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Methamphetamine Drug

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Abstract

Mesamphetamine is the scourge of the age and the most severe type of drugs, and it is also called the killer methamphetamine, shapo or glass ice. This drug is called a killer because it has great damage to the human body and all its organs that sometimes lead to death even if it was used for a short period of time. It is a crystalline drug distinguished by its white and blue color. Its abusers have often made addicts since the first use because it alters the dopamine and serotonin levels of the brain by increasing the doses which makes it permanent and irreversible damage, this reflects the speed of methamphetamine addiction. It allows the person to experience emotional feelings of depression or madness once it expires. This is why meth addicts are considered one of the most dangerous people due to the severe hallucinations this drug causes. Applying a treatment has nothing to do with pulmonary remodeling, it explains why Meth abuser always has an insufficiency of blood vessels and pulmonary arterial hypertension (PAH) all the time due to the chronic abuse of this substance. However, there are several treatments to help the abuser by reducing the symptoms, but applying it in a specific place may help its effectiveness and This facilitates the rehabilitation of the abuser easily.

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Introduction

Amphetamine and its congener methamphetamine (MA) are two of the most often used illegal substances because of their psychostimulant qualities, which provide mood elevation (euphoria), improved self-esteem, and increased physical and mental ability. The capacity of amphetamine-like compounds to promote the release of freshly generated dopamine from dopaminergic neurons is the main mechanism by which they work (Alhazmi *et al.*, 2020). Figure (1) shows the structure of amphetamine and methamphetamine Methamphetamine is a type of stimulant amphetamine with an extremely addictive effect on the central nervous system. It can be injected, snorted, smoked, or ingested orally, so it was grown in popularity as a less priced and more widely accessible stimulant with longer-lasting effects than cocaine. It's quite addicting (Haight *et al.*, 2009; Mclntyre *et al.*, 2011).

The frequent abuse of methamphetamine as medication may cause hallucinations and confusion. It may also cause cardiac rhythm difficulties and excessive blood pressure and affects the brain by boosting the release of dopamine and preventing its reuptake, a neurotransmitter involved in motivation and pleasure that makes the brain experience a strong euphoric or grandiose mood, which has a significant potential for misuse. Dopamine increases heart rate and has been linked to vasoconstriction in different parts of the body so, methamphetamine usage causes a rapid, euphoric rush, which is followed by euphoria, increased focus, and increased activity (Supiyani *et al.*, 2022; Al-Zubaidi *et al.*, 2020).

Addiction to methamphetamine causes cardiomyopathy, congestive heart failure, myocardial infarction, stroke, convulsions, rhabdomyolysis, cardiomyopathy, insanity, and mortality are all possible side effects (Winslow *et al.*, 2007; Segawa *et al.*, 2019).

Methamphetamine (MA) psychosis is a condition of MA intoxication accompanied by psychotic symptoms such as delusions and hallucinations. This psychotic disorder is thought to be a prevalent and significant adverse effect of long-term, high-dose, and/or continuous MA usage. It's often regarded as having a strong resemblance to paranoid schizophrenia (Zibbell *et al.*, 2022). In addition, smokable meth, sometimes known as "ice," has been demonstrated to increase the risk of corneal ulcers, as well as keratitis and endophthalmitis, which can lead to severe vision loss and blindness (Huang *et al.*, 2022).

Methamphetamine is not only the most commonly used synthetic stimulant in the world, but its usage is also on the rise, according to the most recent National Survey on Drug Use and Health. Methamphetamine is commonly self-administered in a binge fashion, and drug starting at a young age is a risk factor for how it will affect brain function and behavior (García-Cabrerizo *et al.*, 2021). The majority of PWID who injected methamphetamine said they shared injecting equipment. Equipment is shared by MSM and non-MSM injectors of methamphetamine (Glick *et al.*, 2018).

Overdose deaths involving cocaine and methamphetamine have been on the rise in the United States for some years (illicit stimulants), Behind IMF, cocaine, and methamphetamine became the second and third most often detected substances in all law enforcement seizures nationally (US Drug Enforcement Administration (DEA) (Srisurapanont *et al.*, 2011).

The most respiratory complications due to the abuse of methamphetamine are pulmonary haemorrhage, pulmonary edema, acute lung damage, pneumothorax, and pulmonary hypertension, (Zamanian *et al.*, 2018). Furthermore, MA addicts have a higher risk of developing neurological illnesses including depression, schizophrenia, and insanity, PAH seems to be a life-threatening condition characterized by tiny pulmonary artery remodeling, increased pulmonary artery tension, and pulmonary arterial resistance, which leads to right ventricular enlargement and ultimate death (RV) (Labazi *et al*, 2021).

MA as well as other stimulants usage was discovered in more than 30% of PAH patients, MA use has also been linked to dilated CMP (Zhao *et al*., 2018) and functional, with pulmonary inflammatory and remodeling being the most common pathological changes in MA-induced lung damage (Lianga *et al*., 2020). Methamphetamine abuse may cause both acute and long-term alterations in dopaminergic neurons (Baladi *et al*., 2014). Moreover, right atrial collapse, poor health-related quality of life (HRQL), and mortality are all symptoms of pulmonary arterial hypertension (PAH) (Kolaitis *et al*., 2020).

