Research Report

Considering Heroin-Assisted Treatment and Supervised Drug Consumption Sites in the United States

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4. Supervised Consumption Sites

International Landscape

SCSs (sometimes known as *safe injection facilities*, *drug consumption rooms*, or *overdose prevention sites*) are facilities that aim to reduce the acute and chronic harms from drug use. They are characterized as a low-threshold intervention,[30] intended to attract individuals facing high risk of drug-related harms (e.g., people who inject drugs, sex workers who use drugs, those who are homeless). SCSs initially focused on reducing the spread of HIV/AIDS, hepatitis C, and other health and social consequences of unhygienic injection drug use (Hedrich, 2004; European Monitoring Centre for Drugs and Drug Addiction, 2017b). Because SCSs permit drug users to consume illicitly obtained substances under trained supervision, they also aim to avert fatal drug overdoses and reduce externalities associated with public drug use.[31] Most SCSs still focus on injection drug use, although some in Europe and Canada allow or include space for smoking crack cocaine and other drugs. SCSs also may or may not be integrated with broader public health and treatment services and vary considerably across countries in form and range of services provided.

Spending taxpayer funds to facilitate consumption of illegal drugs strikes some as incongruous, particularly on first hearing, but the logic of SCSs can, in a way, be seen as paralleling familiar medical interventions, such as chemotherapy and kidney dialysis. Patients receive treatment in outpatient facilities designed for the purposes of transfusing medicines and fluids under staff supervision in a sterile setting, rather than risk error or harm by letting patients attempt such procedures at home on their own. Individuals who inject street-sourced drugs, and who may be homeless, can benefit from such a sterile and safe environment.[32] Further, the increased risk of fatal overdose from the proliferation of potent synthetic opioids makes supervising drug consumption even more relevant today. However, questions remain surrounding the magnitude of the effectiveness and cost-effectiveness of supervised drug consumption under an SCS model.

According to the European Monitoring Centre for Drugs and Drug Addiction (2017b), SCSs traditionally "represent a local response, closely linked to policy choices made by local

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[30] The European Centre for Disease Prevention and Control and the European Monitoring Centre for Drugs and Drug Addiction (2011) describe *low-threshold services* as social and health services that aim to reach as many problematic drug users as early as possible in their drug-using careers and to remain in contact with such individuals to prevent health damage while they continue to use drugs.

[31] Like SEPs, SCSs seek to reduce disease transmission caused by use of unhygienic needles and to connect high-risk populations with social services. An increasing number of SEPs are also distributing naloxone. Indeed, Wheeler et al. (2015) noted that SEPs were some of the early adopters providing naloxone to PWUO.

[32] For more information on this logic model, see Pardo, Caulkins, and Kilmer (2018), which builds on the work of the European Monitoring Centre for Drugs and Drug Addiction (2017a).

stakeholders, based on an evaluation of local need and determined by municipal or regional options." Therefore, they employ a user-oriented service model, sometimes offering a wide array of additional services, including education, access to basic health care, psychosocial counseling, and sometimes testing of drugs for adulterants.

The first SCS opened in Bern, Switzerland, in 1986 amid a policy shift that emphasized survival and low-threshold services that attract the most at-risk populations (Hedrich, 2004). The objectives were twofold: to reduce health harms, including the number of overdoses and the incidence of new HIV infections, and to reduce the nuisance created by public drug use. SCSs slowly expanded to other cities in Switzerland. By the mid-1990s, cities in Germany and the Netherlands started to implement SCSs.

Today, there are some 90 facilities operating in nine countries in Europe, and policymakers in Ireland are planning to open a facility in Dublin (Brophy, 2018). Outside Europe, there is a growing number of facilities in Canada and Australia.[33] Discussions of opening SCSs have started in other cities in North America, such as Denver, Philadelphia, and San Francisco (Brown and Murphy, 2017; Lopez, 2018). Table 4.1 shows the number of cities and approved SCSs reported to be in operation, by country. Until 2016, Vancouver was the only site in North America allowed to operate an SCS, although others are reported to have operated without official approval for some time (Kral and Davidson, 2017). Because overdose deaths continued to increase in 2017, the Canadian government has permitted additional fixed and mobile sites to operate (Wherry, 2017).

Interviews with international key informants noted that there was often vocal opposition to SCSs when initially discussed or opened. This opposition revolved primarily around concerns about enabling drug use and potential negative community effects. However, according to interviewees, objections to SCSs from local stakeholders tended to disappear following their implementation, something that was also observed in numerous places that opened SEPs (Tempalski, 2007). As confirmed by international interviewees in Switzerland, the Netherlands, and British Columbia, SCSs are generally accepted services for people with OUD.

Table 4.1. Supervised Consumption Sites Around the World

Country	Number of Cities with SCSs	Number of SCSs Operating
Netherlands	25	31
Germany	15	24
Canada[a]	11 (5 more planned)	20[b] (11 more planned)
Switzerland	8	12
Spain	7	13
Denmark	4	5

[33] As this report was going to press, it was reported that an SCS opened in Mexicali, near the Mexico-U.S. border (Romero, 2018).

