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Cardiotoxicity associated with methamphetamine use and signs of cardiovascular pathology among methamphetamine users

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CARDIOTOXICITY ASSOCIATED WITH METHAMPHETAMINE USE

AND

SIGNS OF CARDIOVASCULAR PATHOLOGY AMONG METHAMPHETAMINE USERS

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EXECUTIVE SUMMARY

Background

The use of methamphetamine is widespread and, in many countries, is a major drug of abuse. As such, it is important to identify and understand the adverse health effects associated with methamphetamine use and consider the risk of such consequences for users. Although methamphetamine has effects on multiple organ systems, this report will focus on the cardiovascular effects of methamphetamine. Specifically, the aim of this report is to review the evidence for methamphetamine-related cardiovascular pathology and discuss the implications for methamphetamine users.

Methamphetamine cardiotoxicity

Methamphetamine increases catecholamine activity in the branch of the peripheral nervous system responsible for modulating heart rate and blood pressure. Excessive catecholamine activity is thought to be the primary mechanism underlying the cardiotoxic effects of methamphetamine. High catecholamine levels are known to be cardiotoxic, causing narrowing and spasm of the blood vessels, rapid heart rate (tachycardia), high blood pressure (hypertension), and possible death of the heart muscle. Other features of catecholamine toxicity include the formation of fibrous tissue and an increase in the size of heart muscle cells.

Evidence of cardiotoxicity among methamphetamine users

The most widely reported adverse cardiovascular effects of methamphetamine use are chest pain, tachycardia and other cardiac arrhythmias, shortness of breath and high blood pressure. The less frequently observed, but more severe, acute cardiovascular complications of methamphetamine use are acute myocardial infarction, acute aortic dissection, and sudden cardiac death. The medical literature contained several single case reports and case series reports of acute myocardial infarction. Acute myocardial infarction often occurred in the absence of identifiable coronary artery disease.

The forms of chronic cardiovascular disease that are most commonly associated with methamphetamine use are coronary artery disease and cardiomyopathy. Studies of methamphetamine-related fatalities have suggested that methamphetamine users are at risk of the premature and accelerated development of coronary artery disease. Clinical

and experimental evidence alike suggest that the use of methamphetamine, particularly long-term use, can induce cardiomyopathy. As with acute myocardial infarction, cardiomyopathy has been associated with various routes of methamphetamine administration (e.g. oral, smoking and intravenous).

Factors influencing the cardiovascular effects of methamphetamine

The necessary and sufficient dose to produce serious cardiovascular complications or death - that is, the "toxic" dose - is unclear, as the response to a specific dose varies due to individual differences in responsiveness and variations in degree of tolerance. The literature indicates that cardiovascular complications associated with methamphetamine use can occur with all of the major routes of administration: that is, intranasal, oral, smoking, and injecting. While there is no evidence to suggest that any one route of methamphetamine administration should be more strongly associated with cardiotoxicity than another, the risk of complications may be higher with patterns of use that are associated with frequent use and taking higher doses, such as injecting and smoking crystalline methamphetamine. Previous research also suggests that the risk of cardiovascular problems among methamphetamine users is increased when the drug is combined with alcohol, cocaine or opiates. Of particular concern is the concomitant use of methamphetamine and other psychostimulant drugs, such as cocaine, due to their potential synergistic effect on catecholamine activity.

Conclusions and recommendations

Low level use of methamphetamine - for example, sporadic, low dosage use - does not appear to be associated with major acute complications, such as myocardial infarction, or chronic cardiovascular disease, in an otherwise healthy user. Methamphetamine may, however, exacerbate pre-existing underlying cardiac pathology, such as coronary atherosclerosis or cardiomyopathy, thereby increasing the risk of an acute event such as myocardial infarction or even sudden cardiac death. Long-term methamphetamine users appear to be most at risk of cardiovascular damage, such as premature, accelerated coronary artery disease. As such, methamphetamine toxicity is more likely to have a fatal outcome with chronic use.

Given their high levels of polydrug use, methamphetamine users should also be made aware of the increased risk of adverse cardiovascular effects when methamphetamine is

used with other drugs, particularly other psychostimulant drugs. Because of the individual variation in sensitivity to methamphetamine's cardiotoxic properties, treating methamphetamine toxicity should be based on the symptom presentation rather than the reported dose administered.

Further research is needed to establish the risk of serious cardiac events among methamphetamine users, whether there is evidence of a dose-response relationship between methamphetamine use and cardiotoxicity in humans, and also the relative contribution of methamphetamine over other concurrent risk factors, such as tobacco smoking, alcohol and other drug use, obesity, and pre-existing cardiac pathology.

1 INTRODUCTION

Methamphetamine, and its psychogenically less potent chemical analogue, amphetamine, are synthetic stimulant drugs that exert their action by increasing the concentration of the catecholamines in both the peripheral and central nervous systems (Derlet & Heischober, 1990; Albertson et al., 1999). Methamphetamine and amphetamine were first introduced to the consumer market in the 1930s. They were originally used for a range of therapeutic purposes, such as treating asthma, nasal congestion, depression, obesity, narcolepsy and hyperactivity in children. Their stimulant properties were also enjoyed by soldiers in World War II, who were supplied amphetamines to counteract fatigue and increase vigilance.

As the use of amphetamines became widespread, extending beyond therapeutic use to recreational and occupational use, the health consequences and potential for dependence became apparent and, in 1971, amphetamines were placed on the list of internationally controlled substances (United Nations, 1971; Klee, 1997; Yoshida, 1997). Nevertheless, the illicit use of methamphetamine has continued to increase on a global scale (Yoshida, 1997) and is a major drug problem for a number of countries in the Asia-Pacific region and in North America (United Nations Office on Drugs and Crime, 2005). Given the widespread use of methamphetamine, it is important to identify and understand the adverse health effects associated with the drug's use and consider the risk of such consequences for users.

Much of what is understood about the effects of methamphetamine on the cardiovascular system is based on what is known about the cardiovascular effects of cocaine. While there are some differences between the two drugs with respect to their pharmacological actions, the effects of methamphetamine are very similar to those of cocaine (Julien, 2001; Sztajnkrycer et al., 2002). Methamphetamine, however, has a much longer half-life than cocaine (11-12 hrs vs. 45-90 mins), resulting in a longer duration of effects (Cook et al., 1993; Lange & Hillis, 2001; Karch, 2002). Essentially, methamphetamine and cocaine induce the same types of cardiovascular toxicity (Karch, 2002), although there may be differences in the risk and severity of harm to users, with the incidence of cardiovascular complications arising from cocaine use being generally higher than those associated with methamphetamine use (Derlet & Horowitz, 1995;

Karch, 2002). Whilst there is a vast amount of literature pertaining to the cardiotoxicity of cocaine, what is currently known about methamphetamine is largely derived from experimental animal research and fatality studies. Although a search of the literature revealed a number of clinical case reports, there is a dearth of research designed to estimate the prevalence of methamphetamine-related cardiac pathology among the broader population of methamphetamine users.

This review aims to synthesise the literature pertaining to the cardiovascular effects of methamphetamine and its less potent analogue amphetamine. Evidence relating to the cardiovascular properties of amphetamine is included, because it has the same pharmacological mechanism of action as methamphetamine, and also because it is often sold and used interchangeably with methamphetamine on the illicit drug market. A discussion of the mechanisms involved in the action of methamphetamine on the cardiovascular system precedes an introduction to the types of cardiac problems that have been associated with its use. Subsequent sections will review the evidence for methamphetamine-related cardiac pathology and discuss the implications for methamphetamine users.

2 METHAMPHETAMINE CARDIOTOXICITY

Methamphetamine is a stimulant which acts by stimulating the release of catecholaminergic neurotransmitters in both the central and peripheral nervous systems. It is the action of methamphetamine on catecholamines in the peripheral nervous system (i.e. norepinephrine, also known as noradrenaline, and dopamine), which modulates heart rate and blood pressure, that is thought to be the primary mechanism underlying its cardiotoxic effects (Lam & Goldschlager, 1988; Julien, 2001; Karch, 2002; Frishman et al., 2003; Yu et al., 2003; Wijetunga et al., 2004).