The list of significant medical problems linked to MA misuse has been expanded to include IPAH , HIV infection, connective tissue illnesses, medications (like the indirectly serotonin agonist aminorex and dexfenfluramine), and poisons are also known health risks for PAH , The 5-HT1B receptors have been shown to mediate proliferation in human pulmonary artery smooth muscle cells (PASMCs) recently, Crystal meth, a modified amphetamine with strong central nervous system effects, elicits 5-HT release of neurons by serving as 5-HTT substrates, which reversal the typical direction of transmitter flow (Liu*et al*., 2013).

Methamphetamine abuse also induces hepatic damage due to hyperthremia and morphology alteration. The larges absorption of meth was discovered inside the pulmonary, hepatic, and kidneys, indicating its extensive organs distribution and possibility for toxicity, Cardiotoxicity, coronary artery disease cad, aortic dissection and weight-loss aid were previously described as connections within cardiovascular and respiratory systems (Tsai *et al*., 2019).

Acupuncture is being used in medical clinics to cure addiction caused by a variety of variables, including cocaine , nicotine , alcohol , and morphine in rats and mice, acute METH intake impacts both motor function (i.e. increased locomotion activity) and temperature regulation (i.e. increased body temperature) (Kim *et al*., 2011).

Lots of high meth injections result in long-term loss of central monoamine neurotransmitters in the brain. Several observations show a relationship among hyperthermia and methamphetamine-induced neurotoxicity, implying that the reduction of methamphetamine-induced hyperthermia may play a significant role intolerance to the stimulant's neurotoxicity (Johnson-Davis *et al*., 2003).

In individuals and rats, METH causes hyperthermia, which seems to lead to METH-induced neurotoxicity and death (Brown *et al*., 2003). It also induces significant hyperthermia, which has been related to neuronal injury in a way that is reliant on both the quantity and duration of temperature increase, hyperthermia, leads to severe cell injury and mortality, as a result, if METH-induced hyperthermia plays a role in the liver failure and ammonia rises seen after drug administration, this might indicate a pathway through which hyperthermia significantly contributes to METH neurotoxicity (Halpin *et al*., 2013). Therapy with antioxidant and anti-inflammatory drugs seems to be a viable treatment method for reducing the occurrence of METH-induced neurotoxic sequelae, according to growing data.

It was anticipated that administering CCH, which is used to create pure hydrogen, might reduce hyperthermia and inhibit depression-like behaviors produced by METH exposure at large doses, Using the tail suspension test (TST), forced swimming test (FST) and locomotion test rats were injected METH at various ambient conditions to evaluate the impact of hyperthermia in METH-induced depression-like behaviors (LMT) (Wang *et al*., 2021). Chronic stress, in particular, enhances hyperthermic response to serotonin 2 (5-HT2) receptor agonism, prolonged stress also enhances the acute hyperthermic and Cortisol responses to a new stressor as well as the acute neurochemical and hyperthermic response to the addictive substance meth (Doyle, Yamamoto, 2010). Heat shock proteins HSPs are biomolecules produced both in eukaryotic and prokaryotic cells in response to a variety of stressors such as heavy

metals, ischemia, several disease states, and heat stress (Kupermanet *al.*, 1997). This study aims to clarify the effect of methamphetamine on the nervous system, body temperature, damage to the body whose range may extend to organ deformation and other effects that lead to the occurrence of countless chronic diseases.

Methamphetamine induced Pulmonary haemorrhage (PAH) complication of pulmonary arterial hypertension (PAH)

In case of Meth-APAH demonstrated similar pulmonary function to patients with pulmonary arterial hypertension iPAH, but substantially greater DLCO, while having a higher smoking history (Meth-APAH 70 [77.8%] vs. iPAH 31 [32 percent], P, 0.001;), On echocardiogram, patients with Meth-APAH were more likely to show moderate - to - severe right-ventricular (RV) dilation and dysfunction as shown in Fig. 2 (from Zamanian *et al.*, 2018).

Treatment with MA has an effect on pulmonary arterial remodeling. Although lungs from MA-treated mice were compared to those from vehicle-treated mice, no significant pulmonary arterial remodeling was found in both men and females (Labazi *et al.*, 2021).

Impact of MA on pulmonary artery smooth muscle cells (PASMC) proliferation and apoptosis.

In a study by a tertiary care medical hospital in Hawaii, 40 percent of young cardiomyopathy patients are methamphetamine addicts, whereas 5% of congestive heart failure patients in the United States have a history of illegal stimulant drug misuse, and the frequency of methamphetamine-associated congestive heart failure is on the rise. PCNA (proliferation cell nuclear antigen) is a well-known cell proliferation biomarker. PCNA expression did not vary substantially at 24 hours with varied MA doses in our investigation with PASMSc employing PCNA as a maker.We used western blot analysis to determine the amount of Bcl-2 (anti-apoptotic factor), and we discovered that the amount of BCL2 increased significantly with rising MA dose, but there was no notable raise of BCl2 at various time points.When compared to the control group, 5 mM MA substantially suppressed BAX and Caspase-3 production at 36 and 48 hours, while 1 mM and 5 mM MA considerably lowered BAX and Caspase-3 amounts at 48 hours compared to 24 hours (Segawa *et al.*, 2019).

