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Review

Cardiac Complications of Common Drugs of Abuse: Pharmacology, Toxicology, and Management

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ABSTRACT

Cardiovascular complications from drugs of abuse are becoming more apparent because of increased usage worldwide. Substance abuse can cause acute and chronic cardiovascular complications and is increasing in prevalence especially in young adults. These substances contribute to the development of acute coronary syndrome, type 2 myocardial injury, arrhythmias, and cardiomyopathies, and have numerous other cardiovascular complications. Although no screening guidelines exist, clinical awareness of these potential complications and their prevention, clinical presentation, diagnosis, and treatment

RÉSUMÉ

Les complications cardiovasculaires des drogues toxicomanogènes deviennent plus apparentes en raison de l'augmentation de la consommation dans le monde. L'abus de substances peut causer des complications cardiovasculaires aiguës et chroniques et sa prévalence augmente en particulier chez les jeunes adultes. Ces substances contribuent au développement de syndromes coronariens aigus, de lésions myocardiques de type 2, d'arythmies et de cardiomyopathies, et de nombreuses autres complications cardiovasculaires. Bien qu'il n'y ait pas de lignes directrices en matière de dépistage, la con-

Cardiovascular disease (CVD) is the leading cause of global mortality and substance use is a hidden determinant.[1] There continues to be a sharp increase in the usage of drugs of abuse and substance use disorder throughout the world and Canada (Fig. 1).[2-4] Because of this, cardiac complications secondary to drugs of abuse are becoming more apparent. Epidemiological studies suggest that 1 in 5 young adults misuse several substances and that these "polysubstance users" often start using at younger ages, leading to progressive worsening of long-term health.[3,5,6] Specific drugs of abuse such as cocaine, methamphetamines, and alcohol have well known cardiac complications.[7-9] However, with the increasing usage of anabolic-androgenic steroids (AAS), their cardiac complications are also becoming more relevant.[10] With the legalization of cannabis in many jurisdictions, cannabis usage is very common, making cardiac complications more clear in what was thought to be a relatively benign drug.[11,12] Electronic cigarette usage is increasing, making nicotine more popular again despite the public health interventions related to smoking cessation.[13,14] Conventional cigarette usage is still common and tobacco is a well known risk factor for coronary artery disease (CAD); however, other cardiac complications need to be recognized.[15,16] The coexistence of mental illness with substance abuse is a major comorbidity that should be recognized and managed appropriately.[17] It is well known that there is a link between adolescent psychiatric disorders and cardiovascular risk, and the concurrent usage of substances are likely to make this risk more profound.[18] The aim of this review is to highlight the basic epidemiology, cardiovascular complications, and potential disease-specific treatment options of commonly abused substances including methamphetamine, cocaine, alcohol, AAS, cannabis, and tobacco. Because of the limited literature and the nature of the effects of cardiovascular complications and drugs of abuse, most data can demonstrate associations, but not necessarily causation. This should be taken into consideration when reading this review.

Psychostimulant Drugs of Abuse and Addiction: Methamphetamine and Cocaine

Psychostimulants, initially freely available, have evolved into one of the most commonly abused drugs.[8,19] Despite numerous clinical applications for medicinal usage, they are abused for their effects of increased wakefulness, euphoria, and appetite suppression.[19,20] Methamphetamine, colloquially known as "crystal meth," is a synthetic molecule closely related to over-the-counter decongestants whereas cocaine is produced biosynthetically.[8,9] Cocaine and methamphetamine can be referred to as psychostimulant drugs of abuse and addiction (PDAA).[7] The past 12-month prevalence usage as

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are critically important. Management of cardiovascular disease should be coupled with appropriate social and mental health interventions to provide sustained clinical benefit. The higher the number of substances used recreationally, the greater the risk of premature heart disease. Epidemiological studies showed that 1 in 5 young adults misuse several substances and often start using at younger ages with a greater risk for adverse health outcomes over the long term. The aim of this review is to highlight the basic epidemiology, cardiac complications, and disease-specific treatment options of commonly abused substances including methamphetamine, cocaine, alcohol, anabolic-androgenic steroids, cannabis, and tobacco.