Country	Number of Cities with SCSs	Number of SCSs Operating
Norway	2	2
France	2	2
Australia	2	2
Luxembourg	1	1 (1 more planned)
Ireland	1 planned	1 planned

SOURCES: European Monitoring Centre for Drugs and Drug Addiction, 2017b; Health Canada, 2018.
[a] Until 2017, there were only two operational SCSs in Canada.
[b] British Columbia has also deployed low-threshold SCSs in the form of "overdose prevention sites." This count does not include such sites, which aim to reduce overdoses by allowing social workers and other injection drug users to set up facilities on the street to monitor injection drug use and distribute or administer naloxone.

Evidence from Scientific Literature

The existing reviews of scientific evaluations of SCSs report positive findings across a broad range of outcomes (Kerr et al., 2007; McNeil and Small, 2014; Potier et al., 2014; Garcia, 2015; Kennedy, Karamouzian, and Kerr, 2017).[34] In general, the studies evaluated public and SCS client opinions, individual-level outcomes (e.g., access or referral to treatment, changes in drug use practices, risky drug use, social and health outreach), and other outcomes (e.g., morbidity and mortality, crime, public disorder). However, the majority of studies come from a handful of sites; almost 80 percent of the literature base evaluated in systematic reviews comes from Insite in Vancouver or the Medically Supervised Injection Centre (MSIC) in Sydney.

We conducted our own assessment of the individual studies and found that the evidence base concerning the overall effects of SCSs is limited in quality and location. Although we identified 65 outcome-related articles (as opposed to commentaries or studies that gauge opinions), none involved an RCT, and just nine employed a quasi-experimental design with control groups. These nine studies were based on just four SCSs in three cities: Sydney (five studies), Vancouver (two studies), and Barcelona (two studies). There was considerable overlap in the design, methods, authorship, and data employed, so that four of the nine are arguably superseded by later studies using better methods or longer time series, in some sense reducing the effective number of quasi-experimental studies to five.

[34] We also considered one grey literature review that does not detail selection criteria nor report study findings systematically. Rather, that literature review "aims to provide a descriptive analysis of historical background, operational frameworks and outcomes" related to SCSs (Hedrich, 2004). The review focuses largely on individual health outcomes, as well as community-level outcomes, such as crime and public drug use. In most cases, Hedrich (2004) did not discuss study design of articles, although most appear to be descriptive survey-based studies targeted at SCS clients and staff. Findings reported by Hedrich (2004) provide an additional level of detail not captured elsewhere.

While we were writing this report, a meta-analysis of SCSs (May, Bennett, and Holloway, 2018) was published, but it was then retracted because of the "methodological weaknesses linked to the pooling of diverse outcomes into a single composite measure" (*International Journal of Drug Policy*, 2018). It should be noted that the study was not retracted for its selection criteria, which identified a small number of high-quality studies about SCSs.

Unlike these five, most of the studies included in the SCS literature reviews employ methodologies that do not allow for making causal inferences. For example, they might not include control groups or might compare frequent SCS users with those who use the sites less frequently. These studies can provide information about typical clients or costs, but they are not well suited to teasing out the effects of SCSs on individual or population-level outcomes.

In the next subsections, we describe our review of the quasi-experimental studies, as well as those that employ mathematical simulation or modeling. Pardo, Caulkins, and Kilmer (2018) provided additional information about the 65 studies.

Quasi-Experimental Studies

The nine studies employing a quasi-experimental design examined outcomes related to overdose, discarded injection equipment, or crime (Table 4.2). We are not aware of any quasi-experimental studies examining the effect of SCSs on treatment uptake or other health outcomes. The studies used varying analytical approaches. Some earlier studies merely visually compared outcomes between treatment and control cases; later studies included statistical tests.

Table 4.2. Quasi-Experimental Evaluations of Supervised Consumption Sites

Study	Outcomes Measured	Period	Location	Analytical Method	Treatment Designation	Control Designation	SCS Association with Outcome
Freeman et al. (2005)	Incidence of drug-related property and violent crime	September 1999–October 2002	Sydney	Visual comparison across cases; time series analysis with a segmented regression approach within treatment case	Local area command where SCS is located—Kings Cross neighborhood	Rest of Sydney	No visual difference in reported crime trends in treatment and control areas; regression coefficient indicating operation of SCS not statistically significant with incidence of crime reported in treatment area
National Centre in HIV Epidemiology and Clinical Research (2007)	Fatal overdoses, overdose-initiated emergency service calls, and emergency department episodes for opioids	May 1998–April 2006	Sydney	Poisson regression to test significance between treatment and control cases	Postal zone where SCS is located in Kings Cross neighborhood	Rest of state of New South Wales	No significant difference in number of fatal overdoses between treatment and control areas; significant difference in decline of emergency service calls in designated treatment area relative to rest of state
Fitzgerald, Burgess, and Snowball (2010)	Criminal incident reports of robbery, theft, and drug-specific crime	January 1999–March 2010	Sydney	Visual comparison across cases; nonparametric hypothesis test (tau coefficient) to test within-case changes	Local area command where SCS is located—Kings Cross neighborhood	Rest of Sydney	No visual difference in reported theft and robbery incidents between treatment and control case areas; drug-specific crime stable in treatment area, up in rest of Sydney; significant reductions of robbery and crime within cases over time

