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Methylenedioxymethamphetamine (MDMA)-related fatalities in Australia: Demographics, circumstances, toxicology and major organ pathology

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ABSTRACT

Aim: To examine the demographic characteristics, circumstances, toxicology and major organ pathology of MDMA-related deaths in Australia.
Methods: Retrospective review of cases in which MDMA was a cause of death, as identified from the National Coronial Information System.
Results: 82 cases over a 5-year period were identified. The majority of decedents were male (83%), with a median age of 26 years. Deaths were predominantly due to drug toxicity (82%), with MDMA the sole drug causing death in 23% of cases, and combined drug toxicity in 59% of cases. The remaining deaths (18%) were primarily due to pathological events/disease or injury, with MDMA a significant contributing condition. Cardiovascular pathology, typically atherosclerosis, was detected in 58% of decedents, with moderate–severe atherosclerosis in 23% of cases. The prevalence of such pathology is higher than that expected among similarly aged members of the general population. Cerebrovascular pathology, primarily cerebral haemorrhage and hypoxic damage, was present in 12% of cases.
Conclusions: MDMA has contributed to a clinically significant number of deaths in Australia. The prevalence of cardiovascular pathology was similar to that among methamphetamine and cocaine fatalities. Whilst cardiovascular pathology may reflect the use of other stimulants, the cardiotoxic properties of MDMA have been well-documented. Future studies examining MDMA-related morbidity and mortality in the context of other risk factors are recommended. Overall, the current study highlights the need to educate users about the potential harms of MDMA use, particularly that in conjunction with other stimulants, opioids and alcohol, which are known to increase overall toxicity.

1. Introduction

MDMA (3,4-methylenedioxymethamphetamine, "ecstasy"), is an amphetamine derivative, with hallucinogenic and stimulant properties. The popularity of MDMA has increased since the late 1980s, when its use became a feature of the underground dance or "rave" scene (Gill et al., 2002). In Australia, MDMA is the second most widely used illicit drug after cannabis. According to the 2007 National Drug Strategy Household Survey data, 8.9% (1.5 million) of the general population reported lifetime use of MDMA, with 3.5% (0.6 million) reporting use in the preceding 12 months (Australian Institute of Health and Welfare, 2008). Use is most prevalent among 20–29-year-old males, who were more likely to report lifetime (25.7%) and recent (13.8%) use of MDMA.

As the use of MDMA has increased, reports of associated adverse consequences have become more frequent (Burgess et al., 2000). Acute adverse physical effects reported by users include jaw clenching, tooth grinding (bruxism), blurred vision, palpitations, headache, nausea, and increased body temperature (Topp et al., 1999; Kalant, 2001; Gowing et al., 2002; Liechti et al., 2005; Baylen and Rosenberg, 2006). The most widely reported acute psychological effects are anxiety, depression and paranoia (Topp et al., 1999; Baylen and Rosenberg, 2006).

Emergency department and mortality data, in addition to users' reports, suggest that serious complications of MDMA use are less common than those associated with opioids, cocaine, or methamphetamine and, relative to the prevalence of use, are not commonplace (Gowing et al., 2002; Liechti et al., 2005; Darke et al., 2007). Nevertheless, acute toxicity following MDMA use can, and does, occur. Hyperthermia is one of the most widely reported toxic reactions to MDMA and a common finding among MDMA-related fatalities (Kalant, 2001; Gowing et al., 2002; Patel et al., 2005a,b; Darke et al., 2007). Hyperthermia can cause life-threatening complications such as seizures, rhabdomyolysis, acute renal failure, disseminated intravascular coagulation, and severe liver toxicity and failure (Milroy et al., 1996; Kalant, 2001; Gowing et al., 2002;

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Darke et al., 2007). Whilst liver toxicity is often secondary to hyperthermia, it can also occur in the absence of hyperthermia (Milroy et al., 1996; Burgess et al., 2000; Gowing et al., 2002; Darke et al., 2007). In response to increases in body temperature, perspiration, and thirst, induced by MDMA itself, ambient temperature and/or physical activity, users often increase fluid intake. The over-consumption of water can cause dangerous sodium and water imbalances, leading to hyponatraemia, commonly referred to as "water intoxication". Hyponatraemia can cause confusion and reduced consciousness and may induce cerebral oedema (Gowing et al., 2002; Karch, 2002; Schifano, 2004; Darke et al., 2007; Rosenson et al., 2007). The environment in which MDMA is taken is thought to play a role in deaths due to hyperthermia and hyponatraemia, with high ambient temperatures and physical exertion increasing the likelihood of these conditions occurring (Kalant, 2001; Gowing et al., 2002; Patel et al., 2005a,b; Darke et al., 2007; Rosenson et al., 2007). Hyperthermia, however, can also occur in quiet settings (Gowing et al., 2002; Patel et al., 2005a,b).

