International Journal of Research and Review
DOI: https://doi.org/10.52403/ijrr.20210759
Vol.8; Issue: 7; July 2021
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Consequences of the Adopted Fatal Addictive Duplet

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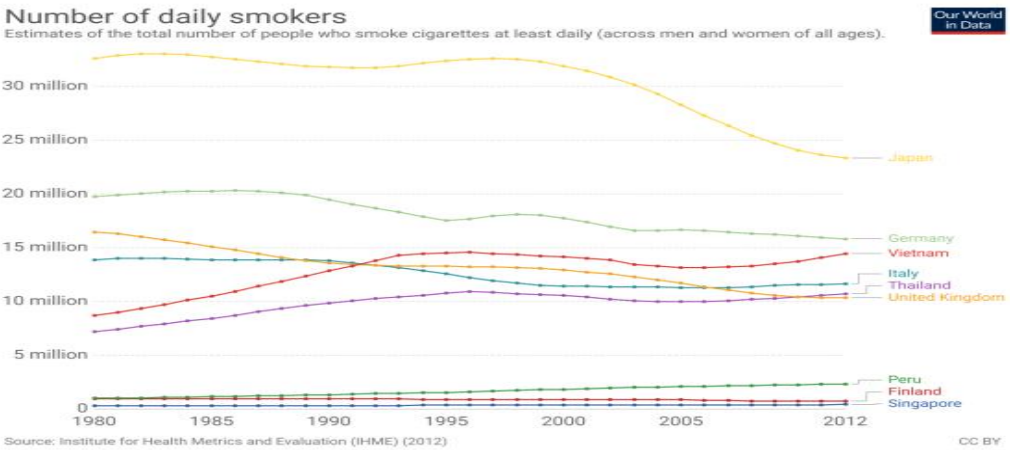
ABSTRACT

This review focus on strong association of smoking and alcohol use with a variety of adverse human health effects, most prominently with cancer and cardiovascular diseases and a number of negative outcomes as a risk factor for diseases and health impacts: crime, road incidence and for some, alcohol dependence. To keep track of alcohol consumption and smoking and its consequences and to raise awareness amongst the public and policy-makers, national monitoring systems to be developed. Tobacco smoking is highly prevalent throughout the world and is, perhaps, the greatest modifiable risk factor for increased morbidity and mortality. Physicians, Pharmacists, Nurses and other healthcare providers have substantial opportunities to influence the pattern of smoking and alcohol usage.

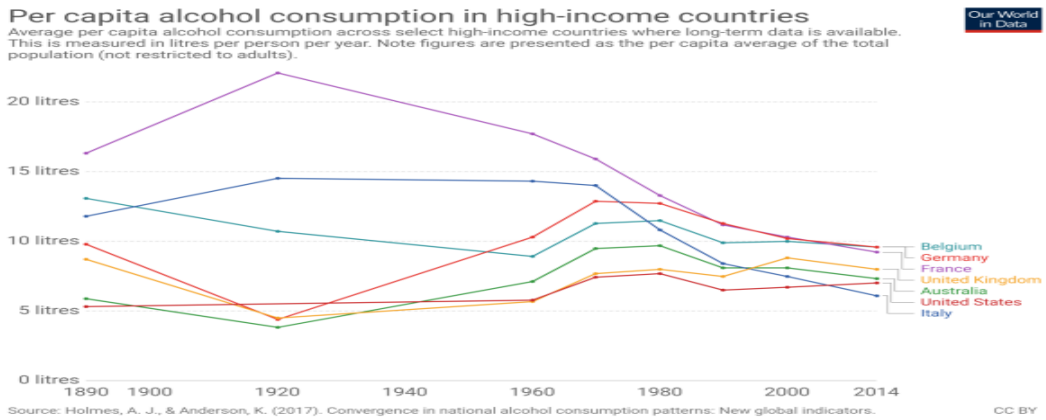
Keywords: Alcohol, Smoking, Coronary Heart Disease, Hepatotoxicity, Cancer, Atherosclerosis, Cytochrome P450 enzymes, Alcohol-Drug Interactions, Smoking-Drug Interactions, Smoking and Alcohol Cessation.