High catecholamine levels are known to be cardiotoxic, causing vasoconstriction (narrowing of blood vessels), vasospasm (sudden contraction of a blood vessel), rapid heart rate (tachycardia), and high blood pressure (hypertension) (Karch, 2002; Yu et al., 2003). Whilst tachycardia and high blood pressure are associated with increased demand for oxygen to the heart muscle, vasoconstriction and vasospasm decrease the cardiac oxygen supply. The co-occurrence of these conditions induced by excess catecholamines

affect the balance of cardiac oxygen supply and demand such that the overall effect is a reduction in the availability of oxygen to the heart (Lam & Goldschlager, 1988; Ragland et al., 1993; Farnsworth et al., 1997; Costa et al., 2001; Sztajnkrycer et al., 2002; Shapiro, 2003; Burnett & Adler, 2004; Stahmer & Baumann, 2005). In the absence of a sufficient supply of oxygen to the heart (a condition known as myocardial ischaemia), the heart muscle cells will eventually die. Excessive levels of catecholamines can thus cause necrosis (death) of the heart muscle. Other features of catecholamine toxicity include the formation of fibrous tissue (fibrosis) and an increase in the size of heart muscle cells (hypertrophy) which generally manifests as an enlargement of the heart (Karch, 2002; Yu et al., 2003). These toxic effects of catecholamine excess have been demonstrated experimentally, with vasoconstriction and lesions indicating cardiac damage and necrosis being evident following the infusion of catecholamines in animals (Rona, 1985; Simons & Downing, 1985; Todd et al., 1985).

Much of the animal model research suggests that catecholamine toxicity is a likely mediator for methamphetamine-induced cardiotoxicity. The cardiac pathology induced by methamphetamine is similar to that found in animals administered catecholamines. Several experimental studies have demonstrated that methamphetamine induces deleterious changes in the cardiac muscle, such as cell degeneration, hypertrophy, necrosis, and fibrosis (Zalis et al., 1967; Kaiho & Ishiyama, 1989; Islam et al., 1995; He et al., 1996; Matoba, 2001; Varner et al., 2002; Yu et al., 2002). These changes have been found following various patterns of methamphetamine exposure, such as acute administration (Zalis et al., 1967; Kaiho & Ishiyama, 1989), chronic administration (Islam et al., 1995; He et al., 1996; Matoba, 2001; Yu et al., 2002) and binge administration (i.e. frequent doses followed by a period of abstinence) (Varner et al., 2002). Indicators of catecholamine toxicity, such as necrosis, fibrosis, hypertrophy and enlargement of the heart, have also been observed in methamphetamine users at autopsy (Smith et al., 1976; Rajs & Falconer, 1979; Matoba et al., 1986; Mori et al., 1992; Karch et al., 1999; Shaw, 1999; Matoba, 2001; Karch, 2002; Nishida et al., 2003).

Methamphetamine has also been shown to have cardiotoxic effects that are independent of the catecholamine-mediated effects described above, which are referred to as "direct" cardiotoxic effects. Investigations of the effects of methamphetamine on heart muscle cells (cardiomyocytes) in the absence of catecholamines have been conducted using

cultures of cells obtained from rat hearts (Welder, 1992; He, 1995; Maeno et al., 2000a; Maeno et al., 2000b; Matoba 2001). These studies found that short-term (24 hrs) (Welder, 1992; He, 1995; Matoba, 2001) and longer term (7 days) (Maeno et al., 2000a; Maeno et al., 2000b) exposure to methamphetamine-induced cellular damage and hypertrophy. The mechanisms underlying the direct or non-catecholamine mediated effects of methamphetamine have yet to be elucidated (Varner et al., 2002).

In summary, methamphetamine can result in excessive catecholamine levels, which can in turn lead to cardiac pathology. This pathology includes both acute vasospasm, which alone can induce a heart attack in some cases, and structural changes in the heart tissue and vascular system following chronic use, which can further exacerbate the consequences of vasospasm, and therefore increase the risk of heart attack, during methamphetamine intoxication. Methamphetamine is also thought to have cardiotoxic properties that are not catecholamine mediated, but these are not well understood (Table 1).

Table 1. Biological mechanisms of methamphetamine-related cardiotoxicity

Mediating factor	Immediate effects	Long-term effects on Myocardium
Catecholamine	Increased heart rate	Necrosis
	Increased blood pressure	Fibrosis
	Vasospasm	Hypertrophy of cells
Non-catecholamine (mediating pathway not known)	Cardiomyocytes	Hypertrophy and other cell damage in the heart

The remainder of this review will examine the evidence for these cardiotoxic effects manifesting in people who use methamphetamine. The following section provides background information on the types of cardiac pathology and cardiotoxic processes that need to be considered when examining methamphetamine's cardiotoxic properties in humans.

3 HUMAN CARDIOVASCULAR PATHOLOGY

The following sections overview the types of cardiac pathology that need to be considered when examining methamphetamine-related cardiotoxicity. This section is provided by way of background to assist the reader to understand the nature of cardiac pathology observed in methamphetamine users.

3.1 Coronary artery disease

Coronary artery disease is a condition most commonly resulting from the narrowing (stenosis) or blockage (occlusion) of the coronary arteries. Coronary artery disease is primarily caused by the accumulation of cholesterol, fats, calcium, cellular debris and other substances in the inner lining of the coronary artery walls. This process is known as atherosclerosis. These deposits, referred to as "atherosclerotic plaques", gradually thicken and calcify, reducing the diameter of the artery lumen and thus restricting blood flow and oxygen supply. Sometimes these plaques can rupture the arterial wall causing the formation of a blood clot (coronary thrombosis) which can totally occlude the artery. The presence of coronary artery disease increases the risk of acute cardiovascular events, such as myocardial ischaemia and infarction, as described in the following sections (Naoumova & Scott, 2003; Garas & Zafari, 2004; Stahmer & Baumann, 2005; Zevitz & Singh, 2005).

3.2 Acute myocardial ischaemia

Myocardial ischaemia refers to an inadequate blood supply, and hence oxygen supply, to the heart muscle, or myocardium. This can be a result of increased myocardial oxygen demand, reduced myocardial oxygen supply, or both. The term "acute myocardial ischaemia" refers to a sudden onset of oxygen deprivation. A reduction in coronary blood flow may be secondary to coronary vasospasm, or as a consequence of coronary artery narrowing. The severity and consequences of the ischaemia depends on the degree and duration of oxygen restriction. Myocardial ischaemia is responsible for most episodes of unstable angina and, if prolonged, can lead to myocardial infarction (heart attack) (Fenton & Baumann, 1995; Zevitz & Singh, 2005).

3.3 Unstable angina

Angina is a symptom of myocardial ischaemia and refers to chest pain resulting from the heart being deprived of oxygen. The primary cause of angina is narrowing of the coronary arteries due to atherosclerosis, with spasm of the coronary arteries a less common cause. Angina pain can radiate to the arms, jaw, neck or back. Stable angina is usually triggered by exertion (e.g. during exercise), strong emotions or extreme temperatures, or situations in which the heart requires more oxygen, and typically ceases after a period of rest or treatment with nitrate medications (e.g. nitroglycerine) that relax and widen the blood vessels. Unstable angina is unpredictable in that it can occur even in the absence of the usual triggers, and the pain is typically more prolonged and severe than with stable angina. The risk of heart attack is greater with unstable angina as it usually occurs when the coronary arteries are severely narrowed or totally occluded. Thus, unstable angina can be a sign of an impending heart attack (Gibbons et al., 2002).

3.4 Acute myocardial infarction

Acute myocardial infarction, commonly known as "heart attack", occurs when a sudden lack of blood supply to the heart (i.e. myocardial ischaemia) results in necrosis of a section of the myocardium. The predominant cause of acute myocardial infarction is atherosclerosis (Grześk et al., 2004). Atherosclerotic plaques in the coronary arterial wall may rupture, promoting the formation of blood clots, with subsequent occlusion of the coronary artery. Other causes of acute myocardial infarction include primary coronary vasospasm, blood clots in another part of the body migrating to the coronary arteries, ventricular hypertrophy (thickening of the ventricle wall), and occlusion secondary to vasculitis (inflammation of the blood vessel walls) (Garas & Zafari, 2004; Stahmer & Baumann, 2005).