Like methamphetamine, MDMA increases heart rate, blood pressure and myocardial oxygen demand (Lester et al., 2000; Karch, 2002). As such, acute MDMA toxicity can result in serious, and potentially fatal, cardiovascular complications, such as cardiac arrhythmias, tachycardia in particular, and hypertension (Burgess et al., 2000; Kalant, 2001; Karch, 2002; Schifano, 2004; Liechti et al., 2005). Aortic dissection (Duflou and Mark, 2000) and acute myocardial infarction induced by MDMA have been reported (Qasim et al., 2001; Lai et al., 2003), but appear to be relatively rare events. Intracranial haemorrhage in association with MDMA use has also been reported (Milroy et al., 1996; Gowing et al., 2002; Karch, 2002; Schifano, 2004) and, whilst there is typically an underlying aneurysm or arteriovenous malformation, MDMA-induced hypertension increases the risk of such an event (Kalant, 2001; Karch, 2002).

Mortality rates associated with illicit drug use are consistently found to be highest among opioid users, with elevated rates of death also found among amphetamine and cocaine users (Darke et al., 2007). In 2005, among those aged 15–54 years, the rate of drug-induced deaths in Australia due to opioids was 32.5 per million persons. The rate of deaths due to methamphetamine and cocaine in 2005 was 5.9 and 1.3 per million persons, respectively (Degenhardt and Roxburgh, 2007a,b). To date, however, there are no national data on rates of MDMA-induced mortality among Australians and no cohort studies examining mortality rates among MDMA users. As such, the extent of MDMA-related mortality in Australia is unknown.

Whilst reports of MDMA-related death are far less common than those of opioid, amphetamine and cocaine-related deaths, the number of MDMA-related deaths appears to be increasing (Gill et al., 2002; Gowing et al., 2002; Karch, 2002; Schifano et al., 2003a,b, 2006; Patel et al., 2004; Schifano, 2004; Darke et al., 2007). Deaths related to MDMA appear to have been primarily due to the toxic reactions described above (Kalant, 2001; Gill et al., 2002; Liechti et al., 2005; Darke et al., 2007), although several deaths due to lethal injuries whilst the deceased person had been under the influence of MDMA (e.g. motor vehicle accidents, falls) have been reported (Kalant, 2001; Gill et al., 2002; Patel et al., 2004). Little is known, however, about the nature of MDMA-related mortality. To date, data on mortality associated with MDMA has been largely limited to single case reports and small-scale case series (Schifano, 2004; Darke et al., 2007). Although larger case series have been conducted in the UK (Schifano et al., 2003a,b) and US (Patel et al., 2004), they have only provided demographic and toxicological findings, and limited information regarding the circumstances of death. Whilst toxicological findings are an essential component of any investigation into cause of death, they are often difficult to interpret in isolation. Autopsy findings play a major role in determining the cause of death and help put toxicological findings into context. There is a paucity of data, however, on the prevalence of pre-existing and perimortem organ pathology among MDMA-related fatalities, with autopsy findings only published as part of single case reports or small-scale case series [e.g. Milroy et al., 1996; Lora-Tamayo et al., 1997; Duflou and Mark, 2000; Raikos et al., 2002; Libiseller et al., 2005].

The current study aimed to investigate the circumstances, toxicology, and associated organ pathology of MDMA-related deaths in Australia across a 5-year period. Specifically the study aimed:

1. To determine the number of MDMA-related fatalities that occurred in Australia between 1 July 2000 and 30 June 2005.
2. To describe the demographic characteristics of decedents and the circumstances of death.
3. To examine toxicological findings from MDMA-related fatalities.
4. To describe the major autopsy findings from MDMA-related fatalities.

2. Methods

2.1. National Coroners Information System

The National Coroners Information System (NCIS) is a centrally administered electronic database of coronial information provided by coroners' courts in each Australian jurisdiction. The NCIS contains information on deaths occurring from 1 July 2000 which have been reported to an Australian coroner. A complete NCIS case file includes demographic information, a police narrative of circumstances, autopsy and toxicology reports, and the coronial finding, which determines whether death was accidental, suicide or homicide, and confirms the medical cause of death. The medical cause of death is comprised of two parts:

I (a): Disease or condition directly leading to death.
I (b,c,d): Antecedent causes (morbid conditions, if any, giving rise to the direct cause of death).
II: Other significant conditions (contributing to death but not related to disease/condition causing death).

In Australia, the criteria for reporting a death vary between jurisdictions. In general, a death is reportable to a coroner where: the person died unexpectedly and the cause of death is unknown; the person died in a violent and unnatural manner; the person died during or as a result of an anaesthetic; the person was "held in care" or in custody immediately before they died; a medical practitioner has been unable to issue a death certificate stating the cause of death; the decedent's identity is unknown.