1. INTRODUCTION

The preventable causes of deaths in the United States are smoking and alcohol which are commonly used together[1]. Studies reported that individuals who consume alcohol are three times more likely to smoke compared to non-alcoholics and individuals who smoke are four times more likely to consume alcohol than the non-smokers[2, 3]. Tobacco-related complications are higher in persons consume both alcohol and smoking including multiple cancers, lung disease, and cardiovascular disease[4] .More alcoholics die of tobacco-related illness than that of alcohol-related problems [5].



Source:http://ghdx.healthdata.org/record/global-smoking-prevalence-and-cigarette-consumption-1980-2012



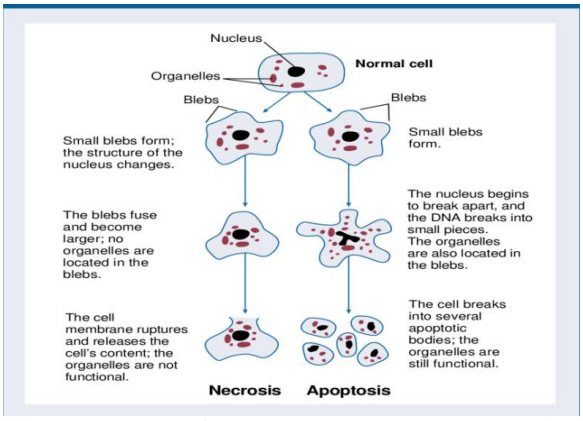
Source: Holmes, A. J., & Anderson, K. (2017). Convergence in national alcohol consumption patterns: New global indicators. Journal of Wine Economics, 12(2), 117-148.

2. Effects of alcohol on human physiology

2.1 Effects of alcohol in Central Nervous System

At neurochemical level, the moderate use of ethanol particularly shows the effect on function of GABA, glutamatergic, serotonergic, dopaminergic, cholinergic, and opioid neuronal systems. Moderate ethanol intake exerts behavioral effects which include actions that the human or animal will identify as reinforcing through either positive (e.g., pleasant, activating) or negative (e.g., anxiolytics, stress reduction) reinforcement mechanism [6]. Different actions of alcohol on the developing organism, including the brain, cause cell death. Necrosis and apoptosis are two general processes of necrobiosis. These processes can be differentiated by completely contrasting patterns of morphological and biochemical changes during cell death.

A major factor which induces apoptosis and necrosis is oxidative stress. Free radicals contain oxygen known as reactive oxygen species (ROS). Usually, antioxidants are the scavenger molecules that are normally found within the cell and control the levels of ROS and other free radicals and eliminate them. Oxidative stress can result if ROS levels exceed the cell's potential to eliminate them, or if the normal antioxidant levels inside the cell are decreased due to a toxic insult such as alcohol. This oxidative stress can result in injury to cellular components, like membranes, DNA and proteins[7, 8].



Structural changes of cells undergoing Necrosis or Apoptosis. *Source: Nanji, A.A. and Hiller-Sturmhöfel, S. (1997) Apoptosis and Necrosis: Two Types of Cell Death in Alcoholic Liver Disease. Alcohol Health and Research World, 21, 325-330.*

2.2 Effects on Cardiovascular System

Alcohol is a known risk factor for stroke and coronary heart disease (CHD). Alcohol increases blood pressure, which may lead to hypertension and thus increase the risk of stroke. HDL cholesterol, which is inversely related to CHD risk, increases with alcohol, and LDL cholesterol, which is positively related to CHD risk[9]. Cardiac arrhythmias caused by regular heavy drinking or binge drinking can provoke the formation of thrombus and spread existing thrombi from the heart. The maintenance of high blood pressure by heavy drinking can cause cerebral arterial degeneration[10].