Study	Outcomes Measured	Period	Location	Analytical Method	Treatment Designation	Control Designation	SCS Association with Outcome
Salmon et al. (2010)	Emergency service calls for opioid-related overdoses	May 1998–May 2006	Sydney	Poisson regression to test significance between treatment and control cases	Where SCS is located in Kings Cross neighborhood; postal zone where SCS is located	Rest of State of New South Wales	Significant difference in decline of emergency service calls in designated treatment area relative to rest of state
Marshall et al. (2011)	Fatal drug overdoses	January 2001–December 2005	Vancouver	Nonparametric hypothesis test (Wilcoxon test); nonlinear modeling of rate difference pre-post	500 meter radius around SCS	Blocks 500-meter radius outside SCS	Significant reductions in the number of overdoses within treatment area compared with rest of city; reductions in overdose rate in person-years exponentially declines farther from SCS
Donnelly and Mahoney (2013)	Criminal incident reports and rates of robbery, theft, and drug-specific crime	January 1999–December 2012	Sydney	Visual comparison across cases; nonparametric hypothesis test (tau coefficient) to test within-case changes	Local area command where SCS is located—Kings Cross neighborhood	Rest of Sydney	No visual difference in reported crime trends incidents between treatment and control case areas; significant reductions of crime within cases over time
Vecino et al. (2013)	Discarded injection material	2004–2012	Barcelona	Nonparametric hypothesis test (Mann-Whitney)	Two districts where SCSs opened	Rest of Barcelona	No significant change in number of improperly discarded syringes in treatment district; statistically significant reduction of discarded injection equipment across city
Espelt et al. (2017)	Discarded injection material	2004–2014	Barcelona	Interrupted time series, Poisson regression	Districts B and C where SCS opened	Nontreatment districts in city	Short-term increase in discarded syringes in treatment and control districts, then decrease and stabilization in number of improperly discarded syringes in public spaces across city
Myer and Belisle (2018)	Reported incidence of violent and property crime	January 2002–December 2004	Vancouver	Time series analysis using autoregressive integrated moving average to compare changes over time within cases	Police District 1, where SCS is located	Police Districts 2–4	Significant reductions in reported property and violent crime in treatment district after SCS opening; no reported reductions in crime in control districts

The comparison areas in these quasi-experimental studies are not always ideal. Preferably, quasi-experimental evaluations will select control areas that are reasonably similar to the treatment area to reduce the potential for confounding effects. The purpose of comparing trends in the treatment area with those in a control region is to allow one to subtract out general trends

over time that are caused by exogenous factors, not the intervention being evaluated (this is known as a *differences-in-differences* approach).

Six of the nine studies use either the whole city or even the entire state as a control case when examining outcomes in the treatment area immediately surrounding the SCS (Donnelly and Mahoney, 2013; Fitzgerald, Burgess, and Snowball, 2010; Freeman et al., 2005; National Centre in HIV Epidemiology and Clinical Research, 2007; Salmon et al., 2010; Vecino et al., 2013). Because SCSs are intentionally sited in areas with high rates of injection drug use, they are usually different from the city or state as a whole. Three of the studies do use as controls some other specific districts within the city, or, in one case, outside a 500-meter radius from the SCS (Espelt et al., 2017; Myer and Belisle, 2018; Marshall et al., 2011), potentially reducing the risk of factors other than the treatment intervention accounting for any observed differences between the treatment and control areas.

Furthermore, the quasi-experimental studies were not all independent. In some cases, subsequent studies examined the same intervention and outcome variables, just with a longer time series and (sometimes) more-sophisticated methods. For example, the three studies examining crime outcomes of the MSIC in Sydney were very similar (Donnelly and Mahoney, 2013; Fitzgerald, Burgess, and Snowball, 2010; Freeman et al., 2005). They all reported that changes in thefts, robberies, and drug-law violations where the SCS was located were similar to changes in the rest of the city, suggesting a null effect.

In contrast, the study from Vancouver of the SCS's effect on crime used a more rigorous analytical design that accounted for underlying trends and seasonality (Myer and Belisle, 2018). It found that there was an abrupt and permanent decline in property and violent crime in the police district where the SCS was located vis-à-vis elsewhere in the city. That is, in some sense, a surprising result. Merely supervising drug use might not be expected to reduce the quantity of drugs used or the quantity of drugs purchased or sold, and those are the activities that can stimulate crime—for example, property crime committed to finance a drug purchase. Supervising drug use is intended to reduce overdose and the spread of blood-borne diseases, but neither of those outcomes directly stimulates crime. It may be that services provided by Vancouver's SCS facility besides the supervision of consumption, such as treatment referral, aid in reducing acquisitive property crime. No study reported an increase in crime associated with SCS operation.