Nuclear factor erythroid-2-related factor 2 (Nrf2) nuclear translocation through pulmonary artery smooth muscle cells (PASMCs)

The findings of western blots and immunofluorescence were similar, indicating that injection of 5mM MA reduced the nuclear translocation of Nrf2 in PASMCs, suppressing anti-oxidative stress. MA-induced PASMC proliferation was tightly and positively and significantly related to PASMC Levels of ROS [16]. Mice given MA and subjected to hypoxia develop pulmonary veins remodeling, which is linked to mitochondrial malfunction and Damage to DNA in the lab, By altering heart cellular signaling (i.e. high calcium entrance and apoptosis), MA causes cardiac damage and dysfunction, Recent research has found that perinatal and adult intake to MA resulted in greater infarct size in female rats in reaction to ischemia-reperfusion, but had no impact on male hearts, indicating a female heart extreme sensitivity to ischemic damage (Labazi *et al.*, 2021). Females are more sensitive to PAH in clinical studies, and a recent clinical investigation found that female sex was the key factor linked with MA-induced PAH. Furthermore, studies have shown that females are more sensitive to several of the behavioral effects of MA than men. Increased locomotor activity, a greater risk of self-administering MA if given free access to drugs, and a higher sensitivity to relapse following a period of forced abstinence are among these, Our findings show that MA's impacts on genes linked to PAH development may play a significant role in MA-induced PAH in females, While MA is one of the risk factors for pulmonary hypertension, it may also function as a "second hit" to underlying genetic (i.e. mutations) or non-genetic (i.e. HIV) diseases Acute MA therapy has been demonstrated to promote

vasoconstriction in brain arterioles and blood - brain disruption in the vascular (Kolaitis *et al*., 2020).

The effect of prolonged MA on the systemic arterial pressure

Results showed that the prolonged MA did not change the systemic arterial pressure. The percentage medial wall thickness of pulmonary arteries was determined as a measure of pulmonary arterial remodeling. As shown in MA group, the medial wall of pulmonary arteries (50–100 lm in diameter) was thickened.

The MA-induced rise in pulmonary arterial medial thickness was considerably decreased by fluoxetine 10 mg/kg rather than 2 mg/kg. A characteristic pathogenic aspect of pulmonary arterial hypertension is PASMC hyperplasia. The 5-HTT and 5-HT1B receptor proteins were mostly found in the pulmonary artery medium. Immunohistochemistry revealed 5-HTT staining in the endothelial and underlying smooth muscle cells. When comparing the MA group to the control group, the staining intensity demonstrated that 5-HTT and 5-TH1B receptor expression was higher in the MA group's pulmonary (Liu *et al*., 2013).

Methamphetamine induced hepatic damage due to hyperthremia and morphology alteration

Methamphetamine is a psychostimulant of the phenethylamine and amphetamine classes of drugs and is a sympathomimetic that accentuates catecholaminergic and serotonergic neurons. Its precursors were first utilized to treat asthmatic and clogged sinuses (ephedrine), and as well as a weight-loss aid (fen-phen), After the stimulating properties were discovered in the early twentieth century, it was widely used as a performance enhancing drug, and later as a pleasure drug in pure forms, Amphetamine-type stimulant, of which meth is the most popular, are the second-most commonly used illegal drug class outside the United States, The largest absorption of meth was discovered inside the pulmonary, hepatic, and kidneys, indicating its extensive organs distribution and possibility for toxicity, Cardiotoxicity, coronary artery disease cad, and aortic dissection, and also weight-loss aid were previously described connections with in cardiovascular and respiratory system. Subsequently, the probability of getting a discharge diagnosis of acute respiratory failure in crystal meth use discharges was 1.77 (95 percent CI 1.59, 1.98; p0.001) times the hazard in non-methamphetamine use discharges in women and 1.24 (95 percent CI 1.12, 1.37; p0.001) times the risk in non-methamphetamine use discharges in men (Tsai *et al*., 2019).

METH-induced excitation and heat are inhibited by BV acupuncture into Zusanli acupoint (ST36)

Except at the lowest dosage (0.01 mg/l), pretreatment with BV (20 l of 0.01, 0.1, 1 or 10 mg/ml) in ST36 attenuated these METH-induced reactions. Pretreatment with 0.1 mg/ml BV decreased METH-induced hyperactivity but did not prevent METH-induced heat.METH-induced hyperactivity and hyperthermia were considerably decreased by higher dosages of BV (1 and 10 mg/ml). When compared to saline-treated rats, the maximum dosage of BV (10mg/ml) dropped body temp by roughly 2°C (Wang*et al*., 2021).

The impact of bee Venum (BV) acupuncture on METH-induced excitation and heat is route of administration dependent

BV injected in ST36 inhibited METH-induced hyperactivity and hyperthermia, but BV administered into other acupuncture points (SP9 or GB39) or a non-acupoint (tail base) had no impact (Kim *et al*., 2011).