2.2. Case selection

MDMA-related deaths occurring between 1 July 2000 and 30 June 2005 were identified from the NCIS. Cause of death is determined by a forensic pathologist on the basis of the circumstances of death, an autopsy, and toxicological analyses. MDMA-related deaths were defined as those in which MDMA or MDA (methylenedioxyamphetamine), a primary metabolite of MDMA, was determined by the pathologist to have been a direct cause of death (i.e. directly leading to death), an antecedent cause of death (i.e. gave rise to the direct cause of death), or a significant contributing factor (i.e. contributed to death but not related to disease/condition causing death), as documented on the medical cause of death certificate. The direct and antecedent causes of death form what is known as the "morbid train of events" that led to death. Depending on the number of events culminating in death, the underlying cause of death will be either the direct cause of death (where no antecedent causes are noted) or the initial antecedent event. Where MDMA contributed to a motor vehicle accident causing death, only those cases in which the decedent was the driver of the car or a pedestrian were selected. That is, cases in which the decedent was the passenger in a car involved in a motor vehicle accident due to MDMA intoxication of the driver were not included.

2.3. Demographics and circumstances of death

Demographic information was extracted from each case file. The circumstances surrounding death were obtained from accompanying police reports, including, where available, the location of the fatal incident, evidence of drug use and route of drug administration, evidence of suicidal intent, drug treatment status, and recent prison history.

Table 1
Demographic characteristics of decedents.

	Females ($n=14$)	Males ($n=68$)	All cases ($n=82$)
Median age (years) (range)	22 (20–40)	28.5* (17–58)	26 (17–58)
Employment (%)			
Employed	43	75*	70
Retired/pensioner	0	3	2
Student	29	4	9
Unemployed	14	9	10
Unknown	14	9	10
Married/de facto (%)	8	20	18
Body mass index (mean) (range)	22.2 (19.7–27.1)	25.6* (17.4–43.6)	25.1 (17.4–43.6)
Treatment status (%)[a]			
In treatment	10	3	4
Type of treatment			
Methadone	10	2	3
Counselling	0	1	1

* Significant gender differences ($p<0.05$).
[a] $n=69$.

2.4. Toxicological results

Quantitative toxicological analysis is routinely conducted in cases of unnatural death, providing information on the blood concentrations of alcohol and other drugs. Recent use of MDMA was determined by the presence of MDMA, as well as MDA, its primary metabolite. Where both MDMA and MDA were detected, it was assumed that MDA was present as a metabolite, rather than ingested as a separate drug. Drug intoxication or toxicity causing or contributing to death is determined by the pathologist on the basis of the toxicological findings. Decisions about the role of drugs in death, however, are not based on toxicology results alone, with the consideration of other available evidence, such as autopsy findings, essential.

2.5. Autopsy reports

In cases of deaths referred to the coroner, a standardised medico-legal forensic autopsy is conducted, entailing a comprehensive examination of all major organs, including microscopy of representative tissue samples. This is a retrospective study. As such, the autopsies reported were not collected prospectively for the study, but were standard forensic autopsies performed as part of the medico-legal responsibilities of the forensic medicine departments in each jurisdiction. Where autopsy reports were available, information relating to the macroscopic and microscopic findings of major organ examination was reviewed.

Information on height and weight, from which body mass index (BMI) was calculated, findings of major organ pathology, and other clinically significant pathology was extracted from autopsy reports. Findings of particular relevance were: findings on cardiovascular, cerebrovascular, pulmonary, hepatic and renal pathology. Coronary atherosclerosis was classified as mild, moderate or severe on the basis of direct comment by the forensic pathologist in the post-mortem report, or as indicated by arterial stenosis ranges of 10–50% (mild), 51–75% (moderate) and >75% (severe).

2.6. Statistical analyses

For continuous variables, *t*-tests were employed. Where distributions were highly skewed, medians were reported. For dichotomous categorical variables, odds ratios (OR) and 95% confidence intervals (95%CI) were reported. In order to determine the variables that were independently associated with major organ pathology, simultaneous logistic regressions, using age, gender and BMI as independent variables, were conducted. All findings were examined for gender differences, and these are reported only where significant. All analyses were conducted using SPSS for Windows, Version 14.0 (SPSS Inc., 2006).

3. Results

3.1. Demographic characteristics

Eighty-two MDMA-related deaths were identified. MDMA was noted as a direct cause of death in 74.4% of cases, as an antecedent cause in 7.3%, and as a significant contributing condition in 18.3%. The median age was 26 years (SD 8.17, range 17–58 years) (Table 1). The majority were male (83%) and almost three-quarters were employed. Males were significantly older (Mann–Whitney $U=245.5$, $p<0.01$) and more likely to be employed (OR 4.00, 95%CI 1.21–13.18). The average BMI was 25.1 (SD 4.51, range 17.4–43.6), with males having a significantly higher BMI than females ($t_{55}=2.10$, $p<0.05$). A minority were in a married/de facto relationship and less than a twentieth were in treatment for drug dependence at the time of death (Table 1).