Two overlapping studies from Sydney that examined overdose-involved outcomes found a statistically significant negative relationship with ambulance service calls for suspected opioid-involved overdoses (National Centre in HIV Epidemiology and Clinical Research, 2007; Salmon et al., 2010). Only the earlier study examined fatal overdoses, and it did not find a statistically significant effect. As mentioned, the SCS in question opened around the same time there was a severe shortage of heroin in Australia's drug markets (Weatherburn et al., 2002), so opioid overdose–involved outcomes fell precipitously in the control areas and even more precipitously near the SCS. That control area was the entire state of New South Wales, so it was not very similar to the treatment area. Therefore, it is plausible that an exogenous shock as dramatic as the

Australian heroin drought might have affected the SCS's neighborhood more strongly than it affected other parts of the state. However, the measured effect appeared strongest during the facility's hours of operation, which would be consistent with the SCS causing additional declines in overdose above and beyond that produced statewide by the heroin drought.

The Vancouver study of overdose outcomes reported even more favorable SCS effects (Marshall et al., 2011). Although overdose fell somewhat in the control areas, declines around the time and place the SCS opened were much greater, with the rate of decline in fatal overdoses falling with greater distance from the facility.

The remaining quasi-experimental studies analyzed SCSs in Barcelona and are very similar to each other (Vecino et al., 2013; Espelt et al., 2017), although the latter applied a more rigorous research design. Results from these two studies are somewhat inconsistent. Vecino et al. (2013) found no significant change in number of improperly discarded syringes in the treatment district but did report a statistically significant reduction of discarded injection equipment across the city. Espelt et al. (2017) extended Vecino et al.'s (2013) analysis by using an interrupted time series with Poisson regression and additional control covariates. After an SCS was opened in the Ciutat Vella district, the authors reported a modest but statistically significant *reduction* in the number of publicly disposed injection materials in the area but no changes in neighboring districts. After an SCS opened in Sant Martí, they reported findings that show a statistically significant and substantial *increase* in publicly disposed injection material. The authors noted that simultaneous police sweeps focused on public drug use might have confounded their analyses.

Mathematical Simulations

A variety of studies use mathematical models to extrapolate from proximate evaluation outcomes to overall effects, often within a cost-effectiveness or benefit-cost framework. Just as we urge caution when interpreting the quasi-experimental studies on SCS outcomes, we suggest the same about the eight studies labeled as "mathematical simulations" in Kennedy, Karamouzian, and Kerr's (2017) review.[35]

Only one was a simulation study in the sense of explicitly simulating the evolution of the state of some system (such as the HIV epidemic), both with and without the SCS (Bayoumi and Zaric, 2008), and that study has been criticized as producing implausible results (Des Jarlais, Arasteh, and Hagan, 2008; Pinkerton, 2010; Andresen and Jozaghi, 2012). The others primarily used Monte Carlo simulation to explore how uncertainty about parameter values could have affected outcomes that were computed from a deterministic model.

With the exception of Hedrich (2004), which was not really a simulation but just assumed that SCSs cut the mortality risk from 0.02 per 1,000 use sessions to zero, and Jozaghi (2014),

[35] There are other simulation studies that project what the benefits might be of opening SCSs in places where they do not exist. We do not discuss them here.

which examined a small, unsanctioned supervised *smoking* facility for crack users, these studies all pertain to the Insite facility in Vancouver.

Milloy et al. (2008) estimated the number of fatal overdoses averted by dividing the number of near-fatal overdoses within the SCS by an assumed ratio of near-fatal to fatal overdoses. That ratio is unknown, with plausible values differing by a factor of six, so the resulting point estimates vary from 1.9 to 11.7 deaths averted per year, and uncertainty about other parameters renders those point estimates into ranges—for example, the 11.7 comes with a plausible range from 5.4 to 18.0.

The four studies modeling Insite's effects on HIV transmission represent two camps that disagree. Andresen and Boyd (2010) and Andresen and Jozaghi (2012) assumed that the SCS causes people who perform all, most, or some of their injections at the site to also behave much more safely when they inject outside the SCS, and their articles credit Insite's SCS with averting 35 and 22 new HIV infections per year, respectively.

Pinkerton (2010, 2011) is sharply critical of Andresen and Boyd, particularly of the models (which indeed seem to have some errors; described in more detail in Pardo et al., 2018) and the assumption that consuming some drugs at Insite also alters the way those individuals use drugs outside Insite's walls. Pinkerton's 2010 and 2011 articles take a more conservative approach and credit the SCS side of Insite's suite of programs with averting only 2.8 and 5.2 new HIV infections per year, respectively, although Pinkerton credits Insite's distribution of injection equipment for use outside Insite (its SEP component) with preventing more HIV infections.

This crucial disagreement about behavioral effects boils down to how one interprets findings, such as those reported by Kerr et al. (2005). Based on a logistic regression, Kerr et al. (2005) found that those who reported using the SCS for all, most, or some of their injections were 70 percent less likely to have reported having shared injection equipment than other users. Pinkerton (2011) noted that Kerr et al. reported a difference in the proportion of people who have shared, not the number of instances of sharing. It is also not certain that Insite caused the observed differences, as Kerr et al. admit. Furthermore, even if Insite did cause behavioral change outside its walls, it is not clear how one could know that Insite's supervising of drug consumption should get the credit, as opposed to its SEP, referrals to treatment, or some other component of its multifaceted operation.

