Blackwell; June 2015.

23. Informed Health Online. How does the liver work? Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG). September 2009[Updated 2016 Aug 22].

24. Jang H-D, Hong J-Y, Han K, et al. Relationship between bone mineral density and alcohol intake: A nationwide health survey analysis of postmenopausal women. Smith B, ed. Plos ONE . June 2017; 12(6): e0180132

25. Barr T, Helms C, Grant K, Messaoudi I. Opposing effects of alcohol on the immune system. Progress In Neuro-psychopharmacology & Biological Psychiatry. February 2016;65:242-251.

26. Piano, M. R.Alcohol's Effects on the Cardiovascular System. Alcohol Research: Current Reviews. January 2017; 38(2): 219.

27. Hillbom M, Juevela S, Numminen H. Alcohol intake and the risk of stroke. European Journal of Preventative Cardiology. August 1999; 6(4): 223-228

28. Tolstrup J. S., Wium-Andersen M. K., Ørsted D. D., Nordestgaard B. G. Alcohol consumption and risk of atrial fibrillation: Observational and genetic estimates of association. European journal of preventive cardiology. April 2016; 23(14): 1514-1523.

29. Agarwal, D. P. Cardioprotective effects of light–moderate consumption of alcohol: a review of putative mechanisms. Alcohol and alcoholism. September 2002; 37(5): 409-415.

30. Ronksley P. E., Brien S. E., Turner B. J., Mukamal K.J., Ghali W. A. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. The British Medical Journal. February 2011; 342 :d671

31. Lippi G., Franchini M., Favaloro E. J., Targher G. Moderate red wine consumption and cardiovascular disease risk: beyond the "French paradox". In Seminars in thrombosis and hemostasis . February 2010; 31: 59-70.

32. Kalla A, Figueredo V.M. Alcohol and cardiovascular disease in the geriatric population. Clinical Cardiology. July 2017 ; 40(7):444-449

33. Umoh NA1, Walker RK, Al-Rubaiee M, Jeffress MA, Haddad GE. (2014) Acute alcohol modulates cardiac function as PI3K/Akt regulates oxidative stress. Alcohol Clin Exp Res. 2014 Jul;38(7):1847-64.

34. Walker R. K., Cousins V. M., Umoh N. A., et al. The good, the bad, and the ugly with alcohol use and abuse on the heart. Alcoholism: Clinical and Experimental Research. August 2013; 37(8): 1253-1260.

35. Gallagher C, Hendriks J. M., Elliott A. D., et al. Alcohol and incident atrial fibrillation–A systematic review and meta-analysis. International Journal of Cardiology. November 2017; 246: 46-52.

36. Shiferaw Y, Aistrup G.L., Wasserstrom J.A. Mechanism for Triggered Waves in Atrial Myocytes. Biophysical Journal. August 2017; 113(3):656-670.

37. Steiner J.L., Lang C.H. Alcoholic Cardiomyopathy: Disrupted Protein Balance and Impaired Cardiomyocyte Contractility. Alcoholism: Clinical and Experimental Research. April 2017; 41(8):1392-1401.

38. Oscar-Berman M. Alcoholism and asymmetries of brain function. Alcohol Health & Research World. January 1992; 16(4):273.

39. Nussbaum R. L., Ellis C. E. Alzheimer's disease and Parkinson's disease. New England Journal of Medicine. April 2003; 348(14): 1356-1364.

40. Huang W, Zhang X, Chen W. Association between alcohol and Alzheimer's disease (Review). Experimental and Therapeutic Medicine. September 2016; 12(3): 1247-1250.

41. Langballe E, Ask H, Tambs K, et al. Alcohol consumption and risk of dementia up to 27 years later in a large, population-based sample: the HUNT study, Norway. European Journal Of Epidemiology. September 2015; 30(9):1049-1056.

42. Dictionary Of Nursing. 2nd ed. London: A&C Black Publishers Ltd; 2007:348-346.

43. Brokate B, Hildebrandt H, Eling P, et al. Frontal lobe dysfunctions in Korsakoff's syndrome and chronic alcoholism: Continuity or discontinuity? Neuropsychology. July 2003;17(3):420-428.