3.2. Direct causes of MDMA-related death

The direct causes of MDMA-related death are presented in Table 2. Cases in which MDMA was determined by a forensic pathologist to be a direct or antecedent cause of death have been separated from those in which MDMA was determined to be a significant contributing condition. It should be noted that there were several cases in which there was more than one direct cause of death. As such, the cause of death categories are not mutually exclusive and do not total 100%.

3.2.1. Cases where MDMA was noted as a direct or antecedent cause of death (n = 67). The direct cause of death among cases in which MDMA was a direct or antecedent cause of death was overwhelmingly drug toxicity (91%). Toxicity was attributed to MDMA alone in 25% of these cases, with combined drug (i.e. MDMA in combina-

Table 2
Direct cause of death according to role of MDMA.

Direct cause of death (%)	All cases ($n=82$)	
	%	*n*
Cases with MDMA as direct or antecedent cause of death ($n=67$)		
Drug toxicity	91	61
MDMA-only	25	17
Combined drug toxicity	66	44
Cardiovascular	10	7
Injury	9	6
Cerebrovascular	7	5
Aspiration of gastric content	4	3
Pulmonary	3	2
Drowning	3	2
Hyperthermia	1	1
Cases with MDMA as a significant contributing condition ($n=15$)		
Injury	47	7
Cardiovascular	13	2
Hanging	13	2
Carbon monoxide poisoning	13	2
Strangulation (homicide)	7	1
Cerebrovascular	7	1
Drowning	7	1

tion with other drugs) toxicity the cause of death in 66% of cases. The most common drugs present with MDMA in cases of combined drug toxicity were opioids (54%), methamphetamine (42%), benzodiazepines (23%) and alcohol (21%).

In 10% of cases, cardiovascular complications or disease arising from, or complicated by, MDMA use was a direct cause of death. Cardiovascular events and pathology causing death included coronary artery atherosclerosis/disease (6 cases), cardiomegaly (2 cases), probable cardiac arrhythmia (1 case), and acute thrombosis (1 case). In 7% of cases, cerebrovascular complications were a direct cause of death. Death in these cases was caused by cerebral haemorrhage (2 cases), brain swelling (1 case), hypoxic brain damage in association with combined drug toxicity (1 case), and structural cerebrovascular abnormalities (1 case).

Injury was a direct cause of death in 9% of cases. In 3 of 6 cases of injury, the injury was sustained in a motor vehicle accident. Other causes of injury were falls (1 case), self-inflicted knife wounds (1 case) and accidental asphyxia (1 case). In cases of MDMA-related death due to injury or homicide, the probable role of MDMA toxicity or intoxication is in causing impaired judgement and consequential increased risk-taking.

Other causes of death included aspiration of gastric contents (3 cases), pulmonary complications (bronchopneumonia) secondary to drug toxicity (2 cases), drowning (2 cases), and a single case of hyperthermia.

3.2.2. Cases where MDMA was noted as a significant contributing condition (n = 15). In almost half of the deaths in which MDMA was a significant contributing condition ($n = 7$), death was caused by injury. In 4 cases, fatal injuries were sustained in a motor vehicle accident. In 2 cases, one of which was a suicide, death was due to a fall. In 1 case, death was due to gunshot wounds (homicide).

Coronary artery disease arising from, or complicated by, MDMA use was a direct cause of death in two cases and cerebral haemorrhage was the direct cause of death in a single case. Other causes of death included hanging (2 cases), carbon monoxide poisoning (2 cases), drowning (1 case), and 1 case of homicide (strangulation).

3.3. Circumstances of death

In 9% of cases, death was by suicide, although, in a further 3 cases, intent was unable to be determined by the coroner (Table 3). Deliberate MDMA overdose was the method of suicide in 2 cases, hanging in 2 cases, carbon monoxide poisoning in 2 cases, and self-inflicted injury (fall) in 1 case.

Table 3
Circumstances of death.

	All cases ($n = 82$)
Location of fatal incident (%)	
Home	62
Public area	15
Road	10
Hospital	2
Other	11
Suicide (%)	
Yes	9
Unable to be determined	4
Route of administration (%)[a]	
Oral	98
Intravenous	2
Intranasal	0
Smoked	0

[a] $n = 64$.

The majority of fatal incidents occurred in a private home (Table 3). Public areas included trade/service areas and sports/recreation areas. Of the 64 cases where the route of MDMA administration was evident, oral ingestion was by far the most common route (Table 3). In 13% of the cases where MDMA was administered orally, however, there was evidence of injection of other drugs, such as syringes found in the vicinity, puncture marks found at autopsy, or a reported history of injecting drug use.