This disagreement has implications for Insite's cost-effectiveness in terms of HIV/AIDS prevention. The majority of the modeling studies assume a benefit of C$210,000 (Canadian dollars) per HIV infection prevented from lifetime averted health care costs. Using Pinkerton's estimates of 2.8 and 5.2 new HIV infections averted per year as a result of Insite's SCS function, this translates into savings of about C$0.6 million or C$1.1 million per year. That is less than Insite's cost of supervising consumption, which the author describes as C$1.5 million of Insite's approximately C$3 million annual budget.[36] Pinkerton argues for cost-effectiveness primarily

[36] It is unclear to what extent this includes fixed costs. Andresen and Boyd (2010, p. 71) noted:

based on Insite's SEP, not its SCS. By contrast, valuing Andresen and Jozaghi's (2012) estimated 22 HIV cases averted per year at C$210,000 per case produces a benefit of C$4.6 million, well in excess of the cost of operating Insite's SCS and, for that matter, all of Insite.

However, the question for policymakers is not necessarily whether to invest in SCS or do nothing but rather how much of scarce funds should be invested in SCS, compared with other alternatives, because supervising drug consumption in a facility such as Insite may be costly. Pinkerton (2010, 2011) credits Insite with supervising 220,000 injections per year, although 2017 data indicate a figure closer to 150,000 (Vancouver Coastal Health, 2018). In round terms, dividing Insite's C$1.5 million in annual SCS costs over roughly 200,000 supervised injections suggests an average cost of approximately C$7.50 per injection, and PWUO often inject multiple times per day.

For someone who averages two injections at Insite per day, monthly and annual costs would be C$450 and C$5,500, respectively. We are not aware of any studies that formally compare the costs associated with SCSs and treatment; however, these back-of-the-envelope calculations suggest that the costs of supervising consumption of a full month's worth of use might be in the same ballpark as the costs of providing methadone in the United States for the same duration,[37] although obtaining precise figures for treatment is surprisingly tricky because costs vary

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> The annual operational cost (2007) of the SIF [supervised injection facility] portion of Insite has been cited as $1.5 million (CTV News, 2008, an interview of Dr. Thomas Kerr, Principal Investigator, Insite). Operational costs of Insite have also been described as $2 million (CBC News, 2003) and $3 million (Health Canada, 2008), but these figures included such other services as addiction counselling and case management, the provision of primary healthcare, public health screening (immunizations and diagnostics), addiction and housing services, education, and peer counselling. We use the $1.5 million figure for two reasons: first, it only considers the operational costs of the SIF portion of Insite; and second, the source is the Principal Investigator contracted by Health Canada to evaluate Insite.

[37] For example, the Washington State Institute for Public Policy (2017) estimated that the annual per-participant costs for methadone were $3,769 (in 2016 dollars):

> We estimate the per-participant costs of providing methadone in addition to standard substance abuse treatment for 12 months. Costs reflect the average of costs reported in numerous cost-effectiveness studies (Rosenhack and Kosten, 2001; Jones et al., 2009; Nordlund et al., 2004; Masson et al, 2004). Costs included vary by study but generally include costs of medication, dispensing, toxicology screens, medical care related to methadone treatment, and when available, costs of equipment, administration, and clinic space. Treatment as usual in this case may include counseling or other services.

The National Institute on Drug Abuse (2018b) reported that,

> although the price for opioid treatment may vary based on a number of factors, recent preliminary cost estimates from the U.S. Department of Defense for treatment in a certified opioid treatment program (OTP) provide a reasonable basis for comparison: methadone treatment, including medication and integrated psychosocial and medical support services (assumes daily visits): $126.00 per week or $6,552.00 per year; buprenorphine for a stable patient provided in a certified OTP, including medication and twice-weekly visits: $115.00 per week or $5,980.00 per year; naltrexone provided in an OTP, including drug, drug administration, and related services: $1,176.50 per month or $14,112.00 per year.

significantly depending on the type of treatment, payer, and setting. Likewise, as far as we can tell, no study has directly compared the benefits produced by investing a similar amount of money in SCS with treatment for OUD, but the results could well depend on what assumptions are made about the extent to which SCSs change the behavior of PWUO outside the SCS facility.

In sum, although Kennedy, Karamouzian, and Kerr (2017)—who use the term *supervised consumption facility* for SCS—reported that "high-quality scientific evidence derived from the observational and simulation studies included in this review demonstrates the effectiveness of supervised consumption facilities in meeting their primary public health and order objectives" and "five [modeling] studies examined the impacts of Insite and found it to be cost-effective," when one examines these modeling studies carefully, they may be somewhat less definitive than the quotes suggest.

Other Studies

Our search also identified 18 studies that compared outcomes across nonsuitable comparison groups. An important example is comparing people who use SCSs frequently with those who use them infrequently or not at all, as in the Kerr et al. (2005) study mentioned earlier. This contrast could introduce selection bias that cannot necessarily be addressed by controlling for observable factors.[38] Another 16 studies were cross-sectional, precluding any causal inferences, or evaluated outcomes without any control case. The remainder of the 65 individual studies identified were descriptive or qualitative in nature and described in the appendix of Pardo, Caulkins, and Kilmer (2018).