naissance des complications possibles et de leur prévention, ainsi que du tableau clinique, du diagnostic et du traitement de celles-ci est d'une importance capitale. Pour que la prise en charge des maladies cardiovasculaires procure des bienfaits cliniques soutenus, elle doit être accompagnée d'interventions sur le plan social et en santé mentale. Plus le nombre de substances à usage récréatif est élevé, plus le risque de maladies cardiaques prématurées est important. Selon des études épidémiologiques, un jeune adulte sur cinq fait un usage abusif de plusieurs substances et commence souvent à consommer celles-ci à un plus jeune âge, ce qui accroît à long terme le risque d'effets défavorables sur la santé. Cette revue a pour objet de mettre en évidence les données épidémiologiques de base, les complications cardiaques et les choix de traitement propres aux maladies liées aux substances couramment consommées de façon abusive, soit la méthamphétamine, la cocaïne, l'alcool, les stéroïdes anabolisants androgènes, le cannabis et le tabac.

per the United Nations Office on Drugs and Crime is estimated to be 0.40% for cocaine and 0.54% for methamphetamine globally, with the North American prevalence being higher at 2.12% and 2.29% for cocaine and methamphetamine, respectively.[2]

Pharmacology

PDAA can be used intravenously, intranasally, or inhaled, with cocaine also used topically, and methamphetamines also used orally.[20] The onset of methamphetamine varies, but ranges from 15 minutes to 3 hours, whereas the onset of cocaine ranges from seconds to minutes.[20] The half-life of cocaine is close to 90 minutes, whereas methamphetamine has a half-life closer to 12 hours.[21] Topically, cocaine acts as a local anesthetic by blocking sodium channels in neurons.[22] In the central nervous system, cocaine inhibits multiple neurotransmitter reuptake transporters.[9] The euphoric effects of increased alertness are from the mesolimbic and mesocortical areas of the brain, where cocaine impairs dopamine reuptake resulting in sustained stimulation of dopaminergic receptors.[23] This causes an addictive affect from the depletion of dopaminergic stores in the presynaptic neurons after chronic usage.[23] Methamphetamine not only blocks the reuptake transporters of catecholamines, but also stimulates the release of them making it more potent than cocaine.[24] High levels of dopamine from PDAA usage leads to the accumulation of reactive oxygen species and oxidative stress causing long-term neurotoxicity.[25] Because methamphetamine is more potent and longer-acting than cocaine, it is thought that cardiac toxicity is exaggerated with methamphetamine usage.[26] PDAA are not direct sympathomimetics, but have sympathomimetic effects through the increased levels of dopamine, norepinephrine, epinephrine, and serotonin.[20]

Cardiovascular complications

Because of the pharmacology of PDAA, acute and chronic cardiac toxicity occurs with its usage (Table 1).[27] The acute cardiac complications of PDAA are severe hypertension, myocardial infarction (MI), stroke, aortic dissection (AD), and cardiac arrhythmias.[27,28] Chronic complications from the usage of PDAA include the development of cardiomyopathies, accelerated atherosclerosis, and some limited evidence suggests that usage might cause pulmonary hypertension.[27,28] PDAA increases the heart rate (HR) and blood pressure (BP) through blocking the reuptake of norepinephrine throughout the sympathetic nervous system.[29] These effects lead to an increase in myocardial demand. Cocaine increases endothelin-1 (vasoconstrictor) production and longer exposure decreases nitric oxide production and endothelial nitric oxide synthase expression, contributing to chronic hypertension.[30]

Myocardial ischemia is a complication of PDAA usage with plaque rupture, increased myocardial demand, accelerated atherosclerosis, and coronary artery vasospasm all contributing.[31] PDAA also causes vasoconstriction of the coronary arteries, in part related to the endothelin-1 and nitric oxide imbalance known as vasospastic angina (Prinzmetal angina).[30,32] These prothrombotic effects are likely enhanced by the vasoconstrictive effects.[31] Cocaine causes platelet activation and an increase in platelet factor-4 which also leads to a prothrombotic state, further contributing to myocardial ischemia.[33] In combination with the hypertensive effects from the catecholamine surge, the procoagulable state and the decreased cerebral flow, strokes are also a complication of PDAA usage.[34] The same principles apply for increasing the risk of AD, but an additional theory is that cocaine-induced apoptosis at the endothelial level also plays a role in arterial dissection.[35]

Within cardiomyocytes, PDAA block sodium/potassium channels, and decrease the depolarization and amplitude of the action potential, with the potential to precipitate cardiac dysrhythmias acutely.[36] Ischemic events cause myocardial scarring, and in combination with the blockage of voltage-gated sodium channels there is also an increased likelihood of arrhythmias from chronic usage.[36] The most common arrythmia is sinus tachycardia from the increased sympathetic tone but PDAA can cause atrial fibrillation (AF), supraventricular tachycardias, ventricular tachycardia, and ventricular fibrillation (VF).[29]