3.5 Cardiomyopathy

Cardiomyopathy is a disease of the myocardium, the muscular wall of the heart. The myocardium contracts to pump blood out of the heart and relaxes to receive blood back into the heart. Cardiomyopathy typically affects the lower chambers of the heart (ventricles), impairing functioning to the point where the heart is unable to effectively pump blood.

There are four types of cardiomyopathy:

- **Dilated** – the most common form of cardiomyopathy characterised by an enlargement and weakening of the myocardium.

- **Hypertrophic** – genetically inherited in the majority of cases and characterised by excessive thickening of the myocardium.

- **Arrhythmogenic right ventricular –** an unusual form of cardiomyopathy associated with abnormal heart rhythms.

- **Restrictive –** the least common form of cardiomyopathy, where the ventricle walls become rigid and are not able to expand as the ventricles fill with blood.

Cardiomyopathy can have various causes: for example, excessive alcohol and other drug use, viral infection, and genetic predisposition, but is not due to hypertension or atherosclerosis. The symptoms of cardiomyopathy include shortness of breath, fatigue and swelling of the limbs (oedema). Depending on the severity of the disease, there is a significant risk of ultimate complete heart failure and death (Saw et al., 2000; Murphy-Lavoie & Preston, 2004; Venugopalan, 2004).

3.6   Acute aortic dissection

Aortic dissections refer to the splitting or "dissecting" of the wall of the aorta, the major artery carrying blood from the heart to the rest of the body. Acute aortic dissections occur as a result of tears in the inner layer of the aortic wall which cause blood to flow into and along the aortic wall. This, in turn, causes the layers within the wall of the aorta to separate and, frequently, rupture. Hypertension is the most common cause of aortic dissection, although certain hereditary connective tissue disorders and congenital defects of the heart and blood vessels can also lead to aortic dissection. Acute aortic dissections are associated with high rates of mortality (Stalwell & Davis, 1999; Weisenfarth, 2004; Osinuga & Reddy, 2005).

Aortic dissections are distinct from aortic aneurysms, which refer to a widening or ballooning of a section of the aorta, which can also subsequently rupture. Aortic aneurysms involve all three layers of the arterial wall (i.e. inner, middle and outer) and are usually caused by atherosclerosis (Stalwell & Davis, 1999; Osinuga & Reddy, 2005).

3.7   Sudden cardiac death

Sudden cardiac death, also known as sudden arrhythmic death, is death resulting from sudden cardiac arrest, a condition in which the heart suddenly and unexpectedly stops beating. Sudden cardiac death is typically caused by an abnormal heart rhythm (arrhythmia). Arrhythmias occur as a result of irregularities in the conduction of electrical impulses through the heart. Under normal circumstances, these electrical impulses regulate the rhythm of the heart beat. The most common types of arrhythmia implicated in sudden cardiac death are ventricular tachycardia (extremely rapid heartbeat) and ventricular fibrillation (an extremely rapid, chaotic rhythm during which the ventricles quiver or "fibrillate", rather than contract). Pre-existing coronary artery disease underlies the majority of cases of sudden cardiac death among adults, and scarring from a previous heart attack is commonly found. Recent research has shown that, among young people (under 35 yrs), presumed primary arrhythmia is the most common cause of sudden cardiac death (Puranik et al., in press). Hypertrophic cardiomyopathy has also been implicated in sudden cardiac death among the young (Maron, 2002; Doolan et al., 2004; Malineni & McCullough, 2004; Puranik et al., in press). The abuse of certain drugs can induce the arrhythmias that cause sudden cardiac death.

Sudden cardiac arrest is often confused with acute myocardial infarction; however, the two conditions differ in the following respects:

1) whereas sudden cardiac arrest is caused by arrhythmias, acute myocardial infarction is due to a disruption in blood supply to the heart causing the heart muscle to die;

2) acute myocardial infarction is often preceded by pain, nausea or sweating. Sudden cardiac arrest is rarely preceded by warning symptoms; and

3) victims of acute myocardial infarction often remain conscious, whereas sudden cardiac victims typically lose consciousness.

4 CARDIOVASCULAR COMPLICATIONS ASSOCIATED WITH METHAMPHETAMINE USE

Methamphetamine has been associated with a variety of both acute and chronic effects on the cardiovascular system. The following sections provide a summary of these effects and a review of the literature regarding the role of methamphetamine in such pathology.

4.1 Acute cardiovascular effects of methamphetamine

The acute cardiovascular effects of methamphetamine have been well-documented. Chest pain, tachycardia and other cardiac arrhythmias, dyspnoea (shortness of breath) and hypertension following the use of methamphetamine are widely reported (Derlet et al., 1989; Chan et al., 1994; Derlet & Horowitz, 1995; Hardman et al., 1996; Logan et al., 1998; Albertson et al., 1999; Guharoy et al., 1999; Waksman et al., 2001; Sztajnkrycer et al., 2002; Frishman et al., 2003; Turnipseed et al., 2003; Wijetunga et al., 2003). Other, less common, cardiovascular complications include acute myocardial ischaemia, acute myocardial infarction, coronary vasospasm, acute aortic dissection and sudden cardiac death (Kalant & Kalant, 1975; Hong et al., 1991; Katsumata et al., 1993; Davis & Swalwell, 1994; Derlet & Horowitz, 1995; Albertson et al., 1999; Shaw, 1999; Swalwell & Davis, 1999; Maeno et al., 2000; Frishman et al., 2003; Nishida et al., 2003).

The evidence for the existence of an acute methamphetamine-induced cardiovascular syndrome is compelling. Tachycardia and hypertension, the most commonly observed signs of cardiovascular toxicity related to methamphetamine use (Chan et al., 1994; Derlet & Horowitz, 1995; Lan et al., 1998; Waksman et al., 2001; Sztajnkrycer et al., 2002; Hung et al., 2003; Wijetunga et al., 2003), have been reliably demonstrated in animal models (Fukunaga et al., 1987; Russo et al., 1991; Schindler et al., 1992; Yoshida et al., 1993; Liu & Varner, 1996; Arora et al., 2001; Varner et al., 2002). While methamphetamine-related increases in blood pressure appear to be dose-related, the effects on heart rate are more complex (Schindler et al., 1992; Arora et al., 2001). In studies of the cardiovascular effects of methamphetamine in animals, heart rate has been shown to increase following low doses (Schindler et al., 1992; Arora et al., 2001). At higher doses, however, an initial decrease in heart rate (bradycardia) preceding the onset of tachycardia, has been observed (Schindler et al., 1992; Varner et al., 2002). This

decrease in heart rate may be a reflex mechanism in response to an increase in blood pressure (Schindler et al., 1992).

An experimentally induced increase in heart rate and blood pressure following methamphetamine administration has also been demonstrated in humans (Perez-Reyes et al., 1991). Moreover, emergency department data has consistently shown chest pain, tachycardia, palpitations, and hypertension to be among the most common presenting physical symptoms upon admission for acute meth/amphetamine intoxication (Derlet et al., 1989; Lan et al., 1998; Guharoy et al., 1999; Richards et al., 1999; Turnipseed et al., 2003). Derlet et al. (1989) found that, among 127 cases of amphetamine toxicity presenting to a U.S. emergency department over a six month period, one-third (34%) of cases were hypertensive, with chest pains and palpitations the major presenting symptoms in 9% and 3% of cases, respectively. In a retrospective study of the clinical features of methamphetamine toxicity, Lan et al. (1998) found that, among emergency department patients presenting over a six year period, 89% were tachycardic and over half (56%) had hypertension.

The following sections (4.1.1-4.1.4) describe the less common, but more severe, acute cardiovascular consequences of methamphetamine use, including acute coronary syndrome, myocardial infarction, aortic dissection and sudden cardiac death.