2.3 Effects on Endocrine System

The most important of the effects on endocrine system are alcohol-induced

'pseudo-Cushing's syndrome' and a syndrome of hypothalamic-pituitary-adrenocortical unresponsiveness. Both of these result from long-term over-indulgence, and impairment of secretion of testosterone which may occur following comparatively short-term drinking. Evidence indicates that many mechanisms are responsible for mediating the effects of alcohol on endocrine function. In a few instances like inhibition of vasopressin secretion and impairment of steroidogenesis resulting in a decrease in testosterone production rate, alcohol appears to influence directly the release or production of individual hormones[11].

2.4 Effect on Pancreas:

Alcohol and its metabolites turn out changes within the acinar cells, which may promote premature activation of intracellular digestive enzyme, thus predisposing the gland to autodigestive injury. Pancreatic stellate cells (PSCs) are activated directly by alcohol and its metabolites and additionally by cytokines and growth factors which are released in alcohol-induced pancreatic necro-inflammation. Activated PSCs are the major cells responsible for causing the fibrosis in alcoholic chronic pancreatitis[12].

2.5 Effect on Liver:

Liver disease in alcoholics is due to malnutrition and also because of ethanol's hepatotoxicity associated to its metabolism by means of alcohol dehydrogenase and cytochrome P450 2E1 (CYP2E1) pathways and the resulting production of toxic acetaldehyde. In addition, alcohol dehydrogenase–mediated metabolism of ethyl alcohol generates nicotinamide adenine dinucleotide (NADH) that promotes steatosis by stimulating the synthesis of fatty acids and opposing their oxidation. Steatosis is also promoted by high dietary lipids and may be attenuated by their replacement with medium-chain triglycerides. Elevated NADH also increases lactate, through reduction of pyruvate, which stimulates synthesis of collagen in myofibroblasts[13].

It is of note that although cirrhosis is usually the primary pathophysiological process that results in development of hepatocellular carcinoma, ALD may progress into liver cancer without necessarily going through cirrhosis[14].

2.6 Effectiveness of Alcohol Management

The evidence shows that although information and education type programs do not reduce alcohol related harm, they have an important role in providing information, and in increasing attention[15].Alcoholism is a harmful condition that typically follows the intake of a huge amount of alcohol which can exhibit itself clinically in many ways and leads to metabolic effects along with gastrointestinal, central nervous, endocrine, pulmonary and cardiac effects. The management is aimed by stabilizing the patient's clinical condition by the elimination of alcohol. It is up to both governments and concerned citizens to encourage public health policies that minimize the harm caused by alcohol.

3. Effects of smoking on human physiology

15-20 years of life is reduced among one smoker in four and half of them die due to complications caused by smoking, which also contributes to 85% of lung cancer[16]. It is prominently fatal to respiratory, cardiovascular, reproductive, integumentary, oral cavity, skeletal systems[17, 18, 19].

3.1 Integumentary System: injury to epithelial and collagen tissue is caused by decreased perfusion of blood and oxygen to the skin contributing to risky surgeries, poor wound healing[17].

3.2 Oral Cavity: Smoking promotes tooth decay and infection because of reduced salivary flow which protects teeth. Smokers have recurrent pharyngitis, oral cancer, lessened sensation to taste and smell, stained teeth and plaque, bad breath[17].

3.4 Respiratory system: Smoking causes shortness of breath, chronic obstructive pulmonary disease, pneumonia, lung cancer, chronic bronchitis[18].

3.5 Reproductive System: Chronic smoking impairs ovulation, cervical[21], cancer decreased sperm count and motility and[17]. Maternal smoking is associated with placental abruption, preterm delivery, placenta Previa, low birth weight[20].

3.6 Heart: Tobacco adversely effects endothelial and smooth muscle cell functions disturbing thrombotic events influencing development of atherosclerosis. Smoking decreases exercise tolerance, increases risk of coronary heart disease blood pressure and tendency to clot[17, 18, 19].