Finally, there are some outcomes, both positive and negative, that are potentially associated with SCSs but are difficult to evaluate. For example, if SCS implementation makes PWUO feel more respected and less stigmatized (as suggested in some of the qualitative literature; see, for example, Kerr et al., 2007; Krusi et al., 2009; Small et al., 2009; Kappel et al., 2016), it would be hard to capture this in a traditional quasi-experimental analysis. This is because (1) quantification of these outcomes is subjective and can be difficult to measure and (2) the effects could spill over to PWUO who do not use SCSs, as well as those in other neighborhoods, thus "contaminating" potential control groups and making it harder to identify an effect. Although the reduction in stigma might manifest itself in increased uptake of health and social services, there is also a dignity aspect to these types of interventions that is hard to measure but nonetheless important to consider. On the potential negative side, SCSs might—at least in theory—extend drug-using careers or reduce property values in their vicinity, but such outcomes were not considered by the quasi-experimental evaluations we reviewed.

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[38] For example, drug users who are more risk averse or who are at a more stable point in their drug-using careers may both use the SCS more frequently and also avoid risky practices when using outside the SCS, but the less risky practices may be caused by the risk aversion or stability, not by the SCS, and might not be adequately accounted for by the control variables.

Legal Status in the United States

We anticipate a situation in which cities and possibly states wish to proceed with SCSs before federal law is changed to allow them. This section reviews some relevant legal considerations for that situation, as well as associated issues, such as whether SCS staff could lose their medical practice licenses or face tort liability for harms caused by users whose consumption they supervise. In many cases, decisive statements are not possible because courts have not yet ruled on these matters.

Federal Law

The general consensus is that SCSs are proscribed under federal law; the fundamental question is whether the federal law definitively preempts state law in this area. Two sections of the CSA are the most relevant to the proscription of an SCS under federal law; one prohibits drug possession, and the other prohibits the use of property for manufacturing, distributing, or using a controlled substance.[39] The CSA additionally explicitly states that the Commerce Clause applies to drug control issues in individual states because

> [c]ontrolled substances manufactured and distributed *intra*state cannot be differentiated from controlled substances manufactured and distributed *inter*state. Thus, it is not feasible to distinguish, in terms of controls, between controlled substances manufactured and distributed *inter*state and controlled substances manufactured and distributed *intra*state. (21 U.S.C. 801[5]; emphasis added)

The application of the CSA to intrastate activity was challenged in *Gonzales v. Raich.* In *Raich*, one concern was that individuals growing cannabis (even for personal use) could affect the market as a whole, but it is unlikely that an SCS would have an impact on the supply and demand sides of the opioid market (Burris et al., 2009). However, other language in *Raich* suggests a broader concern: that allowing intrastate cannabis "would undermine the orderly enforcement of the entire regulatory scheme." This argument can more easily be applied to SCSs; systematically allowing illegal activity to occur could be seen as undermining the general regulatory scheme of the CSA.

However, the supremacy of the CSA was also considered in *Gonzales v. Oregon.* In this case, the state passed the Oregon Death with Dignity Act (ODWDA), which exempted physicians from criminal or civil liability if they prescribed or dispensed a dose of lethal drug to a terminally ill patient (and complied with the safeguards in the ODWDA). Then–U.S. Attorney General John Ashcroft issued a rule declaring that this was not legitimate medical practice and that the actions were unlawful under the CSA (Ashcroft, 2001). The Court held that the ODWDA was exactly the kind of state regulation of medical practice envisioned under the CSA (21 U.S.C. 903). Ashcroft did not have the authority to issue this rule, because the CSA is a

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[39] 21 U.S.C. 844 prohibits drug possession, and 21 U.S.C. 856 (the "crack house" statute) deals with properties in which drug manufacture or use is occurring; 21 U.S.C. 846 makes it a crime to conspire to violate the CSA, and 18 U.S.C. 2 makes it a crime to aid in the commission of any offense against the United States.

statute aimed at combating recreational drug use and trafficking, not regulating the practice of medicine in general; "[t]o read prescriptions for assisted suicide as 'drug abuse' under the CSA is discordant with the phrase's consistent use throughout the Act, not to mention its ordinary meaning" (*Gonzalez v. Oregon*). It is arguable whether applying the CSA to a state SCS would be construed as the same type of federal overreach that the Court rejected in *Gonzales v. Oregon.*

Ultimately, federal suppression of a state SCS would pose a serious question about the extent of Congress's authority under the Commerce Clause and the CSA (Burris et al., 2009). The *Oregon* decision demonstrates the limits of how far the CSA can stretch, and the *Raich* decision holds that states cannot pass laws protecting their citizens from federal enforcement of the CSA. However, neither addressed the question of whether the state law at issue was *preempted* by the CSA.