4.1.1   Acute coronary syndrome

Acute coronary syndrome is a term that encompasses the clinical manifestations of acute myocardial ischaemia (i.e. unstable angina and myocardial infarction). Turnipseed et al. (2003) reviewed the frequency of acute coronary syndrome among U.S. emergency department patients presenting with chest pain following methamphetamine use over a two-year period. Acute coronary syndrome was diagnosed in 25% of patients, with 8% of patients suffering other potentially fatal cardiac complications, such as abnormal ventricular rhythms and contractions. These patients were relatively young, with an average age of 41 yrs, and a low rate of previously diagnosed coronary artery disease. More recently, Wijetunga et al. (2004) described eight cases of acute coronary syndrome among crystal methamphetamine (ice) smokers in Hawaii.

Although chest pain is one of the primary cardiovascular symptoms of acute methamphetamine intoxication reported by emergency department patients (Derlet et al., 1989; Albertson et al., 1999; Richards et al., 1999; Turnipseed et al., 2003; Wijetunga et al., 2003), it often occurs in the absence of any associated electrocardiogram (ECG) abnormalities (Derlet et al., 1989; Derlet & Heischober, 1990; Derlet & Horowitz, 1995; Beebe & Walley, 1995; Turnipseed et al., 2003). Normal ECG findings, however, do not preclude an underlying pathological cardiovascular mechanism, such as myocardial infarction (Derlet et al., 1989; Brady et al., 1999; Alpert et al., 2000). Chest pain may be indicative of an acute coronary syndrome, even in the presence of normal ECG findings (Brady et al., 1999). Previous research has shown that, among a minority of patients (1-4%) presenting to emergency departments with chest pain, unstable angina or myocardial infarction will ultimately be diagnosed, despite normal ECG findings upon initial evaluation (Brady et al., 1999; Alpert et al., 2000).

4.1.2   Acute myocardial infarction

Case reports of acute myocardial infarction following meth/amphetamine use

Acute myocardial infarction as a consequence of methamphetamine use is a relatively uncommon event (Albertson et al., 1999; Furst et al., 1990, Karch et al., 1999; Frishman et al., 2003), the incidence being far lower than that related to cocaine use (Karch, 1996; Karch, 2002; Wijetunga et al., 2004). Previous literature documenting methamphetamine-related myocardial infarction has been overwhelmingly based on individual case reports. To date, there have been 18 published case reports of acute myocardial infarction associated with meth/amphetamine use (Table 2).

As Table 2 illustrates, myocardial infarction was associated with various administration routes (i.e. oral, intravenous, intranasal and smoking) and, in two-thirds of the cases tested, was associated with normal coronary angiographic findings. In cases where coronary pathology was found, thrombosis or stenosis was evident (Furst et al., 1990; Bashour, 1994; Farnsworth et al., 1997; Hung et al. 2003). The only other cardiac risk factors noted were tobacco smoking (Carson et al., 1987; Packe et al., 1990; Ragland et al., 1993; Huang et al., 1993; Appleby et al., 1994; Bashour, 1994; Costa et al., 2001; Ochoa Gómez et al., 2001; Waksman et al., 2001; Hung et al. 2003) and a family history of cardiac disease (Carson et al., 1987; Packe et al., 1990; Bashour, 1994). While most

patients recovered, two cases had a fatal outcome (Hong et al., 1991; Ragland et al., 1993).

The major presenting symptoms of myocardial infarction among methamphetamine users were chest pain (Furst et al., 1990; Ragland et al., 1993; Appleby et al., 1994; Bashour, 1994; Farnsworth et al., 1997; Guharoy et al., 1999; Costa et al., 2001; Ochoa Gómez et al., 2001), epigastric pain (Orzel, 1982; Le Gac et al., 1996), and shortness of breath (Hong et al., 1991; Sztajnkrycer et al., 2002). Where toxicological findings were reported, the presence of methamphetamine and/or amphetamine was confirmed (Furst et al., 1990; Hong et al., 1991; Huang et al., 1993; Ragland et al., 1993; Farnsworth et al., 1997; Guharoy et al., 1999; Costa et al., 2001; Ochoa Gómez et al., 2001; Waksman et al., 2001; Sztajnkrycer et al., 2002).

Details of the patient's history of meth/amphetamine use were not reported or known in all of the cases noted in Table 2; however, regular, long-term illicit use was disclosed in several cases (Hong et al., 1991; Huang et al., 1993; Appleby et al., 1994; Bashour, 1994; Guharoy et al., 1999; Waksman et al., 2001; Hung et al., 2003). Long- and short-term medicinal use of dextroamphetamine and amphetamine, respectively, were also associated with myocardial infarction (Orzel, 1982; Costa et al., 2001), as was first time illicit use of methamphetamine (Farnsworth et al., 1997), although in the latter case there was evidence of pre-existing coronary artery disease.

Other research evidence for meth/amphetamine-related myocardial infarction

Recent reports of methamphetamine-related acute myocardial infarction have also come from studies of acute coronary syndrome among emergency patients who had taken the drug (Turnipseed et al., 2003; Wijetunga et al., 2004). Turnipseed et al. (2003) found that 8 of 30, or 24%, of emergency department patients presenting with chest pain following methamphetamine use were subsequently diagnosed with myocardial infarction. All patients tested positive for methamphetamine and negative for cocaine. While seven out of the eight patients with acute coronary syndrome described by Wijetunga et al. (2004) were diagnosed with myocardial infarction, only three of these patients had the presence of methamphetamine confirmed by urine toxicology. In both of these studies, coronary artery disease, as diagnosed by coronary angiography, was present in a high proportion of the patients tested. Wijetunga et al. (2004) found that five out of the six patients tested had evidence of obstructive coronary artery disease. Turnipseed et al. (2003) found that

all three patients given angiograms were found to have coronary artery disease, with a further two patients having a prior diagnosis of coronary artery disease.

Table 2. **Summary of previously reported cases of myocardial infarction associated with meth/amphetamine use**

Author	Age/Sex	Drug	Route of administration	Coronary angiogram Results
Orzel (1982)	58/M	Dextroamphetamine sulphate[a]	Oral	-
Carson et al. (1987)	33/M	Amphetamine	Intravenous	Normal
Packe et al. (1990)	27/M	Amphetamine	Intravenous	Normal
Furst et al. (1990)	41/M	Crystal methamphetamine	Intranasal	Coronary thrombosis
Veenstra et al. (1990)	40/M	Amphetamine	Oral	Normal
Hong et al. (1991)	31/F	Crystal methamphetamine	Smoking	Normal[b]
Ragland et al. (1993)	37/F	Amphetamine	Intravenous	Normal
Huang et al. (1993)	42/M	Amphetamine	Intranasal	-
Appleby et al. (1994)	31/M	Amphetamine [c]	Oral	-
Bashour (1994)	29/F	Amphetamine	Oral	Coronary thrombosis
Le Gac et al. (1996)	32/M	Amphetamine	Intravenous	Normal
Farnsworth et al. (1997)	35/M	Methamphetamine	Intranasal	Coronary stenosis
Guharoy et al. (1999)	26/M	Crystal methamphetamine	Smoking	-
Waksman et al. (2001)	31/M	Amphetamine & methamphetamine	Intravenous	-
Costa et al. (2001)	34/M	Amphetamine[d]	Oral	Normal
Ochoa Gómez et al. (2001)	21/M	Amphetamine	Intranasal	Normal
Sztajnkrycer et al. (2002)	13/F	Amphetamine[e]	Oral	-
Hung et al. (2003)	27/M	Amphetamine	Intravenous	Coronary stenosis

[a] Long-term dextroamphetamine treatment for narcolepsy

[b] Post-mortem examination

[c] Amphetamines in combination with anabolic steroids, frumil & potassium supplements

[d] Short-term (1 week) amphetamine treatment for weight loss

[e] Recreational overdose of Adderall – a combination pharmaceutical preparation containing dextroamphetamine

Myocardial infarction associated with methamphetamine use has also been noted in autopsy findings. In a U.S. study of the toxicological and pathological profiles of methamphetamine-related deaths, Karch et al. (1999) reviewed the autopsy findings of 413 decedents who tested positive for methamphetamine and found seven cases of myocardial infarction. In a similar study conducted in Japan, Zhu et al. (2000) found 1 out of 15 fatalities involving methamphetamine to be due to myocardial infarction. While Karch et al. (1999) found evidence of pre-existing coronary artery disease among a significant proportion of methamphetamine using decedents (19%), the prevalence of coronary artery pathology among the myocardial infarction cases in particular was not reported.