Impact of meth in peaceful resting situations

Hyperthermia was caused by METH administration in an amount of the drug manner. The observation that METH causes dose-dependent heat in brain structure that is consistently quicker and larger than it does in the head muscle points to neural activation as a source of brain heat and the fundamental impetus driving subsequent body heat., The brain–muscle temperature difference immediately increased following drug injection as a result of this dynamic,

and remained high for 50 (hippocampal) or 110 (NAcc) minutes. When METH was given under calm resting settings, NAcc– and hippocampal–muscle differences increased for three hours, however these differences stayed unusually high for >6 hours when the drug was given in social contact, as a result, increased body temperature is a direct result of the drug's central effect rather than a later result of movement stimulation or another peripheral activity. Hyperthermia caused by METH was structure-specific (stronger and longer-lasting in the NAcc than in the hippocampus). In the absence of medication, it was more strong and more prolonged than hyperthermia found under a range of behavioral situations. It was recently demonstrated that METH contributes to differences in hepatocellular structure 24 hours after exposure, although it was unclear whether these alterations were dosage-dependent prior to current research (Brown *et al*., 2003).

Alteration in liver structure caused by heat and METH

There was significant clearance of cytoplasmic stains in hepatocytes throughout the hepatic lobule 24 hours after METH administration, equivalent to that seen following METH therapy. The alterations in cell structure observed in the liver tissue of METH-treated mice were inhibited by preventing METH-induced heat (Halpin *et al*., 2013). It was shown that coral calcium hydride produced molecular hydrogen inhibits methamphetamine-induced hyperthermia and depressed mood behaviors. When mice received CCH injections (100 and 200 mg/kg, i.g.) before receiving METH injections (10 mg/kg, i.p.) under HAT (28°C) 1 hour later. Two hours later, the body core temperature was recorded every 20 minutes. CCH pretreatment considerably reduced METH-induced hyperthermia (Wang *et al*., 2021).

Administration of Ma to mice that had never been stressed before (control/methamphetamine), led to a significant rise in plasma CORT. The administration of meth to mice that had never been stressed before (control/methamphetamine) led to a significant rise in plasma CORT (p 0.05 vs control/saline). The CORT responses to meth was enhanced in rats that had previously been stressed (p 0.05 vs control/methamphetamine) Crystal meth (7.5 mg/kg q 2 h 4) administration to non-stressed mice (control/methamphetamine) had no effect on hippocampal 5-HT seven days later (p = 0.947 versus control/saline); but nevertheless, methamphetamine administration to rats who had previously been stressed (stress/methamphetamine) did result in a 40percentage depletion in 5-HT 7 days later (p < 0.05 versus con- trol/saline) (Doyle *et al*., 2010).

Socio-demographic and drug use characteristics of the study participants

Females made up 51.2 percent of the 41 participants, who were all non-Hispanic whites. Whereas approximately 73 percent said they were jobless, and over 60 percent said they had been homeless in the previous 30 days.

The bulk of them had been using illegal opioids since they were teenagers. Nearly 90% of those polled said they had ever sought treatment for opioid addiction. Participants reported consuming methamphetamine on an average of 18.2 (SD 8.9) days in the previous 30 days. Moreover, half said they had used powdered cocaine in the previous 30 days, and 44% said they had used non-prescribed benzodiazepines. (Table 1) Early on, 90% of individuals said they had had an unintended drug overdose, and roughly 73% said they had used naloxone to assist reverse an overdose as shown in Table 1.

The results of urine toxicology in Table 1, shows that all participants tested positive for fentanyl/or fentanyl, 61 percent for acetyl fentanyl, and roughly 30 percent for tetrahydrofuran fentanyl, according to the study. A third of the people tested positive for heroin. Methamphetamine was detected in 39 (95%) of the individuals. Those who tested negative for methamphetamine said they had used it during the last 30 days, but not within the 3-day detection window. Cocaine was detected in 58.8% of subjects, whereas benzodiazepines were detected in 36.6 percent. (Table 1) (Daniulaityte *et al*., 2022).

Table 1. Socio-demographic and drug use characteristics of the study participants (Daniulaityte *et al.*, 2022).