3.7 Cancer: tobacco smoke exposure and smokeless tobacco products are associated with cancers of head, neck, gastrointestinal tract, breast, kidney and leukemia[22]. Polymorphic enzymes of Cytochrome P450, glutathione S-transferase, N-acetyltransferase modulate formation of DNA adducts, induction of mutations and chromosomal damage which causes cancer[25-33]. Smokers have three to seven times higher risk for esophageal squamous cell carcinoma compared to non-smokers[32,33].A meta-analysis study reported that 20 to 30 percent of patients suffering from esophageal cancer were addicted to smoking[36].many studies concluded that incidence of liver cancer is higher among smokers[37].High alcohol intake , hepatitis B or C prevent inhibition of tumor growth by DNA adduct formation[40].Smoking is also a major risk factor for cervical cancer[39].The incidence of cervical cancer and renal cell carcinoma depends on duration of smoking and number of cigarettes[40-42]

3.7 Health Benefits of Smoking Cessation

The considerable health benefits of smoking cessation are reduce the risk of smoking related diseases, slows the progression of current smoking related disease, and improves the life span of an individuals by an average of 10 years[16]. Smoking cessation can bring good results regardless of age and how long he/she smoked and improves the person's heart rate, blood pressure and peripheral circulation within 1day, the content of carbon monoxide within the lungs also reduced by 24hours and all nicotine has left from the body within 48hours. Lung function is improved after 1to 3 months by 30% and improve the symptoms like shortness of breath and cough and their frequency is reduced in chronic smoker after 6months of stopping smoking[43, 46] the risk of lung cancer falls by 50-60% after10 years of quitting smoking and risk of heart attack and stroke also reduced after 15years abstinence of smoking[17].

3.8 Promoting Smoking Cessation

Smoking is a common risk factor for majority of individuals suffers with hypertension, diabetes and other heart diseases. In many health care centers smoking status is vital sign along with blood pressure, pulse rate, and temperature recorded by nurses. The presence of treatment may initiate or enhance the quitting[16]. Every discharge protocols of patients suffered with heart attack are taking beta-blockers, aspirin, ACE inhibitors and statins. Adherence to medical therapy also improves the patient condition. Physician plays a important role in promoting smoking cessation by educating the patient about the smoking related problems and medical therapy with the help of other health care professionals[16]. Seventy percent of smokers want to quit, but only 3-7 percent will be successful on their own[44]. Smoking cessation is complex process and it is extremely difficult and may require several strategies and counselling sessions to reach the ultimate goal and to improve the condition. The more effective interventions such as behavioral and pharmacological therapies improve the quit rates only 15-30% in smokers[44]. It is hesitant that physicians continue to work with patients on

an ongoing basis to find cessation manner that work for them. Increasing quit rates up to 1.5- 2fold by using nicotine replacement therapies (such as the patch, gum or inhaler) and Bupropion[45]. The quit rates increased 2- to 3-fold over placebo by using Varenicline. Behavioral therapy, psycho-social therapy also effective tool in promoting smoking cessation. The effective way of turning tide of tobacco smoking is by friends and support of family members and also Government by making policies, wide restrictions and taxes.

4. Drug interactions with alcohol and smoking

Many medications interact with cigarette smoke and alcohol via pharmacokinetic or pharmacodynamics mechanisms. Engaging in both of these social activities can reduce the efficiency of certain drugs or can make drug therapy unpredictable[47].

4.1 Smoking

Pharmacokinetic interactions

The chemicals in Cigarette smoke such as polycyclic aromatic hydrocarbons induces the activity of cytochrome P450 (CYP) 1A2[46] and also CYP2B6.[49]The clinically important drugs (such as antidepressants and antipsychotics) are metabolized by these enzymes and chemicals in cigarette smoke also has procarcinogenic activity[48,50]. In heavy smokers (more 20 cigarettes/day) CYP 1A2 activity is high compared to nonsmokers[52].Nicotine in tobacco not influence the activity of CYP1A2, but activity induced by cigarette smoke. So nicotine replacement therapy does not influence the CYP1A2 activity[49].