Mechanisms underlying methamphetamine-related myocardial infarction

The precise mechanism underlying acute myocardial ischaemia/infarction following the use of methamphetamine is unclear; however, possible causes include coronary artery vasospasm (Hong et al., 1991; Karch, 1996; Le Gac et al., 1996; Costa et al., 2001; Frishman et al., 2003; Hung et al., 2003; Stahmer & Baumann, 2005), the rupture of atherosclerotic plaques (Furst et al., 1990; Ragland et al., 1993; Farnsworth et al., 1997; Costa et al., 2001), and the aggregation of blood platelets (Lam & Goldschlager, 1988; Furst et al., 1990; Ragland et al., 1993; Costa et al., 2001; Waksman et al., 2001; Frishman et al., 2003), all of which are induced by a catecholamine excess and can result in coronary thrombus formation (Bashour, 1994; Costa et al., 2001). Increased catecholamine levels can also lead to increased myocardial oxygen demand (Ragland et al., 1993; Farnsworth et al., 1997; Costa et al., 2001; Stahmer & Baumann, 2005) which, combined with a reduced oxygen supply caused by coronary artery stenosis and/or vasospasm, results in a net deficit of myocardial oxygen, and therefore increased risk of myocardial infarction (Farnsworth et al., 1997; Sztajnkrycer et al., 2002).

As previously discussed, coronary angiogram findings were normal in the majority of myocardial infarction cases in Table 2, suggesting that, in those cases, coronary vasospasm rather than thrombosis was the primary mechanism underlying the infarction (Hong et al., 1991; Ragland et al., 1993; Karch, 1996; Le Gac et al., 1996; Ochoa Gómez et al., 2001; Karch, 2002; Hung et al., 2003; Wijetunga et al., 2004). As coronary vasospasm is often a transient event, it may be difficult to diagnose retrospectively. It is usually confirmed by being medically induced and observed on a simultaneously conducted angiogram. This procedure, known as a "provocation test", is an established

diagnostic procedure used in cases where coronary vasospasm is suspected (Han et al., 2005). Using such a test, Hung et al. (2003) demonstrated that coronary artery vasospasm may precipitate myocardial infarction in amphetamine users. Normal angiographic findings, however, may also occur following thrombosis, particularly if the angiogram is delayed (e.g. Ragland et al., 1993; Le Gac et al., 1996; Costa et al., 2001), because the thrombolytic therapy that is often administered to the patient in the interim can dissolve blood clots and restore normal blood flow to the heart (Bashour, 1994; Hung et al., 2003).

Given the heterogeneity of cardiac risk factors and coronary pathology findings among the above cases, it appears unlikely that a single mechanism can account for methamphetamine-induced myocardial infarction. An interaction of the above mechanisms is more probable (Bashour, 1994; Sztajnkrycer et al., 2002; Turnipseed et al., 2003). Moreover, the role of underlying cardiac pathology, in association with the chronic use of methamphetamine or with other risk factors, cannot be discounted, as will be discussed in a later section of this review.

4.1.3   Acute aortic dissection

Acute aortic dissection is a known complication of the use of methamphetamine (Karch, 2002). Autopsy case reviews have found several cases of aortic dissection associated with acute methamphetamine intoxication (Davis & Swalwell, 1994; Karch et al., 1999; Swalwell & Davis, 1999). In a review of cases in which aortic dissection was the cause of death, Swalwell & Davis (1999) found methamphetamine use to be the most common risk factor for acute aortic dissection after hypertension.

It is the hypertensive effects of methamphetamine that are thought to underlie its role in inducing aortic dissection. Hypertension and weakening of the aortic wall lead to the tears in the inner layer that initiate aortic dissection. Once such a tear has formed, hypertension acts to propagate the dissection and precipitate its rupture (Davis & Swalwell, 1994; Swalwell & Davis, 1999). While methamphetamine-induced hypertension can cause weakening of the aortic wall, methamphetamine may also have a direct degenerative effect on the aorta (Swalwell & Davis, 1999).

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Methamphetamine-induced hypertension is a plausible mechanism for aortic dissection, based on the high incidence of hypertension among aortic dissection cases in general (Swalwell & Davis, 1999). Given, however, that there are no experimental studies of the aetiology of aortic dissection among methamphetamine users, the precise role of methamphetamine in such an event remains undetermined (Karch, 2002).

4.1.4   Sudden cardiac death

The association between methamphetamine use and sudden cardiac death is well-recognised (Kalant & Kalant, 1975; Matoba et al., 1984; Matoba et al., 1986; Derlet & Horowitz, 1995; Albertson et al., 1999; Karch, 2002), particularly in Japan where methamphetamine abuse has been a long-standing problem (Karch, 2002). The cardiac arrhythmias that typically cause sudden cardiac death have been widely documented as indicators of methamphetamine toxicity (McGuigan, 1984; Derlet & Heischober, 1990; Beebe & Walley, 1995; Derlet & Horowitz, 1995; Albertson et al., 1999; Frishman et al., 2003).

Although cardiac arrhythmias and arrhythmic sudden death are often associated with high doses of methamphetamine (Derlet & Horowitz, 1995; Frishman et al., 2003), lower doses of methamphetamine may also cause sudden death due to the development of a hypersensitivity to the effects of methamphetamine (Fukunaga et al., 1987). The sensitisation to methamphetamine is further discussed in Section 5.1.

Pre-existing cardiac pathology, such as myocardial hypertrophy and fibrosis, has been found at autopsy among methamphetamine users dying of sudden death (Matoba et al., 1984; Matoba et al., 1986; Matoba, 2001). These changes of the heart may predispose the user to arrhythmic sudden death such that when they are already present, increased levels of catecholamines can trigger cardiac arrhythmias (Karch, 2002).

4.1.5   Summary of acute cardiotoxic effects of methamphetamine

In summary, there is evidence of acute cardiotoxicity following methamphetamine ingestion in humans. Acute coronary syndrome (i.e. unstable angina and consequent myocardial infarction) has been documented in a number of case reports following methamphetamine and/or amphetamine ingestion. These situations are most likely to

result from a combination of underlying cardiac pathology (methamphetamine-induced or otherwise occurring) and the acute effects of methamphetamine intoxication (i.e. increased heart rate, increased blood pressure and vasoconstriction). Methamphetamine is a risk factor for aortic dissection, which is likely to be related to the hypertensive properties of methamphetamine. Sudden cardiac death is also a well-recognised consequence of methamphetamine intoxication, and results from cardiac arrhythmia. The risk of cardiac arrhythmia occurring during methamphetamine intoxication is augmented by pathology of the myocardium, which may occur with chronic methamphetamine use, as discussed in the following section.

4.2 Chronic cardiovascular effects of methamphetamine

The following sections review the evidence for chronic cardiac pathology associated with methamphetamine use. The forms of chronic cardiovascular disease that are most commonly associated with methamphetamine use are coronary artery disease and cardiomyopathy (Lam & Goldschlager, 1988; Derlet & Horowitz, 1995; Albertson et al., 1999; Karch, 2002; Frishman et al., 2003; Yu et al., 2003; Wijetunga et al., 2003; Wijetunga et al., 2004).