3.4. Toxicology

Quantitative toxicological analysis is routinely conducted in all cases of unnatural or unexpected death (i.e. deaths reportable to the coroner), providing information on the blood concentrations of alcohol and other drugs. Toxicological analysis entails screening for, and quantifying concentrations of, a range of licit and illicit substances, including MDMA and MDA. The results of these analyses are used to help determine cause of death. It is important to note that a drug may be detected in the blood at autopsy, yet not be considered by the pathologist to play a role in the cause of death. The presence and concentrations of MDMA and MDA were examined for all cases for which toxicology results were available, irrespective of the cause of death. The blood concentrations of MDMA and MDA, as well the prevalence of other drugs detected in the decedents' blood, regardless of whether or not they contributed to death, are presented in Table 4.

Toxicology reports, whilst completed for each case, were only available to the authors (i.e. attached to the NCIS case files for viewing) for 68 cases. Of these 68 cases, 97% of the blood samples tested positive for MDMA, 38% for MDA, and 37% for both MDMA and MDA. The median concentrations of MDMA and MDA were 0.85 mg/L (range 0.03–93.0 mg/L) and 0.10 mg/L (range 0.01–1.0 mg/L), respectively (Table 4). There were no significant differences between cases of death due to drug toxicity and cases of death due to injury or disease in the median concentrations of either MDMA (0.85 vs. 0.65, $p = 0.40$) or MDA (0.1 vs. 0.08, $p = 0.25$).

Other drugs were detected in 87% of cases, the most common being methamphetamine or its primary metabolite amphetamine, morphine and alcohol (Table 4). Females were significantly more likely to test positive for methamphetamine/amphetamine (OR 8.83, 95%CI 1.01–76.96) and miscellaneous other drugs (OR 5.5, 95%CI 1.14–26.63).

Table 4
Toxicological findings based on blood samples.

Drug detected	$n = 68$
Median blood concentrations	
MDMA (mg/L) (range)	0.85 (0.03–93.0)
MDA (mg/L) (range)	0.10 (0.01–1.0)
Presence of other drugs (%)[a]	87
Methamphetamine/amphetamine	50
Morphine	32
Alcohol	30
Codeine	25
Benzodiazepines	20
Antidepressants	18
THC	13
Cocaine/benzoylecgonine	10
Methadone	3
GHB	3
Ketamine	2
Antipsychotics	0
Miscellaneous other drugs (e.g. antihistamines, paracetamol)	20

[a] $n = 69$ (excerpt of toxicology results available from autopsy report for 1 case).

3.5. Major organ pathology

Full autopsy reports were available to the authors for 55 cases. In a further 6 cases, findings of major organ pathology were noted in the certified cause of death. Of those cases for which autopsy reports were available, 22% had no significant major organ pathology of any type. Information regarding the presence or absence of cardiac and cerebrovascular pathology was available for 57 cases. Cardiovascular pathology was noted in 58% of these cases, most commonly aortic and coronary artery atherosclerosis (44%), followed by cardiomegaly (18%) and ventricular hypertrophy (7%) (Table 5). Atherosclerosis was typically located in the coronary arteries (35%), with involvement of the aorta in 24% of cases. Atherosclerosis was moderate or severe in 23% of cases. Cerebrovascular pathology was noted in 12% of cases, and included hypoxia (5%), non-traumatic (4%) and traumatic (2%) cerebral haemorrhage, cerebral oedema (4%) and cerebrovascular malformations (4%).

In order to determine whether or not the presence of cardiovascular pathology was associated with some of the risk factors typical among the general population, multivariate logistic regression analyses were conducted, with age, gender and BMI entered as independent variables. These were not significantly associated with the presence of overall cardiovascular pathology. Similar analyses were conducted to determine the independent predictors of specific types of cardiovascular pathology (e.g. atherosclerosis, cardiomegaly and myocardial hypertrophy). Older age was associated with the presence of any atherosclerosis, i.e. mild, moderate or severe (OR 1.11, 95%CI 1.01–1.22), whilst a higher BMI was associated with moderate–severe atherosclerosis (OR 1.24, 95%CI 1.02–1.50). The presence of cardiomegaly and myocardial hypertrophy, however, were not significantly predicted by any of the aforementioned variables.

Information regarding pathology of other major organs was available in 56 cases. Hepatic pathology was observed in 31% of cases, with steatosis (26%) and histologic features of hepatitis C (HCV) infection (11%) the most prevalent forms (Table 5). Pulmonary pathology was noted in 29% of cases, with bronchopneumonia the most common finding (9%), followed by emphysema (4%). Renal pathology was noted in 7% of cases and was predominantly in the form of fibrosis (5%). Other organ pathology was noted in 5% of cases, and included pathology of the spleen (2%) and stomach (2%).

Table 5
Major organ pathology.