Intravenous drug usage of PDAA is a common cause of infective endocarditis and patients can present acutely or subacutely.[37] Commonly with intravenous drug usage, the tricuspid valve is infected, and the most common pathogen is *staphylococcus aureus*.[37,38] Cocaine users have increased rates of

atherosclerosis and more pronounced atherosclerosis upon presentation of acute chest pain, compared with control groups.[39] Histamine release from mast cells increases the endothelial permeability leading to leukocyte migration and low-density lipoprotein migration, contributing to atherosclerosis.[40,41]

Acutely, PDAA can cause Takotsubo stress cardiomyopathy secondary to the catecholamine surge (Fig. 2).[42] However, with chronic PDAA usage, oxidative stress is a major cause of myocardial damage causing a dilated cardiomyopathy with a reduced ejection fraction.[43] In addition, accelerated apoptosis, increased p53 activity, cardiomyocyte necrosis, fatty acid toxicity, and defects in intracellular calcium hemostasis contribute to the development of cardiomyopathy.[43,44] PDAA can also cause a hypertrophic cardiomyopathy secondary to elevated BP with chronic usage.[42]

Treatment

The treatment for PDAA-associated cardiac complications is specific to the different effects it can cause (Table 2). Because the theory of β-blockade causing unopposed α stimulation resulting in a paradoxical increase in BP and coronary artery vasoconstriction, clinicians have advocated against the use of β-blockers for the treatment of PDAA toxicity.[45] As per the American Heart Association guidelines, when a patient with suspected PDAA use is seen with chest pain compatible with MI and ST-segment elevation, sublingual nitroglycerin or calcium channel blocker should be administered immediately.[46] If there is no response, coronary angiography should be performed to rule out type 1 MI.[46] The American Heart Association guidelines recommend for PDAA-associated hypertension and sinus tachycardia, administration of combined α- and β-blocking agents be given provided they have already recently received a vasodilator.[46] If an MI and AD has been excluded, other sources recommend ongoing treatment with benzodiazepines and nitrates.[36] For cardiac arrhythmias, in addition to routine care, consideration of sodium bicarbonate treatment for counteracting cocaine's sodium-blocking effect and intravenous lipid emulsion therapy might be helpful in those with extreme cocaine overdose due to cocaine's lipophilic properties.[36,47] Treatment for AD, heart failure, cardiomyopathies, and stroke should be treated as per guidelines with the addition of cessation of using the PDAA.[36] Although there is no pharmacotherapy approved for PDAA cessation, a multidisciplinary approach for the addiction likely has some utility.[48]

Ethanol

Ethanol (alcohol) use has been established as a leading risk factor for premature death and disability with connections to numerous diseases including liver cirrhosis, cancer, and nutritional deficiencies.[49,50] Previous research suggested that low to moderate doses of alcohol consumption is cardioprotective and reduces all-cause mortality; however, these findings have been criticized because of poor methodological design and sample size.[49] More recent evidence has suggested that alcohol provides nonsignificant health benefits and is causative of CVD.[49,51]

Pharmacology

Alcohol induces several acute and long-term effects mediated by the alcohol molecule itself and its active metabolites. The pathogenesis of alcohol in the context of the cardiovascular system (CVS) varies, depending on acute or chronic alcohol consumption. Both are demarcated by dilation, thinning, and impaired contraction of 1 or both ventricles with severity associated with disease progression.[52] Acute consumption promotes myocardial inflammation, which can be clinically detectable by an elevated serum troponin level.[53] Cardiovascular pathogenesis secondary to alcohol consumption, specifically alcoholic cardiomyopathy (ACM), also includes a myriad of pathophysiological mechanisms mediated by alcohol and its principal metabolites including acetaldehyde and ethyl esters.[54] Cardiomyocyte hypertrophy, apoptosis and necrosis, uncoupling of excitation-contraction, oxidative damage, mitochondrial degeneration, and