4.2.1 Coronary artery disease

Methamphetamine-related fatality research suggests that methamphetamine users are at risk of the premature and accelerated development of coronary artery disease (Logan et al., 1998; Karch et al., 1999; Karch, 2002; Wijetunga et al., 2004). The most compelling evidence for an association between methamphetamine and coronary artery disease is provided by the findings of Karch et al. (1999). In a study of methamphetamine-related deaths, Karch et al. (1999) found moderate coronary artery disease in 10% of 413 methamphetamine using decedents, and severe coronary artery disease in 6% of cases. Overall, coronary artery disease ranging from minimal to severe was found in 19% of methamphetamine users compared to 5% in age-matched drug-free controls. Coronary artery disease was found not only to be more prevalent among methamphetamine users than among controls, but to occur at a significantly younger age than among the general population (Karch et al., 1999; Karch, 2002). Although methamphetamine users with coronary artery disease were older than controls, they were not significantly different in terms of other risk factors for coronary artery disease; for example, body mass index,

gender and race. Methamphetamine users with coronary artery disease did, however, have significantly greater heart weights, an abnormal finding irrespective of age, suggesting that the higher prevalence of coronary artery pathology was not merely a function of increased age (Karch et al., 1999). Methamphetamine users whose deaths were a direct result of methamphetamine toxicity were older, had greater heart weights and a higher prevalence of coronary artery disease than decedents in whom the presence of methamphetamine was deemed to be an incidental finding. These findings led Karch et al. (1999) to suggest that there may be a long "incubation" period prior to methamphetamine-related death, as these types of cardiac pathology take time to develop.

In the aforementioned studies of acute coronary syndrome, coronary artery disease, as diagnosed by coronary angiography, was present in a high proportion of the patients tested. Wijetunga et al. (2004) found that five out of the six patients tested had evidence of obstructive coronary artery disease. Turnipseed et al. (2003) found that all three patients given angiograms were found to have coronary artery disease, with a further two patients having a prior diagnosis of coronary artery disease.

Other studies of drug-related mortality have demonstrated an association between amphetamines and cardiovascular disease present at the time of death. Logan et al. (1998), for example, found underlying atherosclerosis to be present in a number of methamphetamine-related deaths. In a recent coronial study, Webb et al. (2003) also noted that amphetamines had been implicated in deaths due to underlying cardiovascular disease, although the specific type of cardiovascular pathology was not reported.

4.2.2   Cardiomyopathy

While there is a substantial amount of clinical and experimental evidence to suggest that the use of methamphetamine, particularly long-term use, can potentially induce cardiomyopathy, the association is less well documented than that between cocaine use and cardiomyopathy (Karch, 2002). As is the case with myocardial infarction, much of the evidence for methamphetamine-induced cardiomyopathy in humans is in the form of single case reports, summarised in Table 3.

The only case series of methamphetamine-related cardiomyopathy in the literature was reported by Wijetunga et al. (2003), who identified and described the characteristics of 21 crystal methamphetamine users with a diagnosis of cardiomyopathy. The majority of these patients were male (90%) and under 45 years of age (67%) and, wherever documented, the route of administration was smoking (n=19). As Table 3 illustrates, however, cardiomyopathy has been associated with various routes of methamphetamine administration (i.e. oral, intravenous and smoking).

There was no history of cardiac disease in any of the cases presented in Table 3, and the coronary arteries were normal in all patients tested (Smith et al., 1976; Call et al., 1982; O'Neill et al., 1983; Jacobs, 1989; Hong et al., 1991). This is consistent with the findings of Wijetunga et al. (2003), who found that coronary artery disease was predominantly absent (83% of patients tested, n=5). Indeed, a diagnosis of cardiomyopathy should not be given when coronary artery disease is present (Karch, 2002).

Table 3. Summary of previously reported cases of cardiomyopathy associated with meth/amphetamine use

Author	Age/Sex	Drug	Route of administration	Onset
Smith et al. (1976)	45/F	Dextroamphetamine	Oral	Chronic
Call et al. (1982)	22/F	Amphetamine	Intravenous	Acute
O'Neill et al. (1983)	24/M	Amphetamine	Intravenous	Acute
Ayres (1983)	38/M	Dextroamphetamine	Oral	Chronic
Jacobs (1989)	48/F	Methamphetamine	Oral	Chronic
Hong et al. (1991)	34/F	Crystal methamphetamine	Smoking	Chronic
Crean & Pohl (2004)	30/F	Amphetamine	Oral	Chronic

The long-term prognosis associated with methamphetamine-related cardiomyopathy is unclear. In the case reported by Smith et al. (1976), the patient died 10 weeks after being discharged from hospital and, in the case described by Ayres (1983), the patient died over one year later. There are, however, cases in which a recovery of cardiovascular functioning following medical treatment and the discontinuation of methamphetamine was observed (Call et al., 1982; Jacobs, 1989; Crean & Pohl, 2004). In the other cases

presented in Table 3, as well as those described by Wijetunga et al. (2003), the patient's progress was either not followed up beyond one year, or not followed up at all.

Dilated cardiomyopathy is the form of cardiomyopathy most commonly associated with methamphetamine use (Jacobs, 1989; Hong et al., 1991; Wijetunga et al., 2003; Yu et al., 2003; Crean & Pohl, 2004). Methamphetamine users subsequently diagnosed with dilated cardiomyopathy typically present with shortness of breath and fatigue and, upon examination, the heart is generally found to be enlarged, dilated and demonstrating decreased contractile function (Smith et al., 1976; Jacobs, 1989; Frishman et al., 2003). Cardiomyopathy is typically a chronic disease of gradual onset and has usually been associated with chronic meth/amphetamine use (Smith et al., 1976; Ayres, 1983; Jacobs, 1989; Hong et al., 1991; Wijetunga et al., 2003; Crean & Pohl, 2004); however, acute onset cardiomyopathy following the administration of amphetamine has also been described (Call et al., 1982; O'Neill et al., 1983).

Forensic research has provided further evidence for an association between methamphetamine and cardiomyopathy, demonstrating the presence of cardiomyopathy in cases of methamphetamine-related death (Zhu et al., 2000). In cases of dilated cardiomyopathy, autopsy examination typically reveals enlargement of the heart with dilation of the cardiac chambers, particularly the left ventricle, and areas of fibrosis. Consistent with an appropriate diagnosis of cardiomyopathy, these findings typically occur in the absence of significant coronary artery disease (Smith et al., 1976; Frishman et al., 2003). Isolated cases of hypertrophic cardiomyopathy among deceased methamphetamine users have also been reported (Tanaka et al., 1989; Logan et al., 1998); however, there is little evidence to suggest that the use of methamphetamine causes hypertrophic cardiomyopathy, although it may exacerbate the condition when already present.

Experimental studies have also suggested a link between methamphetamine use and cardiomyopathy, finding that chronic administration of methamphetamine to rats induces cardiac lesions similar to those seen in methamphetamine-related cardiomyopathy in humans (Islam et al., 1995; He et al., 1996; Varner et al., 2002).

The mechanisms underlying methamphetamine-induced cardiomyopathy are still unclear (Crean & Pohl, 2004); however, possible explanations include catecholamine-mediated effects, such as myocardial necrosis or recurrent coronary artery vasospasm (O'Neill et al., 1983; Jacobs, 1989; Bashour, 1994; Albertson et al., 1999; Frishman et al., 2003; Wijetunga et al., 2003). While animal research suggests that methamphetamine has direct (i.e. non-catecholamine mediated) cardiotoxic effects (Welder, 1992; He, 1995; Maeno et al., 2000a; Maeno et al., 2000b; Matoba, 2001), the contribution of such effects to the development of cardiomyopathy in humans has not been ascertained because of the difficulty controlling for catecholamine levels.

4.2.3 Summary of the chronic effects of methamphetamine on cardiac functioning

The two main forms of cardiac pathology associated with methamphetamine use are coronary artery disease and cardiomyopathy. Methamphetamine use is associated with an acceleration of coronary artery disease, and it has been found that the prevalence of coronary artery disease at death is higher among methamphetamine users than among age-matched controls. The observation of cardiomyopathy among methamphetamine users is consistent with experimental animal research demonstrating that methamphetamine, and more generally elevated catecholamine levels, can damage the myocardium. The evidence that cardiomyopathy occurs in humans is based on a number of case reports, a single case series study, and observed pathology of the myocardium among deceased methamphetamine users.