Drugs interaction with smoking	**Mechanisms**
Warfarin	Smoking induces the activity of CYP1A2, Smoking may therefore potentially interact with warfarin by increasing its clearance and reducing its effect. Because of Warfarin less active R isomer is eliminated to a minor extent by CYP1A2[53] Consequently, INR should be closely monitored when there is a change in patients smoking status[52]
Clopidogrel and prasugrel	Clopidogrel and prasugrel converted into their active metabolites by CYP isoenzymes (including CYP2C19, 3A4/5, 1A2, 2B6 and 2C9) these metabolites are bind to the receptors on platelets irreversibly. Cigarette smoke induce the activity of CYP1A2 results it could increase the antiplatelet efficacy of these thienopyridine drugs[55.]
Caffeine	Caffeine depends on CYP1A2 for its metabolism. Cigarette smoke enhance the activity of CYP1A2,To achieve the same plasma caffeine concentration smokers requires 4 times of caffeine in smokers compared to non-smokers[56]
Heparin	cigarette smoke activates thrombosis with enhanced heparin binding to antithrombin III, results faster clearance of heparin[57]
Antipsychotics	Heavy smoking may reduce the blood levels of antipsychotic medications by as much as 50 percent, Because of Cigarette smoke consists of polycyclic hydrocarbons stimulate the hepatic microsomal system, inducing liver enzymes to increase the metabolism of psychotropic medications[58]
Insulin	Smoking cause release of Endogenous substances that antagonize the effects of insulin, and decreases its absorption[59]

Pharmacodynamic interactions- Pharmacodynamic drug interactions with tobacco smoke are due to nicotine.

Benzodiazepines	Nicotine stimulates the CNS[60] and this might explain the sedation noticed in smokers compared to non-smokers taking benzodiazepines[61]
Oral contraceptives	Smoking increases the adverse effects with oral contraceptive pills (specifically thromboembolism, ischemic stroke and myocardial infarction)[60]
Corticosteroids	The efficacy of inhaled corticosteroids may be decreased in asthmatic patients in smokers,[60] so these patients might need higher doses of inhaled corticosteroids for asthma control[62] Proposed mechanisms of corticosteroid insensitivity involve suppression of histone deacetylase expression by smoking, causing inflammatory gene expression and decrease in glucocorticoid function[63] Clearance of corticosteroids from the lungs may be altered by increased mucus secretion or airway permeability[64]
Beta blockers	Smoking also inhibits nicotine mediated sympathetic activation which reduces the Antihypertensive and heart rate control effects of several Beta blockers[65]
Opioids	Laboratory based human self-control studies have shown that nicotine and opiates (e.g., heroin, morphine, methadone) interact to increase total drug abuse. For example, heroin[66] or methadone[67] administration increases smoking while methadone also increases the subjective ratings of smoking satisfaction[67]. Nicotine and opiates also produce cross-tolerance[68] or cross-sensitization[69] such that exposure to one drug alters the response to the other in CPP procedures, depending on the duration of administration.
Antihypertensives	Clinical experiments as well as population studies, both prospective and cross- sectional, have established that commonly used antihypertensive drugs affect the plasma lipid and lipoprotein profile adversely, potentially increasing the risk of coronary morbidity[70]

4.2 Alcohol:

People normally complaints euphoria after drinking alcohol, although it depends on the social setting. However the interaction between many medications and alcohol can lead to a significant increase in risk of illness, injury, or even death[71]