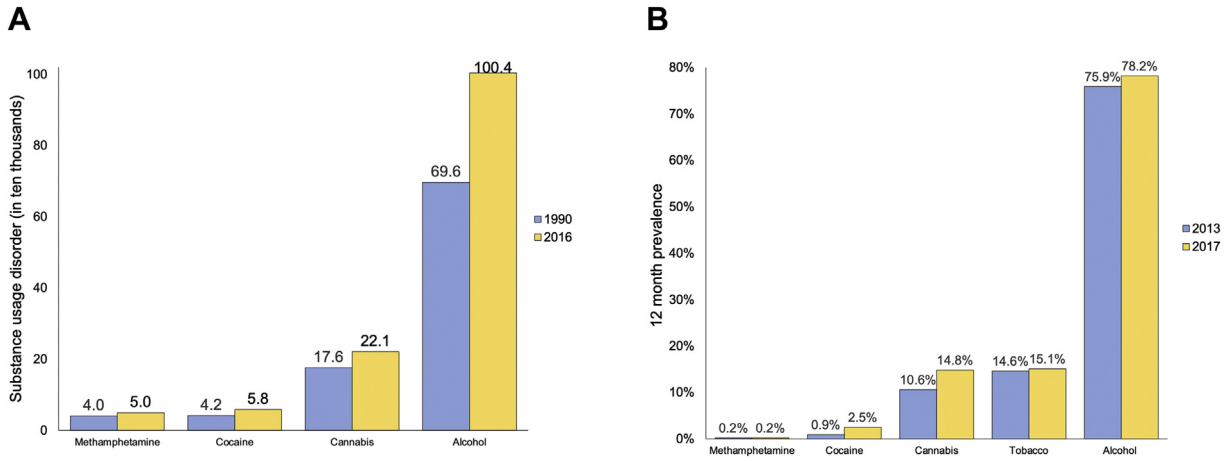

Figure 1. Prevalence of substance use globally and in Canada. Substance usage disorder globally in 1990 compared with that in 2016 (**A**). Global substance use disorder, in 10 thousands. Estimates from the Global Burden of Disease Study 2016. Twelve-month prevalence of drugs of abuse usage in Canada in 2013 compared with that in 2017 (**B**). Self-reported survey data for methamphetamine, cocaine, cannabis, tobacco, and alcohol from Health Canada. First survey of this nature was in 2013, with the most recent survey in 2017.

Table 1. Acute and chronic cardiovascular complications of drugs of abuse

	Acute	Chronic
PDAA	Hypertensive crisis[27-29] Myocardial infarction[27,28,31] Stroke[27,28,34] Aortic dissection[27,28,35] Cardiac arrhythmias[27,28,36] Infective endocarditis[27,28,37] Stress cardiomyopathy[27,28,42]	Cardiomyopathies[27,28,43,44] Accelerated atherosclerosis[27,28,40] Pulmonary hypertension[27,28]
Alcohol	Atrial tachyarrhythmias[57] Decreased contractility[52] Myocardial inflammation[53] Hypertension[60]	Atrial fibrillation[59] Coronary artery disease[60-63] Cardiomyopathies[61,62]
AAS	Cardiac arrhythmias[84] Myocardial infarction[78]	Accelerated atherosclerosis[10,78-82] Cardiomyopathies[78,80-82] Metabolic syndrome[93] Hypertension[92]
Cannabis	Tachycardia[104-106] Hypertension[104-106] Myocardial infarction[109] Stress cardiomyopathy[120] Cardiac arrhythmias[115-118] Prolonged hypotension[99,102]	Prothrombotic state[111,112] Coronary artery disease[77,87-91] Hypertension[104-106]
Tobacco	Myocardial infarction[138,139]	Hypertension[129,130] Coronary artery disease[13,124] Cardiomyopathies[15,16]

AAS, anabolic-androgenic steroids; PDAA, psychostimulant drugs of abuse and addiction.

myocardial fibrosis are the major determinants of the adverse cardiac remodelling.[55,56]

Cardiovascular complications

Cardiovascular complications tend to be observed when consumption passes the unique individual alcohol threshold leading to elevated susceptibility (Table 1). An acute cardiac complication of binge drinking is AF (holiday heart syndrome).[57] Holiday heart syndrome was first coined in 1978 when patients presented with AF to hospital after a binge drinking weekend.[57] Current hypotheses suggest a combination of cellular and electrophysiologic damage from the toxicity of alcohol causing atrial conduction abnormalities.[58]