Currently there is no evidence regarding the prevalence or prognosis of cardiomyopathy among methamphetamine users. Nor is there any substantive information on the increased risk of coronary artery disease attributable to methamphetamine use.

5 FACTORS AFFECTING CARDIOTOXICITY RELATED TO METHAMPHETAMINE USE

5.1 The effects of dose

The severity of the cardiovascular effects of methamphetamine is often thought to be dose-related, in that higher doses result in greater toxicity and a more severe physiological reaction. Blood pressure, for example, has been reported to increase in a dose-related manner (Schindler et al., 1992; Frishman et al., 2003). Moreover, symptoms such as tachycardia, palpitations and arrhythmias are often described as signs of severe methamphetamine toxicity, implying that they are induced by high doses of the drug (McGuigan, 1984; Lan et al., 1988; Frishman et al., 2003). The development of tolerance with chronic use of methamphetamine, however, complicates the dose-effect relationship. As is the case with other types of drugs, such as alcohol and opiates, chronic users are able to use higher doses with less adverse effect (Derlet et al., 1989; Julian, 2001).

There is some evidence that tolerance to the tachycardic effects of methamphetamine may develop with repeated administration (Fukunaga et al., 1987; Perez-Reyes et al., 1991; Lan et al., 1998; Albertson et al., 1999; Yu et al., 2003). Perez-Reyes et al. (1991) found that after administering daily oral doses of slow-release methamphetamine to human subjects for 15 days there was a decrease in the magnitude of heart rate acceleration in response to a test dose of methamphetamine, indicating that tolerance to the tachycardic effects had developed. The findings of animal research regarding the development of such tolerance, however, have been mixed. Fukunaga et al. (1987), for example, found that tolerance to the increase in heart rate developed during the administration of methamphetamine to rats twice daily for four days. Varner et al. (2000), however, used the same dosing schedule yet did not observe this effect, although a lower dose of methamphetamine and different administration route was used in this study (3 mg/kg intravenously vs. 10 mg/kg intraperitoneally).

Methamphetamine-induced cardiac arrhythmias, as well as sudden cardiac death resulting from such arrhythmias, have been associated with large doses of methamphetamine (Fukunaga et al., 1987; Frishman et al., 2003). However, even small doses of methamphetamine have been known to cause death (Fukunaga et al., 1987; Karch, 2002).

Autopsy reports have shown that methamphetamine-related death can be associated with low or high levels of methamphetamine in the blood, with toxicological findings of fatality studies typically yielding a broad range of methamphetamine concentrations (Fukunaga et al., 1987; Bailey & Shaw, 1989; Logan et al., 1998; Zhu et al., 2000; Karch, 2002). In circumstances where methamphetamine-related cardiac disease is present and there is a history of chronic methamphetamine abuse, post-mortem toxicology may reveal only low concentrations of methamphetamine in the blood, or even no detectable level of methamphetamine (Karch, 2002).

Sensitisation or "reverse-tolerance" to the cardiovascular effects of methamphetamine has been suggested as a contributory factor in methamphetamine-induced cardiac arrhythmias, and related sudden cardiac death, in cases where low doses of methamphetamine lead to death (Fukunaga et al., 1987). Sensitisation to the tachycardic and hypertensive effects of methamphetamine has been postulated to occur with intermittent administration of methamphetamine. Experimental studies have found greater increases in heart rate and blood pressure when rats received multiple doses of methamphetamine followed by intervals of several days than when there were only short intervals between dosing (Fukunaga et al., 1987; Yoshida et al., 1993; Varner et al., 2000). Such findings suggest that a similar phenomenon may occur in humans after periods of abstinence following long-term or binge use of methamphetamine, which may account for some cases in which low doses of methamphetamine result in death (Fukunaga et al., 1987).

The necessary and sufficient dose to produce serious cardiovascular complications or death - that is, the "toxic" dose - is unclear, as the response to a specific dose varies due to individual differences in responsiveness and variations in degree of tolerance. Thus, estimating the level of methamphetamine toxicity should be based on the clinical presentation, rather than on the reported dose administered (McGuigan, 1984; Lan et al., 1998; Derlet et al., 1989; Chan et al., 1994; Albertson et al., 1999; Julien, 2001).

5.2 Route of administration

The literature indicates that cardiovascular complications associated with methamphetamine use can occur with all of the major routes of administration: that is,

intranasal, oral, smoking, and injecting. While there is no evidence to suggest that any one route of methamphetamine administration should be more strongly associated with cardiotoxicity than another, the risk of complications are likely to be higher with administration routes that deliver a higher dose of the drug and are associated with frequent use (e.g. injecting methamphetamine and smoking of crystalline methamphetamine) (Darke et al., 1994; Hall & Hando, 1994; McKetin et al., 2005). Thus, the risk of an adverse event following the use of methamphetamine may accumulate with increasing episodes of use. To date, there are no studies that have investigated the relative risk of cardiovascular complications associated with different forms of methamphetamine administration.

5.3 Interactions with other drugs

Illicit drug users rarely use only one type of drug. Polydrug use is the norm among the majority of illicit drug using populations and methamphetamine users are no exception (Hall & Hando, 1994; Darke & Hall, 1995; Lan et al., 1998; Matsumoto et al., 2002; Jenner & McKetin, 2004; Roberts, 2004; McKetin et al., 2005). As such, the implications of using methamphetamine with other drugs should be considered.

Previous research suggests that when methamphetamine is combined with alcohol, cocaine or opiates, toxicity is increased (Mendelson et al., 1995; Albertson et al., 1999). Accordingly, methamphetamine-related fatality studies frequently report the detection of these drugs, as well as methamphetamine, in post-mortem blood and urine samples (Bailey & Shaw, 1989; Logan et al., 1998; Karch et al., 1999). In a study designed to investigate the interactive effects of methamphetamine and ethanol in humans, Mendelson et al. (1995) found that the combination of methamphetamine and ethanol increased heart rate beyond that induced by methamphetamine alone. Rate pressure product (heart rate multiplied by systolic blood pressure) - an index of cardiac workload and oxygen consumption - also increased more when methamphetamine was combined with ethanol than when only methamphetamine was administered.

Using methamphetamine with cocaine also places the user at considerable risk of adverse cardiovascular effects. Cocaine is a powerful vasoconstrictor and there appears to be a synergistic vasoconstrictive effect when the two drugs are combined (Lam &

Goldschlager, 1988). Animal research has shown that the cardiotoxic effects on the heart - for example, decreased contractile function and cardiac muscle cell damage - are greater when methamphetamine is combined with cocaine than when either drug is administered alone (Welder, 1992). The possibility that the cardiovascular symptoms and diseases associated with methamphetamine use are, in part, attributable to recent or past cocaine use cannot be excluded, given that cocaine is a cardiotoxic drug that is part of the polydrug use repertoire of many methamphetamine users. Nevertheless, the weight of evidence suggests that methamphetamine alone can induce such pathology.

The majority of regular methamphetamine users also smoke tobacco, which is a known risk factor for heart disease. Therefore we cannot discount the possibility that tobacco is responsible for, or at least contributes to, some of the cardiac pathology found among methamphetamine users.

6 CONCLUSION

6.1 Overview of the evidence for methamphetamine-related cardiotoxicity

It is clear from the literature that methamphetamine has cardiotoxic potential. The various mechanisms through which methamphetamine can lead to cardiac pathology are outlined in Table 4. Methamphetamine produces its toxic effects by increasing catecholamine levels, which can have direct toxic effects on heart tissue, in addition to causing vasospasm, which can reduce blood supply to the heart. These conditions increase the risk of myocardial ischaemia and infarction, particularly in the context of methamphetamine intoxication, which increases heart rate, blood pressure and cardiac oxygen demand.