44. *Alcohol Research & Health* "*Alcoholic Brain Damage*" (*Vol. 27*, *No. 2*, *2003*)

45. Mariën P., Paquier P. F. A synthesis of the role of the cerebellum in cognition. Aphasiology. January 2005; 19(1): 3-19.

46. Letenneur L. Risk of dementia and alcohol and wine consumption: a review of recent results. Biological research. January 2004; 37(2): 189-193.

47. Kong L. M., Zheng W. B., Lian G. P., et. al. Acute Effects of Alcohol on the Human Brain: Diffusion Tensor Imaging Study. American Journal Of Neuroradiology. May 2012; 33(5): 928-934.

48. Allan A. M., Harris R. A. Gamma-aminobutyric acid and alcohol actions: neurochemical studies of long sleep and short sleep mice. Life sciences. November 1986; 39(21), 2005-2015.

49. Bjork J. M., Gilman J. M. The effects of acute alcohol administration on the human brain: insights from neuroimaging. Neuropharmacology. September 2014; 84: 101-110.

50. Preidt R. Opioids and Alcohol a Dangerous Cocktail; Drinking while taking the painkillers can hamper breathing, especially among seniors, study finds. Consumer Health News. February 2017.

51. Nathanson V, Jayesinghe N, Roycroft G. Is it all Right for Women to Drink Small Amounts of Alcohol in Pregnancy? No. Obstetric Anesthesia Digest. June 2008; 28(2): 67-68.

52. Substance Abuse and Mental Health Services Administration (SAMHSA). Data Spotlight: More than 7 Million Children Live with a Parent with Alcohol Problems, 2012.

53. National Institute on Alcohol Abuse and Alcoholism (NIAAA). Alcohol Alert, No. 67, "Underage Drinking," 2006.

54. Weitzman E, Nelson T, Wechsler H. Taking up binge drinking in college: the influences of person, social group, and environment. Journal of Adolescent Health, January 2003; 32(1): 26 - 35

55. Zhou Y, Zheng J, Li S, et al. Alcoholic beverage consumption and chronic diseases. International journal of environmental research and public health. May 2016; 13(6): 522.

56. Stockley, C. S. Is it merely a myth that alcoholic beverages such as red wine can be cardioprotective? Journal of the science of food and agriculture. July 2012; 92(9): 1815-1821.

57. Krenz M, Korthuis R. J. Moderate ethanol ingestion and cardiovascular protection: from epidemiologic associations to cellular mechanisms. Journal of molecular and cellular cardiology. January 2012; 52(1): 93-104.

Figure Legends:

Figure 1: Demonstrates known systems that show pathophysiological changes as a result of chronic alcohol abuse and the clinical presentations.

Figure 2: Schematic and two-dimensional echocardiograms of a four chamber view of a normal heart as well as a heart with cardiac chamber enlargement with decreased systolic function that can result from chronic alcohol abuse. Bottom right is an electrocardiogram demonstrating indicating chamber enlargement and arrhythmias resulting from alcohol abuse.

Figure 3: The central nervous system includes the brain and spinal cord. This schematic demonstrates that the spinal cord and areas of the brain (i.e. central nervous system) can be negatively impacted by alcohol abuse.