N = 41 Characteristic	Mean	Std. Dev.	Number/ Percent/
Socio-demographics			
Female		21	51.2%
Male		20	48.8%
Ethnicity (White, non-Hispanic)		41	100%
Age, years (Mean, Std.Dev)	38.3		7.7
Education (Some college or more)		20	48.8%
Marital status (married or living with someone as married)		17	41.5
Reported current unemployment		30	73.2%
Reported homelessness in the past 30 days		14	61.5%
Drug use characteristics			
Used heroin/fentanyl in the past 30 days		41	100%
Used methamphetamine in the past 30 days		41	100%
Powdered cocaine use in the past 30 days		24	58.5%
Crack cocaine use in the past 30 days		22	53.7%
Non-prescribed benzodiazepine use in the past 30 days		18	43.9%
Age of first illicit opioid use (Mean, Std. Dev.)	19.3		5.1
Age of first methamphetamine use (Mean, Std. Dev.)	27.8		9.00
Ever received medication for opioid use disorder		36	87.8%
Days of methamphetamine use (past 30 days, mean, std. dev.)	18.2		8.8
Urine toxicology analysis for non-pharmaceutical fentanyl, analogs* and other drugs			
Heroin		12	29.3%
Fentanyl		41	100.0%
Norfentanyl		41	100.0%
Despropionyl fentanyl		32	78.1%
Acetyl fentanyl		25	61.0%
Tetrahydrofuran fentanyl		12	29.3%
Valeryl isovaleryl fentanyl		6	14.6%
Carfentanil		5	12.2%
Fluoro fentanyl		3	7.3%
Benzyl fentanyl		2	4.9%
Butyryl isobutyryl fentanyl		2	4.9%
Acryl fentanyl		1	2.4%
Methamphetamine (and/or metabolite amphetamine)		39	95.1%
Cocaine		24	58.1%
Benzodiazepines		15	36.6%
Marijuana		12	29.3%
Opioid overdose-related attitudes and experiences			
Ever experienced an unintentional opioid-related overdose (OD)		36	87.8%
Ever obtained take-home naloxone		36	87.8%
Ever used naloxone to help an OD victim		30	73.1%
Number of occasions ever used naloxone to help an OD victim	9.6		18.1
Ever used methamphetamine to reduce the risk of an opioid OD		19	46.3%
Ever used methamphetamine to help an opioid OD victim		20	48%
Number of occasions ever used methamphetamine to help an opioid OD victim	2.3		4.1

Information on estimated potency of fentanyl analogs

It was found that acetyl fentanyl potency ratio to morphine is 15.7 and to fentanyl 0.29; Tetrahydrofuran potency ratio to fentanyl was estimated 0.2; Carfentanil potency ratio to fentanyl 30-100; Acryl fentanyl potency to fentanyl was estimated to be 0.3 for acetyl fentanyl, 0.75 acryloylfentanyl 1.2 Participants mentioned using social networks and personal experimentation to learn about methamphetamine as a treatment for opioid withdrawal symptoms. Many participants said that methamphetamine relieved weariness, alleviated the acute physical symptoms of opiate withdrawal, and provided a psychological diversion, but some acknowledged that methamphetamine usage may

result in extra health problems. Participants stressed the necessity of timing and dose while using methamphetamine as a self-treatment approach (Silverstein *et al.*, 2021).

Patients who were addicted to methamphetamine or heroin scored considerably worse on all RBANS subtests and overall scores (all p 0.05). Furthermore, individuals who were addicted to methamphetamine exhibited more delayed memory impairment than those who were addicted to heroin (p = 0.02). Furthermore, among methamphetamine patients, various drug-related characteristics such as abstinence, age at first drug use, and duration of drug use were independently correlated with memory and visuospatial/constructional index (all p 0.05). In heroin addicts, however, none of the drug-related factors were connected with cognitive function (all p > 0.05) (Tian *et al.*, 2022).

Cortisol

Cortisol production is an important part of the human stress response. Drug misuse and amphetamine neurotoxicity have been linked to abnormalities in the stress response in individuals After METH treatment, we examined total 24-hour cortisol emission in urine. When compared to the saline interval, METH delivery resulted in substantial rises (B30–40%) in levels of cortisol both throughout the METH Ramp-up and METH Management periods (Madden *et al.*, 2005).

Review analysis

Because of its psychostimulant qualities, methamphetamine is one of the most often used illicit substances. It makes individuals feel better and gives them greater self-esteem, as well as physical and mental power. It is the primary mechanism by which methamphetamines function. It has the potential to cause dopamine-producing neurons to release more of the new dopamine they have produced (Supiyani *et al.*, 2022). Since 2009, methamphetamine injection among PWID in King County, Washington, has grown. Non-MSMs accounted for the majority of the rise in methamphetamine injection. Methamphetamine injections with heroin ("goofballs") are very prevalent (Glick *et al.*, 2018).

Meth-APAH is more prevalent in males than iPAH, probably owing to patterns of (meth) amphetamine use, in this first prospective cohort study on Meth-APAH to our knowledge. Meth-APAH has more severe pulmonary vascular disease than iPAH, as shown by greater right atrial pressure, less stroke volume index, and a much more dilated and dysfunctional RV at baseline, Furthermore, I was found that hospitalized (meth)amphetamine users had a 2.6-fold greater probability of having an ICD-coded PAH diagnosis compared to nonusers, a result that is particularly noticeable in female (meth)amphetamine users, utilizing a comprehensive, big, state-wide database, Chronic (meth)amphetamine use (and maybe intermittent relapse) may have additional health implications, such like systemic, infectious, and neurocognitive illnesses, which may cause worse results, Despite the fact that our research does not pinpoint the pathway by which (meth)amphetamine use leads to pulmonary arterial disease and poorer outcomes, there is a wealth of data linking (meth)amphetamine use to PAH. Amine-class stimulants aminorex fumarate, 5-methyl-aminorex, and fenfluramine, all of which are known to induce high blood pressure, have comparable molecular structures to (meth)amphetamine, (Meth)amphetamine, like these anorexigenic, stimulates the release dopamine, norepinephrine, and serotonin, as well as the creation of reactive oxygen species. Human lungs had the fastest absorption and accumulation of (meth) amphetamine (24 percent–31 percent of injected dosage) compared to other solid organs, suggesting an organ-specific sensitivity to (meth)amphetamine toxicity (Srisurapanont *et al.*, 2011). Furthermore, persistent amphetamine exposure causes HIF1a (hypoxia-inducible factor 1-a) suppression and alteration of adaptive responses to mitochondrial oxidative stress in hypoxic mice, culminating in DNA damage and eventually vascular injury, It's probable that chronic and repetitive (meth)amphetamine inhalational intake is linked to

severe pulmonary damage, given the evidence of acute respiratory toxicity (Zamanian *et al.*, 2018; Baladi *et al.*, 2014).