Common chronic complications of alcohol usage are persistent atrial arrhythmias, atherosclerosis, hypertension, and ACM. A recent meta-analysis identified that the relative risk (RR) for AF increased by 10% for each drink per day consumed.[59] Heavy long-term alcohol consumption is also associated with ventricular arrythmias, systematic atherosclerosis, sudden cardiac death, beriberi cardiomyopathy, and cirrhotic cardiomyopathy.[60-63] Rapid withdrawal of alcohol might increase the risk of coronary events and QT prolongation.[64,65] ACM is a major cardiac complication secondary to alcohol consumption and a leading cause of nonischemic cardiomyopathy, comprising approximately 21%-36% of all nonischemic cardiomyopathies (Fig. 2).[66] ACM is caused by long-term alcohol exposure, but it is unclear the duration and amount of consumption required; although variations in genetics, sex, metabolism, and lifestyle factors might lead to differences in the alcohol threshold required to induce ACM.[67] The 4-year mortality for ACM can range up to 50%, making it a major cause of premature death.[68]

Treatment

Treatment of ACM is primarily driven by alcohol abstinence or reduction of alcohol consumption although the efficacy of this strategy remains unclear (Table 2).[69] Upon presentation to hospital, alcohol withdrawal can be serious, the mainstay of treatment is the use of the benzodiazepines and the Clinical Institute Withdrawal Assessment for Alcohol—Revised (CIWA-Ar) but consideration of QT monitoring should also be given.[64,65,70] Pharmacotherapies currently established for alcohol abstinence or reduction of alcohol consumption are targeted at reducing the psychological craving associated with alcohol ingestion and often involve specialized teams and medical therapy tailored to the patients' clinical and demographic characteristics. Treatment of heart failure secondary to ACM is nonspecific outside of targeted alcohol cessation/reduction.

Anabolic-Androgenic Steroids

AAS are synthetic derivatives of testosterone, which have been used for decades to enhance physique and athletic performance by increasing muscle mass and strength.[71] Drugs that are commonly used in this class include testosterone, androstenedione, stanozolol, nandrolone, and methandrostenolone.[10,72] Lifetime prevalence rates of AAS use around the globe have been estimated at 3.3%, with a rate of 6.4% for men and 1.6% for women.[73] Historically, the use of AAS was primarily limited to sport but has shifted into a public health concern with increasing ease of access.[74] Over recent years, the idealized male body has shifted toward higher levels of masculinity and has been reflected by an increased prevalence of muscle dysmorphia and subsequent AAS use in young men.[75]

Pharmacology

Although AAS can increase fat-free mass and muscle size and strength, there are also long-term adverse effects of these drugs on the body. These include but are not limited to the reproductive, musculoskeletal, renal, immunological, and endocrine systems.[71,76] The effects of AAS throughout the body are regulated at the cellular level through steroid-converting enzymes at each target tissue.[72] In the CVS, AAS might bind directly to androgen receptors in the heart and major arteries resulting in growth-promoting effects on cardiac tissue, whereas high doses of AAS also reduces vasodilation which furthers these growth-promoting effects.[77]

Cardiovascular complications

Direct cardiotoxic effects of AAS include cardiac hypertrophy resulting in ventricular dysfunction and accelerated coronary atherosclerosis (Table 1, Fig. 2).[10,78-82] Long-term AAS use might result in reduced left ventricular systolic and diastolic function, which might increase the risk of heart failure in these individuals.[78,80-82] AAS users tend to have more left ventricular hypertrophy, which correlated with the degree of systolic and diastolic dysfunction.[78] Strength-trained athletes (ie, power lifters who might be more likely to abuse AAS) might already have hearts with more a concentric pattern of left ventricular growth, predisposing them to