Type of pathology (%)	$n = 57$
Cardiovascular pathology	58
Atherosclerosis	44
Severity of atherosclerosis	
Mild	18
Moderate	9
Severe	14
Unspecified	2
Sites of atherosclerosis	
Coronary arteries	35
Aorta	24
Cardiomegaly	18
Ventricular hypertrophy	7
Ischaemic heart disease	6
Cerebrovascular pathology	12
Pulmonary pathology[a]	29
Hepatic pathology[b]	31
Renal pathology[c]	7

[a] $n = 56$.
[b] $n = 55$.
[c] $n = 55$.

3.6. Comparisons between MDMA-only and combined drug deaths

Cases in which MDMA was a direct or antecedent cause of death ($n = 67$) were selected for further analysis. Comparisons were made between cases where MDMA alone was the cause of death and cases where MDMA in combination with other drugs caused death (Table 6).

The MDMA-only and combined drug groups did not differ in terms of demographic characteristics or median blood concentrations of MDMA and MDA (Table 6). In order to determine whether or not death due to combined toxicity was associated with the presence of overall cardiovascular pathology, multivariate logistic regression analyses were conducted, with age, gender, BMI and combined toxicity (yes/no) entered as independent variables. Combined drug toxicity was the only significant predictor of overall cardiovascular pathology (OR 5.78, 95%CI 1.47–22.72). Similar analyses were conducted to determine the independent predictors of atherosclerosis, cardiomegaly and myocardial hypertrophy. Older age was associated with the presence of any atherosclerosis, i.e. mild, moderate or severe (OR 1.13, 95%CI 1.02–1.24), whilst combined drug toxicity was associated with moderate–severe atherosclerosis (OR 9.72, 95%CI 1.18–79.87). The presence of cardiomegaly and myocardial hypertrophy were not significantly predicted by any of the independent variables.

4. Discussion

MDMA has contributed to a clinically significant number of deaths in Australia. MDMA was a direct cause of death in the majority of cases, although, consistent with previous studies of MDMA and other drug-related fatalities (Gill et al., 2002; Schifano et al., 2003a,b; Patel et al., 2004; Darke et al., 2007), combined drug toxicity was more common than toxicity due to MDMA alone. Nevertheless, MDMA alone was a direct cause of death in over 1 in 5 cases. These findings indicate that MDMA toxicity is itself a primary cause of death and not merely a contributor to risk behaviours that result in death. In a minority of cases, however, MDMA toxicity or intoxication was a causal factor in death due to lethal injury.

Decedents were typically males in their mid to late twenties, a demographic profile similar to MDMA-related fatalities studied elsewhere (Darke et al., 2007), and the majority were employed. In Australia, regular MDMA users are usually male, aged in their mid-twenties and either employed or enrolled in tertiary education (Degenhardt and Dunn, 2007). As such, the decedents in the current study do not appear to differ demographically from living MDMA users. Contrary to the belief that MDMA-related deaths typically occur in particular environments, such as dance parties, where physical exertion combined with inadequate or excessive levels of hydration can lead to fatal hyperthermia and hyponatraemia, the majority of these deaths occurred in a private home. Moreover, there was only one documented case of death due to hyperthermia. These findings suggest not only that MDMA is used among a more heterogeneous population and wider variety of environments than the traditional image of MDMA as a “dance party drug” would suggest, but that the potential risks associated with the consumption of MDMA, particularly in conjunction with other drugs, are not limited to particular settings or activities of the user. As such, consideration of the morbidity and mortality associated with the use of MDMA should extend to all users and to use in a range of contexts.

Suicidal intent was evident in a minority of cases. The role of MDMA in the development of suicidal ideation and intent in these

Table 6
Comparisons between MDMA-only and combined toxicity cases for deaths where MDMA was a direct or antecedent cause of death.

	MDMA-only ($n = 19$)	Combined toxicity ($n = 48$)	All cases ($n = 67$)
Demographics			
Mean age (years) (range)	28.6 (20–50)	27.4 (17–45)	27.7 (17–50)
% Male	74	85	82
Blood concentrations[a]			
MDMA (median mg/L) (range)	0.7 (0.30–64.0)	0.9 (0.03–93.0)	0.85 (0.03–93.0)
MDA (median mg/L) (range)	0.11 (0.05–0.70)	0.10 (0.01–1.0)	0.10 (0.01–1.0)
Major organ pathology[b]			
Cardiovascular pathology	22	69*	59
Atherosclerosis	11	49	41
Severity of atherosclerosis			
Mild	11	12	12
Moderate	0	15	12
Severe	0	18	14
Unspecified	0	3	2
Cardiomegaly	0	24	19
Ventricular hypertrophy	0	6	5
Ischaemic heart disease	0	6	5
Cerebrovascular pathology	27	6	11
Cerebral haemorrhage	18	0	5
Pulmonary pathology	33	29	30
Hepatic pathology	0	42	33
Steatosis	0	33	26
Renal pathology	11	3	5

[a] $n = 54$.
[b] $n = 44$.
* $p < 0.05$.

cases is unclear, although cases of suicidal ideation and suicide following the use of MDMA have been documented (Cohen, 1996). As with all psychostimulants that are typically associated with a "euphoric" effect, MDMA can induce adverse psychological effects and users should be aware of this possibility.