Triple combined treatment, injectable prostacyclin treatment, and supplementary oxygen were less likely to be given to Meth-APAH patients, Participants with Meth-APAH were more likely than hose with idiopathic PAH to see in the emergency room and to be hospitalized (Kolaitis *et al.*., 2020). PG01037 was unable to prevent DAT reductions caused by meth. Furthermore, 7 days after medication delivery, PG01037 did not reduce long-term deficiencies in SERT function or declines in dopamine and 5HT levels (Baladi *et al.*, 2014).

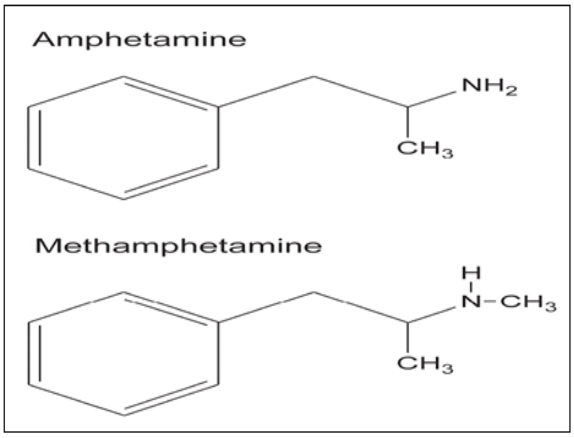

Fig. 1. Structures of amphetamine and its congener methamphetamine (Alhazmi *et al.*, 2020).

Many studies are now being conducted in order to determine the best efficient therapy strategy for treating METH abuse. Acupuncture may enhance METH addiction response, according to one of these studies, although its effectiveness is still debatable, and the treatment mechanism is still yet to be established (Kim *et al.*, 2021).

MA usage has been linked to arrhythmia and cardiomyopathy in the cardiac, Our findings back with recent in vitro studies that showed increase in cell volume in rat cardiomyocytes after MA therapy, MA has also been demonstrated to boost endothelin, angiotensin, serotonin, and adrenergic signaling systems, which are recognized vasoconstrictors and have been linked to the development and pathophysiology of PAH (Labazi *et al.*, 2021).

Vasoconstriction, tachycardia, hypertension, and/or direct myocardial toxicity, very little known regarding the pathophysiology and risk factors for dilated CMP in chronic MA abusers. The relevance of concurrent use of these illegal drugs with MA is that methamphetamine toxicity is exacerbated when coupled with drink or cocaine according to logistical regression analysis. The absorbance of MA in the body is largely concentrated in the lung, suggesting that the lungs may be a key target for MA-related harm due to their greater consumption, which may cause anomalies in respiratory structure (Zhao *et al.*, 2018).

Male preponderance in MA-CMP has been repeatedly shown in earlier studies, with male predominance ranging from 64% to 93 percent. MA users, like any illegal drug users, use a broad range of additional drugs. When illegal MA is self-administered by injectable or inhalation routes, blood levels should be great enough to induce serotonin transporter protein, resulting in a rise in 5-hydroxytryptamine levels in vivo and subsequently PAH formation. In pulmonary endothelial cells, 94.4 percent of patients were heterozygous for a single-nucleotide variation that was anticipated to lower the activity of carboxylesterase 1, an enzyme implicated in the metabolism of MA and most amphetamine derivative medications. Reduced expression or activity of this important enzyme might lead to changes in drug metabolism and persistent organ damage (Zhao *et al.*, 2018).

MA caused a considerable unbalance in proliferation and death in PASMCs by up-regulating PCNA and Bcl-2 and decreasing the expression of BAX and Caspase 3. We discovered that a large quantity of MA (i.e. 5mM) effectively blocked Nef2 from translocating to the nucleus and inhibiting anti-oxidation, These observations imply that prolonged MA uptake pulmonary artery remodeling via a Nrf2-mediated redox system imbalance, aggravating oxidative stress, and that Nrf2 might be a target for MA-induced pulmonary damage therapy, These findings showed that long-term treatment of MA enhanced PASMC

proliferation while inhibiting apoptosis, suggesting that prolonged exposure to MA may also cause pulmonary artery remodeling, According to the results, persistent MA exposure may suppress the Nrf2-mediated antioxidant defense mechanism (Segawa *et al.*, 2019; Lianga *et al.*, 2020). The actual mechanism of MA-induced pulmonary artery remodeling, though, remains, unknown. Oxidative stress occurs when the generation of reactive oxygen species (ROS) in cells surpasses, their clearance, resulting in an anti-oxidative responses that are out of balance and oxidative stress, Nrf2, an endogenous anti-oxidative enzyme, is required for the equilibrium of redox processes to be maintained, As a result, the oxidative and anti-oxidative unbalance might be linked to Nrf2 deactivation, caused by excessive ROS generation (Lianga *et al.*, 2020).