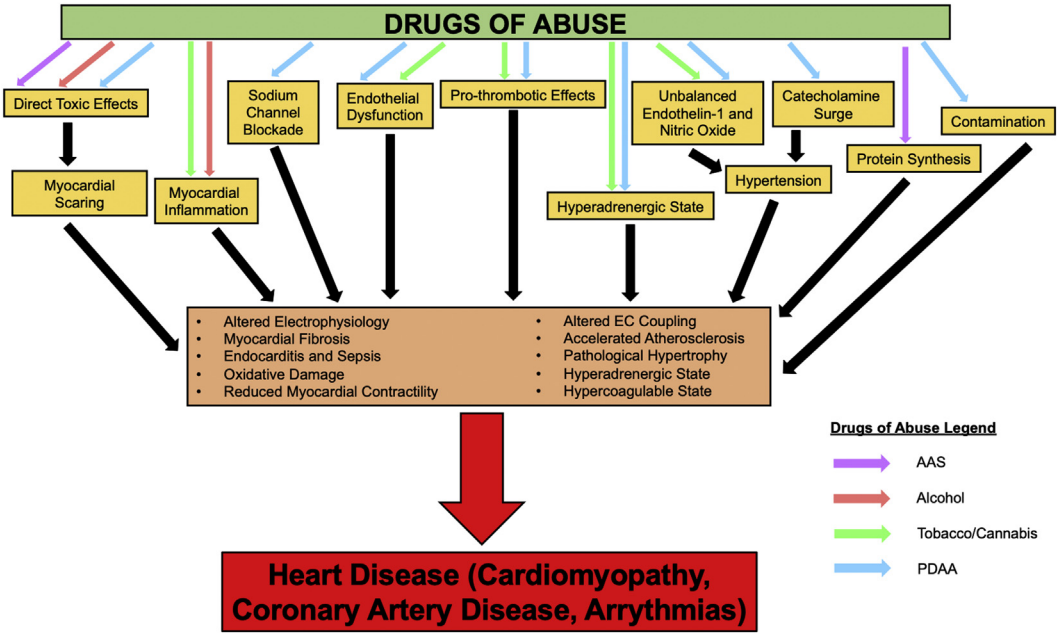

Figure 2. Drugs of abuse and the common pathophysiological mechanisms of heart disease resulting from their usage. Considerable overlap exists between different classes of drugs of abuse in the mechanisms leading to heart disease. The heart disease resulting from drugs of abuse includes dilated and hypertrophic cardiomyopathies, coronary artery disease, and increased arrhythmia burden. AAS, anabolic-androgenic steroids; EC, excitation-contraction; PDAA, psychostimulants drugs of abuse.

increased risk from AAS use and resulting changes to myocardial growth.[79,83]

Other direct cardiac effects of AAS include increased arrythmia risk, which might predispose individuals to sudden cardiac arrest.[77] Chronic coadministration of AAS with moderate-intensity endurance exercise resulted in VF occurrence in rats.[84] Other translational work also showed that supraphysiological doses of AAS caused electrical remodelling of the left ventricle, in addition to morphological remodelling of both ventricles.[85] Many AAS users use a variety of AAS and might combine drugs such as diuretics to achieve stacking effects, which can be lethal.[86]

AAS users have also been reported to have higher coronary plaque volume relative to nonusers and experienced early MI whereas nonusers in the same study had no history of MI or stenting.[78] There is evidence suggesting that AAS induces alterations in lipid metabolism, such as a reduction in high-density lipoprotein and an increase in low-density lipoprotein, effects that cumulatively increase risk of CAD.[77,87-91] AAS might contribute to dyslipidemia and CAD because of impaired cholesterol efflux, which is mediated by high-density lipoprotein.[89] Chronic AAS can lead to increased systolic BP and is also associated with increased aortic stiffness secondary to reduced plasma concentrations of natriuretic peptides (atrial and brain natriuretic peptides).[92] Taken together, the role of AAS in dyslipidemia and hypertension points to AAS' detrimental effect on metabolism and the role they play in contributing to metabolic syndrome in its users despite decreasing their body fat percentage.[93]

Treatment

To reduce CVD risk, cessation of AAS is highly recommended because it has been shown to improve lipid profiles, insulin sensitivity, and BP (Table 2).[93] Discontinuation of AAS remains challenging because of the various withdrawal effects of AAS including hypogonadism, depression, and libido reduction.[86,93] Despite few evidence-driven approaches for treatment of AAS withdrawal, testosterone replacement therapies, selective estrogen receptor modulators, human chorionic gonadotropin, and aromatase inhibitors have been suggested.[93-95]

Cannabis

Cannabis is a term used to describe preparations from the *Cannabis sativa* or *C indica* plants.[96] These psychoactive plants contain more than 400 chemical entities, including Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol.[11,96] Cannabis is now one of the most frequently used psychoactive substances in the world, with estimations that up to 4.9% of the world's population have tried cannabis.[11,12]