The toxicological findings of cases were similar to those of other studies in that drugs other than MDMA, typically amphetamines, morphine and alcohol, were detected at autopsy (Gill et al., 2002; Schifano et al., 2003a,b; Patel et al., 2004; Darke et al., 2007). In contrast to MDMA fatalities in other countries (Gill et al., 2002; Schifano et al., 2003a,b; Patel et al., 2004), where cocaine toxicity is a common feature (Patel et al., 2004; Darke et al., 2007), cocaine was detected in a small minority of cases, reflecting the relatively low prevalence of cocaine use in Australia. The large proportion of deaths directly caused by combined drug toxicity reflects the fact that polydrug use is the norm among MDMA users (Schifano, 2004; Liechti et al., 2005; Degenhardt and Dunn, 2007). In cases where methamphetamine and ketamine toxicity contributed to death, however, it is difficult to determine whether or not the use of these drugs was intentional. Tablets sold as ecstasy often contain substances other than MDMA, such as methamphetamine, ketamine, MDA, PMA and MDEA (Quinn et al., 2004; Hall and Henry, 2006; Degenhardt and Dunn, 2007). Nevertheless, the fact that half of the toxicology reports noted the detection of methamphetamine in the blood is consistent with the polydrug use patterns of living MDMA users. In a recent survey of regular ecstasy users across Australia, over half (59%) reported methamphetamine use in the previous 6 months (Stafford et al., 2008).

The fact that opioids, ethanol and cocaine toxicity are frequently found among MDMA-related fatalities strongly suggests that using a combination of these drugs may increase the risk of lethal toxicity. Combined drug toxicity involving opioids and/or alcohol has been consistently demonstrated in studies of methamphetamine-related (Bailey and Shaw, 1989; Logan et al., 1998; Karch et al., 1999) and cocaine-related fatalities (Wetli and Wright, 1979; Bailey and Shaw, 1989; Tardiff et al., 1996; Coffin et al., 2003; Darke et al., 2005). Previous research has demonstrated that when methamphetamine is combined with opioids, cocaine or alcohol, toxicity is increased (Mendelson et al., 1995; Albertson et al., 1999; Darke et al., 2007; Kaye et al., 2007). Similarly, when cocaine is combined with opioids or alcohol, the resultant toxicity is greater than that due to each drug by itself (Kaye and Darke, 2004; Darke et al., 2007). It is reasonable to expect that when MDMA, which has similar stimulant properties to methamphetamine, is combined with such drugs, toxicity will likewise increase. It has been proposed that when MDMA is used with other stimulants, such as cocaine and methamphetamine, a synergistic interaction leads to an increase in the physiological effects of each drug (Gouzoulis-Mayfrank and Daumann, 2006; Schifano et al., 2006). Indeed, alcohol is known to potentiate the physiopathological effects of MDMA (Schifano, 2004; Darke et al., 2007).

In accordance with previous research (Milroy et al., 1996; Gill et al., 2002; Gowing et al., 2002; Gable, 2004; Hall and Henry, 2006), cases displayed a wide range of MDMA concentrations. Moreover, MDMA/MDA concentrations did not significantly differ between toxicity-induced deaths and deaths due to injury or disease, nor between MDMA-only deaths and combined toxicity deaths. There does not appear to be a clear dose–response for MDMA toxicity (Kalant, 2001; Gowing et al., 2002; Karch, 2002; Darke et al., 2007), with frequent overlap between lethal and non-lethal blood concentrations of MDMA (Kalant, 2001; Gowing et al., 2002; Karch, 2002). As such, MDMA concentrations should not be interpreted in isolation from other factors.

Pre-existing pathology is another factor that complicates the dose–response relationship. There is strong evidence to suggest that the chronic use of methamphetamine and/or cocaine can cause the premature and accelerated development of coronary artery disease and cardiomyopathy, and that pre-existing cardiac pathology can be exacerbated by use of these drugs (Logan et al., 1998; Karch et al., 1999; Karch, 2002; Kaye et al., 2007). Coronary artery disease,

for example, has been found to occur at a far greater rate among methamphetamine users than among age-matched controls, and at a significantly younger age than among the general population (Karch et al., 1999; Karch, 2002). In a study of methamphetamine-related deaths, Karch et al. (1999) found moderate–severe coronary artery disease in 16% of cases with a mean age of 36.8 years.