The Supremacy Clause in Article VI of the U.S. Constitution states that "the laws of the United States . . . shall be the supreme law of the land" (U.S. Const. art. VI, cl. 2), establishing that federal law preempts state law on a certain issue if the two cannot coexist. However, a preemption analysis first requires a court to assess the purpose of the federal legislation to determine whether Congress intended to preempt state law. The CSA was drafted "to control illicit trafficking and to regulate legitimate uses of psychotropic substances in this country" (21 U.S.C. 801a[1]) and authorizes federal control of drugs (both legal and illegal) under the Commerce Clause of the Constitution. The statute specifically disclaims the government's intent to preempt state law:

> No provision of this subchapter shall be construed as indicating an intent on the part of Congress to occupy the field in which that provision operates, including criminal penalties, to the exclusion of any State law on the same subject matter which would otherwise be within the authority of the State, unless there is a positive conflict between that provision of this subchapter and that State law so that the two cannot consistently stand together. (21 U.S.C. 903)

Given this statutory language, there is no express preemption of state laws in this domain. Preemption,[40] however, does not necessarily need to be explicit; implied preemption may be established through judicial interpretation. There are several types of implied preemption. The one most likely applicable to a state-authorized SCS is *obstacle preemption,* in which the state law is somehow an obstacle to the purposes of the federal scheme. Assessing whether a state law "'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress' is a matter of judgment, to be informed by examining the federal statute as a whole and identifying its purpose and intended effects" (*Crosby v. National Foreign Trade Council,* quoting *Hines v. Davidowitz*).

One can imagine arguments as to why laws authorizing SCSs are not inconsistent with the purposes and objectives of the CSA. For example, creating a space in which PWUO can interact

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[40] The preemption doctrine is the idea that a higher legal authority (here, the federal government) will displace or preempt the law of a lower legal authority (here, a state government).

with the medical system and perhaps become more comfortable with seeking treatment could be argued to be in line with the CSA objective of "combating drug abuse."

There is also case law suggesting that the CSA need not preempt state statutes that decriminalize or even legalize possession of drugs. Several state courts have ruled that their medical cannabis statutes are not preempted by federal law, and the U.S. Supreme Court has denied to review those decisions in several of the cases.[41] The cases that have found that state laws are preempted by federal law are those addressing laws that required affirmative steps (e.g., providing unemployment benefits for those fired for medical cannabis use) rather than legalization or decriminalization.[42] Note though that no *federal* courts have yet addressed the preemption argument with regard to medical cannabis statutes or other drug laws.

Even if a court did find that the CSA preempted state law, the federal government still could not compel a state to enforce the CSA or otherwise "enact or administer a federal regulatory program" (*Printz v. United States*). Nor could a state be compelled to pass a law coextensive with the CSA, as this would be considered commandeering:[43] "No matter how powerful the federal interest involved, the Constitution simply does not give Congress the authority to require the States to regulate" (*New York v. United States*).

In an article about state cannabis laws, Erwin Chemerinsky and colleagues set forth one way a state could exploit the limits on commandeering to counteract preemption (Chemerinsky et al., 2015). First, a state could repeal all its drug laws, and the federal government could not require the state to reenact those laws or to enforce the federal laws without running afoul of anticommandeering. The state could then pass new laws criminalizing opioid possession for all those who do not have a card or other evidence of participating in an SCS. Passing such a law that, in fact, criminalizes opioid possession for most people would be difficult to deem an "obstacle" to the CSA.

In the absence of explicit authorization on the federal level, the 2009 Ogden Memorandum (Ogden, 2009) and 2013 Cole Memorandum (Cole, 2013) show that the federal government can

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[41] See, for example, *Ter Beek v. City of Wyoming* (unanimous decision holding that the CSA does not preempt the Michigan Medical Marihuana Act); *People v. Crouse* (holding that the CSA does not preempt state cannabis provisions and ordering the return of seized medical cannabis to the patient); *Town of Wakefield v. Coakley* (rejecting conflict and obstacle preemption arguments against state medical cannabis provisions); *San Diego County v. San Diego NORML* (allowing patients to obtain medical cannabis identification cards because they do not positively conflict with the CSA; simultaneous compliance with both sets of laws is not impossible, and the identification card provisions do not pose significant impediment to the objectives of the CSA); and *City of Garden Grove v. Superior Court* (holding that a medical cannabis patient was entitled under state law to the return of seized cannabis and that this return was not precluded by federal preemption). But see Mikos, 2013 (discussing both cases that have found preemption and those that have not).

[42] See, for example, *Emerald Steel Fabricators, Inc. v. Bureau of Labor & Indus.*; and *Washburn v. Columbia Forest Prods., Inc.*; but see also Bolitho, 2017 (criticizing the Obama administration's derogation of their duty under the Take Care Clause).

[43] In this context, *commandeering* refers to the federal government forcing a state to take an action that it otherwise would not—here, enforcing federal law. Commandeering has been held to be unconstitutional under the Tenth Amendment ("The powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved to the States respectively, or to the people").

chose to deprioritize enforcing federal drug law in situations where persons are complying with state law, although these policies can easily change (e.g., the rescinding of the Cole Memorandum in January 2018). Although the attorney general could issue a regulation under the CSA that created exceptions to criminal liability for proprietors, employees, and clients of SCSs (21 U.S.C. 871), this seems unlikely in the immediate future.[44]

Congress has another option that is intermediate between explicit authorization and merely deprioritizing enforcement against SCSs. The Rohrabacher-Blumenauer Amendment blocks the U.S. Department of Justice from using federal funds to prevent state implementation of medical cannabis laws.[45] Congress could pass a similar statute forbidding federal funds from being used to prevent implementation of SCSs, although SCSs do not enjoy the same level of popular support as medical cannabis (McGinty et al., 2018; Quinnipiac University, 2018).