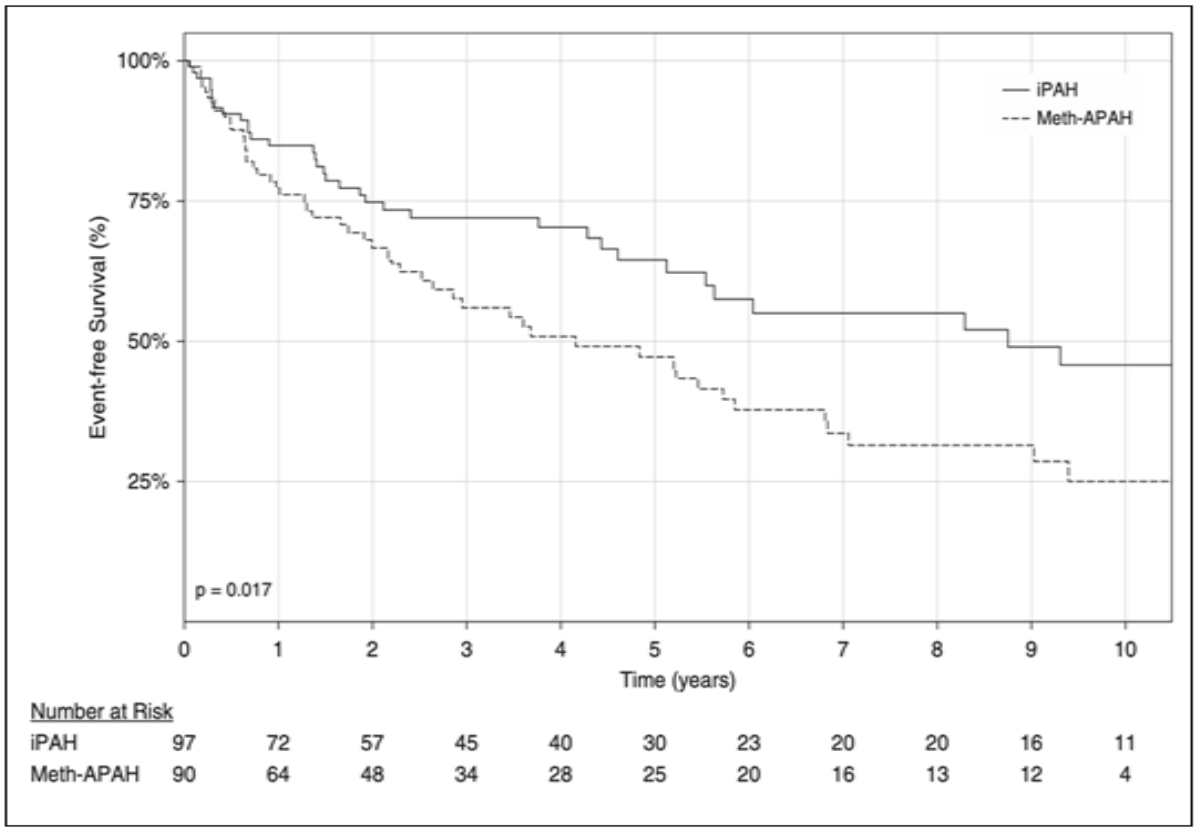

Fig. 2. Shows the MA duration and associated pulmonary arterial hypertension (from Zamanian *et al.*, 2018).

Understanding the hemodynamic variations between Meth-APAH and idiopathic PAH will help in understanding the cardiopulmonary effects of methamphetamine usage, In Meth-APAH, adjuvant therapy for right ventricular remodeling, including spironolactone, is more effective than in other etiologies, Finally, a greater knowledge of the effect of screening and drug rehabilitation in individuals with Meth-APAH is needed to see whether the hemodynamic alterations may be improved if the methamphetamine use is stopped (Baladi *et al.*, 2014; Kolaitis *et al.*, 2020). Moreover, the MA-induced pulmonary arterial remodeling was linked to the overexpression of 5-HTT and 5-HT1B receptors. Fluoxetine reduced MA-induced pulmonary artery remodeling, which was linked to a reduction in 5-HTT and 5-HT1B receptor activation (Liu *et al.*, 2013).

The link between methamphetamine use and poor pulmonary outcomes such as COPD exacerbation, acute pneumonia, or acute respiratory failure is consistent with recognized pulmonary problems of acute respiratory failure linked to another inhaled stimulant, "crack" Cocaine. Furthermore, some research suggests that methamphetamine consumption disrupts host immunity, putting

methamphetamine users at higher risk of contracting a variety of infections, furthermore, methamphetamine's intoxicating impacts incline individuals to participate in hazardous behavior, which raises the chance of contracting transmissible microorganisms or establishing immunodeficiency (e.g., HIV and AIDS), Finally, because the ICD-9 code for "severe respiratory failure" is so broad, it could include any type of respiratory failure, like edema (cardiogenic or noncardiogenic), acute respiratory distress syndrome, or diffuse alveolar harm, that have all been related to methamphetamine use and in case of reports (Tsai*et al.*, 2019).