Pharmacology

Cannabinoid (CB) receptors are distributed throughout the central nervous system and other peripheral tissues, including in the arteries and heart.[97] The biological effects of CBs are primarily mediated through the endocannabinoid system (ECS) via G protein-coupled receptors: CB_1 and CB_2.[98,99] The ECS is a modulatory system consisting of CB receptors, endogenous CBs (endocannabinoids), and enzymes that regulate levels of these compounds.[100] In the CVS, CB receptors are found in the myocardium, vascular endothelial and smooth muscle cells, and circulating blood cells.[101] Additionally, the CVS can be modulated by upstream effects of CBs on the peripheral nervous system. CB_1 receptors mediate CB-induced cardiovascular depressive effects such as hypotension and reduced myocardial contractility.[99,101,102]

Table 2. Treatment options

	Drug-specific treatment	Treatment	
PDAA	MI: Sublingual NTG or CCB[46] Hypertension: Benzodiazepines and vasodilators. If persistent, consider combined α- and β-blocking agents[46] Persistent cardiac arrhythmias: Consideration of sodium bicarbonate and intravenous lipid emulsion in extreme cases[36,47]	Cessation of the offending agent; referral to a drug rehabilitation program	Continue with guideline-directed therapies
Alcohol	Withdrawal: CIWA-Ar protocol[70] Correct possible QT prolongation[64,65]		
AAS	Withdrawal: TRT, SERM, hCG, and aromatase inhibitors[93-95]		
Cannabis	Hyperadrenergic state: Consideration of β-blockade[125]		
Tobacco	Cessation in an acute cardiac presentation: NRT[139] Bupropion: might benefit long term[139,143] Varenicline: caution in ACS[139]		

AAS, anabolic-androgenic steroids; ACS, acute coronary syndrome; CCB, calcium channel blocker; CIWA-Ar, **C**linical **I**nstitute **W**ithdrawal **A**ssessment for **A**lcohol-**R**evised; hCG, human chorionic gonadotropin; MI, myocardial infarction; NRT, nicotine replacement therapy; NTG, nitroglycerin; PDAA, psychostimulant drugs of abuse and addiction; SERM, selective estrogen receptor modulators; TRT, testosterone replacement therapy.

Alternatively, CB_2 receptor agonists have less pronounced cardiovascular effects.[103]

Cardiovascular complications

The acute CVS effects of CBs are typically driven by activation of the sympathetic nervous system in addition to inhibition of the parasympathetic nervous system, which results in an elevation of HR and systolic BP (Table 1).[104-106] Taken together, the autonomic dysregulation resulting from cannabis use increases cardiac workload and myocardial oxygen demand.[105] Cannabis is also associated with acute coronary syndrome (ACS), which at times occurs in patients without any classic cardiovascular risk factors.[107,108] A recent cross-sectional study has provided evidence that a history of MI was more common among recent cannabis users.[109] MI in these patients might occur in the absence of detectable atherosclerotic CAD.[110,111] Increased myocardial oxygen demand, reduced oxygen supply, microvascular/coronary artery spasm, and the prothrombotic state arising from cannabis use contribute to increased acute coronary syndrome risk.[105,111-113]

The hyperadrenergic state resulting from cannabis use leads to cardiac tachyarrhythmia in the short-term and Δ9-THC increases sinus node automaticity and facilitates A-V nodal conduction (Fig. 2).[105,114] Other arrythmias associated with cannabis use include VF, AF, sinus bradycardia, and second-degree atrioventricular block.[115-118] The mechanisms driving clinical arrythmias in cannabis users are not well known, but it is likely that adrenergic stimulation, myocardial ischemia, and microvascular dysfunction all contribute to AF development and perpetuation in cannabis users.[119] There is also an association between stress cardiomyopathy and cannabis use,[120-122] which is likely driven through a combination of the hyperadrenergic state and modulation of the ECS resulting in reduced myocardial contractility.[120]

Treatment

It is crucial for physicians and other health care professionals to be aware of the potential health complications of cannabis in the midst of its growing legalization worldwide and increasing evidence of its temporal association with cardiovascular complications.[109,123] Specifically, patients with preexisting cardiovascular risk factors, strong family history of heart disease, or other heart conditions should be cautioned against cannabis use.[124] There is evidence that β-blockade might blunt the response of the CVS to Δ9-THC, but this has not been extensively studied (Table 2).[125] As legalization progresses around the globe, long-term follow-up studies and clinical practices should be in place to monitor the health outcomes of cannabis users.