Little systematic research has been conducted into the cardiotoxic effects of methamphetamine in humans. Most of the evidence for methamphetamine-related cardiac pathology in humans is based on case reports of acute coronary syndrome following methamphetamine intoxication, and autopsy reports where methamphetamine use has been implicated in cardiac-related death. These case reports suggest that it is not uncommon for methamphetamine users to present to emergency departments with

symptoms of acute coronary syndrome, but that fatalities arising from methamphetamine-related cardiac complaints appear to be comparatively rare. When fatalities have occurred among methamphetamine users, three main types of pathology have been implicated:

1) myocardial infarction, attributed to increased catecholamine levels causing vasoconstriction, together with increased oxygen demand to the heart, possibly compounded by thrombosis or other pre-existing cardiac pathology;

2) sudden cardiac death, caused by cardiac arrhythmia; and

3) aortic dissection, which is likely to be caused by methamphetamine-induced hypertension.

In addition to these acute forms of cardiac pathology, methamphetamine use has also been associated with chronic cardiac pathology. Methamphetamine's ability to increase catecholamine levels and induce vasospasm can lead to long-lasting damage to the heart muscle, through cell death, scarring and changes to the cell structure within the cardiac muscle tissue. The precise mechanisms underlying these changes have not been fully elucidated; however, these types of pathologies have been demonstrated in experimental animal studies following methamphetamine administration, lending support to the causal role of methamphetamine when these types of cardiac tissue pathology are observed in methamphetamine-related deaths.

Of significant public health concern is methamphetamine's association with coronary artery disease. Again, through its potential to increase catecholamine levels, methamphetamine use can increase atherosclerosis and the formation of coronary artery thrombosis, increasing the potential for occlusion of the coronary arteries and consequent myocardial infarction. The risks associated with coronary artery disease are likely to be compounded by both the chronic effects of methamphetamine on the heart tissue (i.e. myocardial hypertrophy, fibrosis and necrosis), and the effects of methamphetamine intoxication (i.e. increased heart rate and blood pressure, and constriction of the coronary arteries). The prevalence of coronary artery disease observed among methamphetamine users at autopsy is almost four times the prevalence than among age-matched controls, suggesting that coronary artery disease is a likely cause of premature mortality among methamphetamine users. However, it is not clear from

this study, or any other studies conducted in the area, to what extent other confounding factors, such as tobacco smoking and alcohol and other drug consumption, play a role in the chronic cardiac pathology observed among methamphetamine users.

The evidence that currently exists around methamphetamine-related cardiac pathology is far from conclusive; however, there is sufficient evidence for methamphetamine-related cardiotoxicity to warrant concern and further investigation of this problem. Based on the existing literature there is a real possibility that:

1) methamphetamine users are at elevated risk from cardiac pathology relative to the remainder of the population;

2) this risk is not likely to be limited to the duration of their methamphetamine use, because of the long-lasting pathology associated with methamphetamine use;

3) the risk of cardiac pathology is going to be greatest among people who are chronic methamphetamine users, because they will be compounding the long-term and acute cardiotoxic risks associated with methamphetamine; and

4) methamphetamine use is likely to exacerbate the risk of cardiac pathology from other causes, and may therefore lead to premature mortality among methamphetamine users.

Table 4. Potentially fatal cardiac pathology reported among methamphetamine users

Pathology	Mechanism(s)	Evidence	Notes
Acute cardiac pathology			
Myocardial infarction	Coronary vasospasm; Thrombus formation; Increased oxygen demand in conjunction with above events	Case reports (n = 18)	Other risk factors may be involved in precipitating infarction, including a history of cardiac pathology and tobacco smoking
Aortic dissection	Unconfirmed – likely to be hypertension	Autopsy case reports (several)	
Sudden cardiac death	Cardiac arrhythmia	Autopsy case reports (several) Autopsy review Experimental animal studies	Well recognised consequence of methamphetamine toxicity in Japan
Chronic cardiac pathology			
Cardiomyopathy	Unclear, but includes myocardial necrosis, recurrent coronary vasospasm	Case reports (n = 7); Case series (n = 21); Autopsy case reports; Experimental animal studies	Typically dilated cardiomyopathy. Occurs/is only diagnosed in the absence of coronary artery disease
Coronary artery disease	Atherosclerosis	Autopsy reviews, including a review of methamphetamine-related deaths and age matched controls; Case reports	Likely to be exacerbated by other risk factors for coronary artery disease, such as tobacco smoking

6.1.1   Implications for methamphetamine users

The research to date indicates that the most common cardiovascular effects of methamphetamine use are an acute increase in heart rate and blood pressure. In the majority of cases, these symptoms may abate without further consequence. Nevertheless, in the context of chronic use and pre-existing cardiovascular pathology, these changes in cardiovascular functioning can trigger more serious and potentially fatal events.

Low level use of methamphetamine - for example, sporadic, low dosage use - does not appear to be associated with major acute complications such as myocardial infarction, or chronic cardiovascular disease, in an otherwise healthy user. Methamphetamine may, however, exacerbate pre-existing underlying cardiac pathology, such as coronary atherosclerosis or cardiomyopathy (Logan et al., 1998). As previously discussed, underlying cardiac disease increases the risk of an acute event, such as myocardial infarction or even sudden cardiac death. Methamphetamine use may have serious implications, for example, in young users with genetically inherited hypertrophic cardiomyopathy, which is often not detected until after death. Using methamphetamine may exacerbate this condition with fatal consequences (e.g. sudden cardiac death). Most users would be unaware of their cardiovascular health, given that underlying cardiac pathology is often only detected when the user presents with acute symptoms following methamphetamine intoxication or upon post-mortem examination. Thus, in the majority of cases, methamphetamine users would be unable to accurately assess the risk of complications arising from their methamphetamine use.

Long-term methamphetamine users appear to be most at risk of cardiovascular damage, such as premature, accelerated coronary artery disease and enlargement of the heart (Karch et al., 1999; Karch, 2002). Karch et al. (1999) suggest that methamphetamine toxicity becomes more evident, and more likely to have a fatal outcome, with chronic use. The findings from Karch et al.'s research also suggest that there may be an "incubation" period of several years prior to methamphetamine-related death, as increased heart size and coronary artery disease take time to develop.

6.1.2   Implications for future research

In reviewing the literature, areas of weakness in the research to date as well as opportunities for further research have been identified. Although there are a number of case series reports investigating cases of acute methamphetamine toxicity presenting to emergency departments (Derlet et al., 1989; Chan et al., 1994; Lan et al., 1998; Richards et al., 1999; Turnipseed et al., 2003; Wijetunga et al., 2004), there is a lack of research designed to estimate the incidence of such problems within the wider methamphetamine-using population. In the absence of prevalence studies, it is difficult to accurately estimate the incidence of adverse cardiovascular events and determine the extent and risk of such harm among methamphetamine users. As such, further research of this type is recommended. Further research into the prevalence and incidence of methamphetamine-related cardiac pathology should pay careful attention to the contribution of tobacco smoking, polydrug use, and other risk factors for cardiac pathology.

Given that the current extent of knowledge about the mechanisms underlying the cardiotoxicity of methamphetamine is still limited, further experimental research designed to elucidate the nature of such mechanisms is also suggested. Finally, future research may also investigate whether there is a dose-response relationship between cardiovascular pathology and patterns of methamphetamine use (e.g. frequency, route and typical dose), and to what extent the risk of cardiovascular pathology accumulates with chronic use of methamphetamine.

6.1.3   Conclusions and recommendations

In conclusion, while the more serious complications of methamphetamine use, such as myocardial infarction, aortic dissection and cardiomyopathy, are not commonly reported, there is enough clinical and experimental evidence to suggest that methamphetamine has adverse and potentially fatal effects on the cardiovascular system. As such, the use of methamphetamine should be regarded as an issue of public health concern.

The risk of cardiac events occurring is unable to be determined purely on the basis of dose and level of use. Other factors, such as individual variations in responsiveness, tolerance, and pre-existing cardiovascular health, interact to play an important but unquantifiable role in the physical reaction to any one occasion of use. For this reason,

information about the potential for methamphetamine to induce cardiovascular complications should be targeted to all users of the drug, not just dependent and chronic users.

Given their high levels of polydrug use, methamphetamine users should also be made aware of the increased risk of adverse cardiovascular effects when methamphetamine is used with other drugs, particularly other psychostimulant drugs such as cocaine and ecstasy.

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