Figure 1

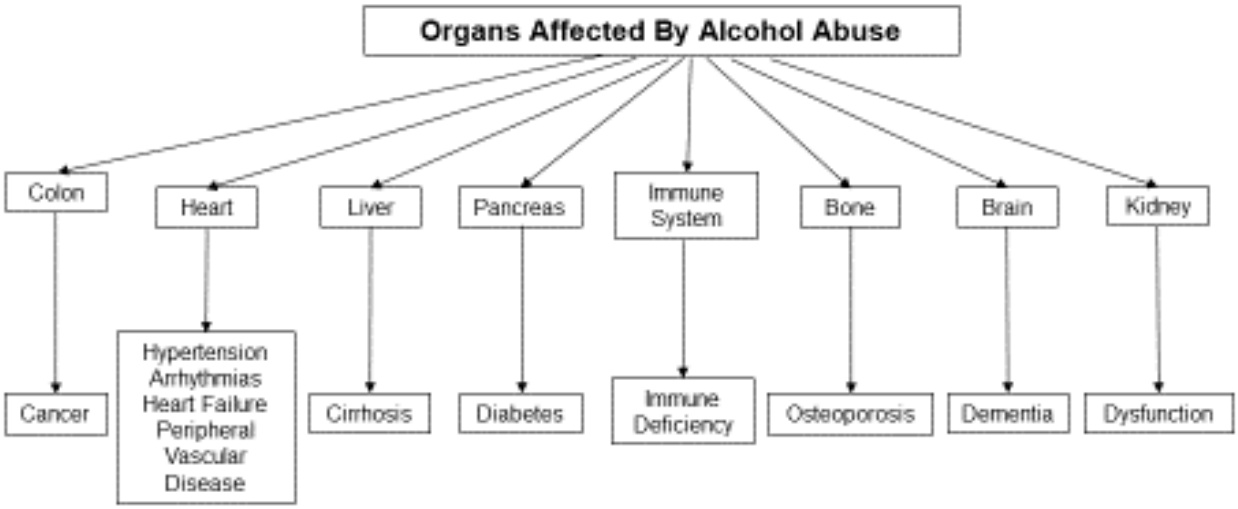

Figure 2

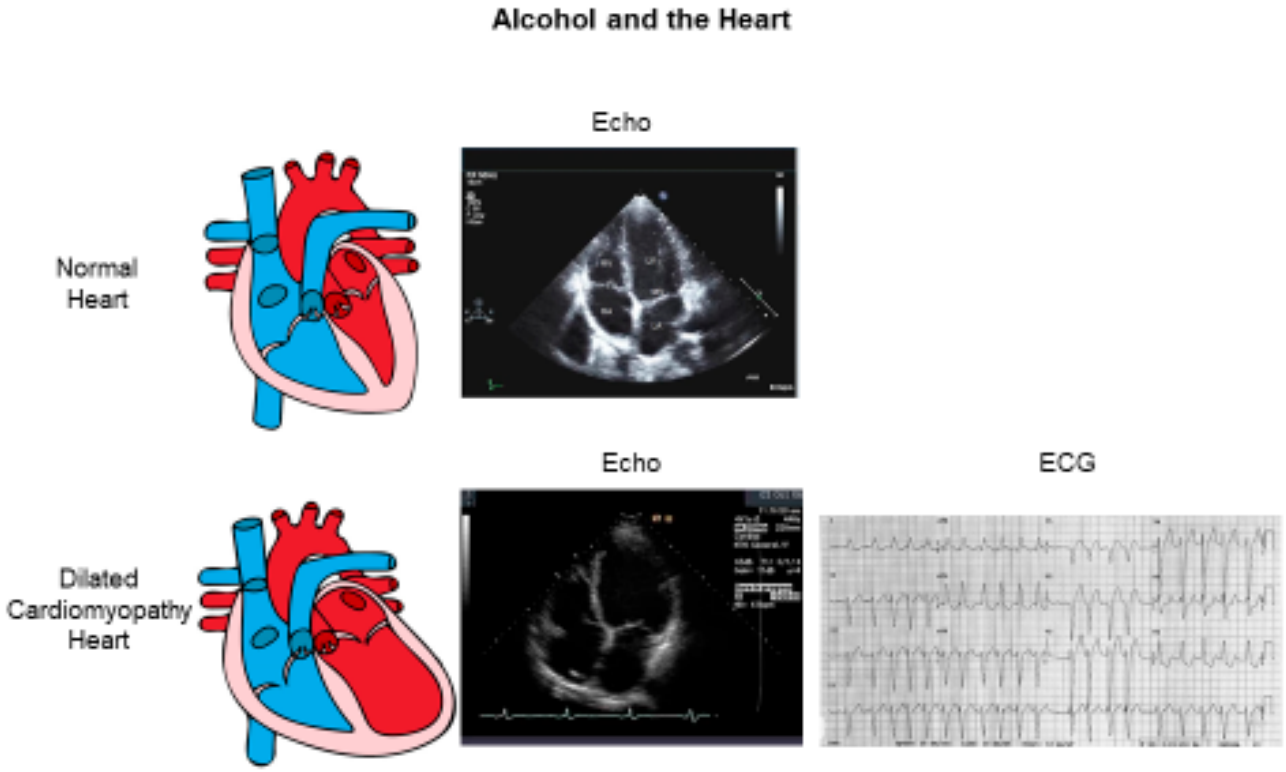

Figure 3