Even though acupressure seems to be a suitable candidate for treating METH dependence in pilot research, the therapeutic efficacy and specific mechanism of acupuncture on substance abuse are currently unknown, Similarly, BV injection into ST36 without METH had no effect on locomotor activity or body temperature, suggesting that BV acupuncture into ST36 had no effect on normal body conditions. These data imply that choosing a particular acupoint is a critical aspect in achieving a pharmacological benefit via BV acupressure, The impact of BV on METH-induced hyperactivity and hyperthermia was depending on the region injected and the degree of the stimulant (BV dose). In mice, the ST36 is by far the most effective site for BV to have an impact on METH addiction (Kim *et al.*, 2011).

METH causes dosages hyperthermia in brain regions that develop quickly and is larger than in the head muscle implies that neural activation is a cause of brain temperature and the principal impetus underlying subsequent body hyperthermia (Brown *et al.*, 2003).

After 24 hours from exposure to METH, alterations in hepatocellular ultrastructure were observed, indicating overall cellular stress and injury, METH-induced liver damage has been linked to an increase in central and peripheral ammonia, as well as long-term reductions in brain dopamine levels, although the mechanisms through which METH produces hepatic alterations are unclear, External temperature rises paired with high METH concentrations have been demonstrated to cause hepatocyte injury in vitro, indicating that hyperthermia may play a role in METH hepatotoxicity (Halpin *et al.*, 2013).

Prior studies has shown that the withdrawals of amphetamine-type psychostimulants and severe depressive illness in humans have striking behavioral parallels, Anxiety and depression are linked to a change in hippocampus synaptic plasticity, according to growing research. As a consequence, it's been hypothesized that a rise in METH-induced oxidative stress products and inflammatory factors leads to a reduction in synaptic synthesis of proteins and structural failure, eventually leading to depressed symptoms (Brown *et al.*, 2003; Wang *et al.*, 2021).

Prolonged stress and meth together decreased hippocampus 5-HT, while meth showed little impact on its own, a first rise might be an immediate reaction to hyperthermia, while the secondary induction could represent the cell preparing for a general increase in synthesis of proteins to replace damaged proteins (Doyle, Yamamoto, 2010; Kuperman*et al.*, 1997). Overdoses became an ever-present aspect of everyday life for persons who use illegal opiates in regions like Dayton, Ohio, and many other cities across the US as NPF availability expanded. According to qualitative interview data, many people use methamphetamine as a non-medical harm reduction technique to manage fentanyl-related overdose risks and incidents. These ideas and practices are based on a general understanding of how methamphetamine stimulates the cardiovascular system as well as direct personal experience. The use of methamphetamine for opioid overdose reversal is based on situational risk assessments, which are influenced by a lack of fast availability of naloxone, the interpretation of overdose symptomatology, and simple access to numerous and cheap methamphetamine (Daniulaityte *et al.*, 2022). Methamphetamine usage as a strategy to self-manage opioid withdrawal among PWUIO in the Dayton region must be researched in connection to past and emerging patterns of illicit

opioid use and related dangers. More study is needed to determine the long-term health effects of this new polydrug strategy (Silverstein *et al.*, 2021).

Patients who have been addicted to heroin or methamphetamine for a long time may have various cognitive abnormalities, substantial declines in food consumption when the METH dosage was raised, a change that also happens in persons taking METH and other substituted amphetamines (Tian *et al.*, 2022; Madden *et al.*, 2005).

Conclusion

Methamphetamine users are daily struggling to be a life every day so, addiction to methamphetamine is not easy it's considered a matter of concern because it goes beyond of that it is not only a stimulant drug but it was used in the past as a treatment for many diseases, nowadays it is considered as a drug that induces schizophrenia or madness. Its the responsibility of the PAH (pulmonary arterial hypertension) diseases that lead to infection, exacerbation of the heart right ventricle (RV), and failure. it might cause severe un-countless damage to several organs; brain, heart, lungs and liver for example in the brain its impact on neurotransmitters leads to an imbalance which causes differences in the body temperature or it may lead to liver damage and distractions, Which is at the end disrupts the function of the liver and its efficiency, Likewise, for kidney excretion, heart rhythm, eye coordination and movement; these effects continue until it includes other organs and thus, the person reaches into a hopeless stage of addiction then death occurs. The impact of Methamphetamine depends based on Population Distribution, weight, or age, as well as the gender of chronic diseases .All of these factors contribute to meth abuse. It is important to know the route of exposure or the amount that a person takes to help us in applying the right treatment or the right dose to prevent it from interacting with the body or when involves in the occurrence of the risk factor Current studies have indicated that meth may have a greater effect on women's hearts instead of men, due to their heat sensitivity .Those complications that meth caused helped us to understand the quality of life that leads to the possibility of drug abuse not only in meth and the hypersensitivity that induced depression.

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