Drugs interacts with alcohol	**Mechanisms**
Non-Steroidal Anti-Inflammatory Drugs and Statins	NSAIDS like aspirin, ibuprofen, naproxen, ketoprofen, and nabumetone when taken with alcohol increase the threat of liver injury or stomach bleeding. The increased metabolism of HMG-CoA reductase inhibitors like atorvastatin, cerivastatin, lovastatin, pravastatin and simvastatin due to this interaction increases the risk of liver damage in alcoholics[72]
Disulfiram and Antibiotics	Disulfiram-alcohol interaction is a typical example of the inhibitory metabolic effects caused by a Drug-alcohol interaction[73]. Disulfiram inhibits aldehyde dehydrogenase, thus inhibiting oxidation of acetaldehyde, an oxidation product of alcohol results in accumulation of acetaldehyde and progress of unpleasant effects characteristic of disulfiram reaction. Disulfiram like reaction is seen in patients receiving cephalosporin's like cefotetan, cefamondole, cefmetazole and following consumption of alcohol. Methylthiotetrazole which is an essential substituent of all the above antibiotics is the main cause of reaction[74].
Antidepressants	Alcohol increases the sedative effects of tricyclic antidepressants (TCAs) through pharmacodynamic interactions. In addition, alcohol can cause pharmacokinetic interactions with TCAs.
Antihistamines	Antihistamines may cause drowsiness, sedation, and low blood pressure (i.e., hypotension), especially in elderly patients. Through pharmacodynamic interactions, alcohol can substantially increases the sedating effects of these agents and may increase a person's risk of falling or impair his or her ability to drive or operate other alternatives of machinery
Benzodiazepines	Simultaneous consumption of BZDs and average amounts of alcohol can cause synergistic sedative effects, leading to substantial CNS impairment. It is worth noting that both barbiturates and benzodiazepines can impair memory, as alcohol. Consequently, the amalgamation of these medications with alcohol would exacerbate this memory-impairing effect.
Muscle relaxants	Several muscle relaxants (e.g., carisoprodol, cyclobenzaprine, and baclofen), if taken with alcohol, may produce a narcotic-like reaction that is characterized by fatigue, dizziness, agitation, euphoria, and confusion[75]

CONCLUSION

Cigarette and alcohol use share common etiological factors and frequently develop simultaneously. Adolescents are more likely to be involved in health risk habits or delinquency, such as smoking, alcohol consumption, or drug abuse when they are exposed to certain surroundings; it increases pleasure and sociability in the minds of every individual. To reduce the burden of alcohol-related problems, consider average consumption of alcohol and patterns of drinking. To reduce the health burden of alcohol, avoiding the combination of drinking and driving. Worldwide, especially, in developing countries like china, India smoking and alcohol consumption plays important role on lives and its contribution to the overall burden of disease is expected to increase in the future. To keep track of alcohol consumption and smoking and its consequences and to raise awareness amongst the public and policy-makers, national monitoring systems to be developed. Tobacco smoking is highly prevailing throughout the world and is perhaps, the greatest modifiable risk factor for increased morbidity and mortality. Smoking cessation is associated with immediate and long-term health benefits, resulting in improved general health and a reduced risk of smoking-related diseases.

Physicians, Pharmacists, Nurses and other healthcare providers have substantial opportunities to influence the pattern of smoking and alcohol usage. The motivation to attempt cessation of these habits is to be encouraged and it would only be successful with the willingness of the individual. Familiarity with the strategies involved in cessation of smoking, alcohol and practicing the same would be an effective health intervention. A combination of behavioral counseling and pharmacotherapy would reduce the withdrawal syndromes which increases the abstinence rates. From the evidence of the recent literature there are several medications available helping smokers and alcoholics to quit with demonstrated efficacy according to the patient interest and medical history. The warning tags displayed in different occasions and even on the containers of alcohol and tobacco products are mostly futile. Employment of effective public

health awareness programs, ban of production that practically help out the nation's burden are to be concerned.

Acknowledgement: None

Conflict of Interest: None

Source of Funding: None

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How to cite this article: Vanjari NK, Sirichandana G, Shaik A et.al. Consequences of the adopted fatal addictive duplet. *International Journal of Research and Review*. 2021; 8(7): 410-419. DOI: *https://doi.org/10.52403/ijrr.20210759*

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