Tobacco and Nicotine

Tobacco use is a worldwide public health concern killing more than 8 million people a year.[126] Despite public health interventions, vaping nicotine liquids continues to gain increasing popularity as young users start with vaping nicotine before transitioning to smoking tobacco, and chronic tobacco smokers transition to vaping nicotine liquids.[14,126,127] Tobacco is commonly smoked in cigarettes, and cigarette smoke is a mixture of nicotine, carbon monoxide, and oxidant chemicals, toxic to the CVS.[128]

Pharmacology

Tobacco has an increased risk in causing CVD through numerous mechanisms, including a procoagulable state, endothelial damage, and reduced oxygen delivery.[13,124] These

mechanisms can exacerbate CAD but also are an independent risk factor for developing heart failure.[15,16] Tobacco-smoking has shown mitochondrial oxidative stress, contributing to endothelial dysfunction causing an association with hypertension.[129,130] Smoking is also associated with a reasonably increased prevalence of type 2 diabetes (RR, 1.37) in observational studies,[131] likely driven by associated changes in body composition and insulin sensitivity.[132] Tobacco also elicits the generation of free radicals that likely cause damage to the myocardium.[133] Inflammatory markers are increased in association with tobacco smoking, specifically C-reactive protein, white blood cell count, and fibrinogen.[134] Additionally smoking can contribute to the development of atrial fibrosis through toxic effects from nicotine.[135] Electronic cigarettes have a moderate cardiovascular risk compared with combustible tobacco products, which have the greatest risk.[14,133] This is potentially secondary to the proatherogenic proteins found in tobacco cigarette smokers but not in electronic cigarette vapers.[133]

Cardiovascular complications

With the increase in cardiovascular risk factors and the direct effect on atherosclerosis, smoking is associated with an increase in CAD and dose-response relationship with the risk of ischemic stroke (Table 1).[136,137] Nicotine provides sympathetic stimulation increasing resting HR, BP, and cardiac output, all contributing to increased myocardial demand potentially worsening any CAD the patient might have, causing acute ischemic events (Fig. 2).[138,139] Smokers have increased risk of chronic obstructive pulmonary disease, which is a risk factor for AF, however, smoking might contribute to an increased risk of AF through sympathetic stimulation from nicotine and atrial fibrosis (RR, 1.32).[140,141] The mechanisms all contribute to an increased risk of heart failure despite adjusting for these risk factors.[142] This risk is likely attributed to damage to the myocardium at the cellular level through increased levels of inflammation in the body but studies at this time are limited.[142]

Treatment

Although there is no specific treatment for cardiac complications secondary to tobacco, the hallmark of treatment is smoking cessation (Table 2).[142] Smoking cessation intervention programs should be encouraged by all clinicians, which has been shown to reduce mortality.[139] Nicotine replacement therapy is a viable option to use in patients with acute CVD presentations despite the increase in sympathetic activation, and can decrease acute withdrawal symptoms.[139] Bupropion helps with outpatient smoking cessation but is not effective during an admission for an acute cardiovascular event because it requires long-term use.[139,143] Varenicline is another option that is also safe for patients with stable CVD but requires caution in patients with an acute cardiovascular event because of conflicting evidence.[139]

Heart Transplantation and Left Ventricular Assist Devices

Consensus guidelines state that substance usage (including tobacco and alcohol) is an absolute contraindication to heart transplantation.[144,145] There are no guidelines for duration of substance cessation before transplantation, however, the general consensus is that tobacco smoking should not be used for more than 6 months before transplantation, which seems reasonable to apply this timeline to other substances as well.[144,145] Under appropriate circumstances, left ventricular assist devices have been shown to be successful in bridging for improvement of patients with severe dilated cardiomyopathy after chronic methamphetamine usage.[146] Left ventricular assist devices are something that can be considered when recovery is expected or as a bridge to transplantation. Local guidelines should be referenced before making these important decisions.

Conclusion

PDAA, alcohol, AAS, cannabis, and tobacco are frequently used recreational and legal substances that contribute to CVD. These substances all contribute to the development of cardiomyopathies, heart failure, and arrhythmias through independent mechanisms and have numerous other cardiac complications. It is important for clinicians to approach cessation with their patients, and to be aware of these cardiac complications. Although no screening guidelines exist, if the clinician is aware of these complications and their symptoms, treatment can be provided earlier. With time there will be more information regarding these substances and their complications, and further research is still needed on other illicit drugs such as opioids. There is a growing need for a nationwide education campaign on the potential long-term damage being done to the CVS in patients with substance use disorders. Further studies are needed to develop screening guidelines and specific treatment guidelines for cardiovascular complications secondary to drugs of abuse.

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