MDMA may also have cardiotoxic effects and may similarly exacerbate pre-existing cardiac pathology (Milroy et al., 1996; Qasim et al., 2001; Gowing et al., 2002; Patel et al., 2005a,b). Cardiovascular pathology was detected in almost 6 in 10 of the autopsies reviewed for the present study. Almost a quarter of decedents had moderate or severe atherosclerosis, and nearly 1 in 5 cases had cardiomegaly. These findings are consistent with those of autopsy studies of cocaine and methamphetamine users (Logan et al., 1998; Karch et al., 1999; Zhu et al., 2000; Karch, 2002; Darke et al., 2005; Kaye et al., 2007, 2008) and, more recently, MDMA users, in whom higher rates of cardiomegaly and myocardial hypertrophy have been found at autopsy (59% of MDMA-positive vs. 19% of MDMA-negative fatalities) (Patel et al., 2005a,b).

Given that decedents in the present study were relatively young – mostly in their twenties and early thirties – this type of pathology would appear to be more prevalent than would be expected among a general population sample of a similar age. Cardiomegaly, however, is an abnormal finding, irrespective of age (Karch et al., 1999). Moreover, the levels of cardiovascular pathology found among MDMA, cocaine and methamphetamine-related fatalities are substantially greater than those among opioid (29%) and non-drug-related fatalities (24%) (Darke et al., 2005; Kaye et al., 2008). These differences suggest that psychostimulant use in particular, rather than illicit drug use *per se*, may be associated with an increased risk of the development or exacerbation of such pathology.

Cardiovascular pathology was more prevalent among deaths due to combined drug toxicity than among those due to MDMA alone. Combined toxicity was an independent predictor of overall cardiovascular pathology and of the presence of moderate–severe atherosclerosis in particular. As such, the role of other drugs (e.g. methamphetamine, cocaine and nicotine) in contributing to such pathology cannot be discounted. Nevertheless, using MDMA in the presence of pre-existing pathology, alone or with other drugs, may increase the likelihood of an acute event.

Whether the cardiovascular pathology observed in this sample was due to chronic past use of MDMA, the use of other psychostimulants, or to other risk factors, such as smoking, the potential cardiotoxicity of MDMA has been well-documented in the literature. The risk of cardiovascular complications 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 MDMA to induce or exacerbate cardiovascular pathology should be targeted to all users of the drug, not just chronic users.

Cerebrovascular pathology was evident in a minority of cases. Whilst non-traumatic cerebral haemorrhage and cerebral oedema induced by MDMA has been reported elsewhere (Milroy et al., 1996; Gowing et al., 2002; Karch, 2002; Schifano, 2004), there was a relatively low prevalence of such pathology among this case series. A higher rate of cerebrovascular pathology has been found among methamphetamine-related fatalities (Kaye et al., 2008), suggesting that the risk of cerebrovascular accidents is greater with methamphetamine than with MDMA. Indeed, the association between methamphetamine use and cerebrovascular accidents has been widely documented (Kalant and Kalant, 1975; Logan et al., 1998; Petitti et al., 1998; Karch et al., 1999; Zhu et al., 2000; Westover et al., 2007).

Levels of other major organ pathology, particularly hepatic pathology, were lower among MDMA fatalities than those observed among methamphetamine-related fatalities in Australia (Kaye et al., 2008). Nevertheless, a third of decedents had some form of hepatic and/or pulmonary pathology. The types of hepatic pathology detected were typically chronic changes, rather than the acute toxicity that has previously been associated with MDMA (Milroy et al., 1996; Kalant, 2001; Gowing et al., 2002; Darke et al., 2007). Without collateral information as to the presence of other risk factors for pre-existing pathology and the extent of other drug use, it is difficult to determine why rates of hepatic, pulmonary and renal pathology would be higher among methamphetamine-related fatalities, although decedents in the present study were, on average, younger than those in the methamphetamine fatality study (26 median years vs. 31 median years) (Kaye et al., 2008).

The main limitation of the current study is that NCIS case files were often incomplete. Information pertaining to risk factors for cardiovascular and cerebrovascular pathology, such as smoking and a positive relevant family history, was also unavailable, as was the extent of past drug use. Such information, however, is unlikely to be obtained from any retrospective study based on coronial files. Prospective cohort studies may provide a better understanding of the interaction between MDMA use and other mortality risk factors.

In order to determine the effect of long-term MDMA use on the development of chronic cardiovascular pathology (e.g. coronary artery disease), longitudinal cohort studies of MDMA users are recommended. Such studies may be able to control for the effects of other risk factors, such as family history, smoking and other drug use in particular.

The current study is the most comprehensive large-scale examination of MDMA-related mortality to date. This study indicates that in Australia, as elsewhere, MDMA contributes to a clinically significant number of fatalities. Overall, the current study highlights the need to educate users about the potential harms of MDMA use, particularly that in conjunction with other stimulants, opioids and alcohol, which are known to increase the net toxicity.

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Contributors

Shane Darke, Johan Duflou and Sharlene Kaye designed the study and wrote the protocol. Sharlene Kaye managed the literature searches and summaries of previous related work, undertook the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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