State and Local Authority

The baseline ability for states or municipalities to open an SCS falls under their broad "police powers,"[46] which include regulating public health. On the state level, the strongest legal path to an SCS would be authorization by a state legislature or by a referendum in ballot-initiative states. This course of action would decrease the likelihood of the SCS facing nuisance lawsuits or other violations of state land-use law. It would also provide the strongest position for both avoiding a challenge from the federal government and facing that challenge if it is brought to court; a similar situation currently exists in states that have authorized medicinal or recreational cannabis.

Another state-level approach would be administrative authorization of an SCS. This could take the form of an executive order from the governor or a regulation issued by a health agency. Executive power, however, generally only extends to authorizing activities that do not conflict with existing law, and executive authority to alter controlled substances rules is generally narrow, so a dissenting state legislature could challenge such an action as exceeding the executive's authority. On the other hand, health agencies in all states have rule-making authority to protect public health, and, in some states, health commissioners have the legal authority to

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[44] The U.S. attorney for Vermont has specifically denounced one county's intention to open an SCS (U.S. Department of Justice, U.S. Attorney's Office, District of Vermont, 2017), and in April 2018, a DEA spokesperson told the *Washington Post* that SCSs violate the CSA and are "subject to being prosecuted" (Cunningham, 2018). More recently, Deputy Attorney General Rod Rosenstein published an op-ed in the *New York Times* arguing that SCSs "create serious public safety risks," "destroy the surrounding community," "normalize drug use and facilitate addiction," and do not help PWUO to stop using (Rosenstein, 2018).

[45] The current authorization of the amendment is included in the Consolidated Appropriations Act, 2018 (Pub. L. 115-141), passed on March 23, 2018.

[46] In constitutional law, the "police power" is a state's authority to regulate behavior within its borders for the betterment of its residents' health, safety, and general welfare. It is a loose, nebulous concept, which makes defining the boundaries and scope of the states' police powers a thorny legal question.

allow activity related to controlled substances that would otherwise be prohibited under state law.[47]

A third approach would be authorization by a municipal governing body.[48] Most cities have police powers within their borders analogous to the police powers of the state and therefore have wide discretion when it comes to implementing public health programs that are supported by reasonable evidence of efficacy.[49] However, a local ordinance would be vulnerable to a challenge based on preemption by state drug laws. The SCS could also be vulnerable to interference by local police, as many municipal police departments are deputized to enforce state laws (Sherman, Hunter, and Rouhani, 2017).[50]

Before opening an SCS, a state or locality could seek a declaratory judgment in a federal court,[51] which would lead to an official judicial interpretation of the applicability of the Controlled Substances Act to SCSs. This has the advantage of offering legal certainty, but if the court disagreed with the arguments above, it is possible that an SCS would be unable to open when it might have had the potential to operate indefinitely under legal uncertainty.

Legal Issues for SCS Operators

The biggest legal issue for operators of an SCS would be the "crack house statute," which states that it is criminally unlawful to

> 1. knowingly open, lease, rent, use, or maintain any place, whether permanently or temporarily, for the purpose of manufacturing, distributing, or using any controlled substance;
> 2. manage or control any place, whether permanently or temporarily, either as an owner, lessee, agent, employee, occupant, or mortgagee, and knowingly and intentionally rent, lease profit from, or make available for use, with or without compensation, the place for the purpose of unlawfully manufacturing, storing, distributing, or using a controlled substance. (21 U.S.C. 856)

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[47] For example, New York public health law PBH Section 3381 does not itself decriminalize possession of hypodermic needles but rather allows the public health commissioner to authorize groups of individuals to possess the otherwise-illegal hypodermic syringes and needles under PEN Section 220.45 (see New York State Senate, undated). See also *L.B. v. Town of Chester* ("Once an individual is authorized by the Commissioner, that ends their liability as an 'unlawful' possessor under the Penal Law").

[48] See Wilson, 2018, for an argument for using cities' home-rule powers to create local strategies to combat drug addiction.

[49] This is the direction taken by some cities in establishing SEPs without authorization from their state governments (Burris et al., 1996).

[50] However, see *Smith v. Hickenlooper* (holding that law enforcement officers cannot claim a "crisis of conscience" as to whether to enforce the state versus federal law).

[51] A *declaratory judgment* provides a binding legal ruling resolving legal uncertainties for litigants in the early stages of a case or controversy, but it does not provide for enforcement of any remedies. It is generally requested when litigation seems likely or as part of a counterclaim to litigation that has already been filed.

If found liable, property owners could be subject to criminal penalties, civil penalties, and civil forfeiture of the property on which the SCS was run (21 U.S.C. 856[b], 856[d]; 21 U.S.C. 881). However, conviction under the statute requires that the operation of the facility be "knowingly open[ed] . . . for the purpose of manufacturing, distributing, or using" a controlled substance (21 U.S.C. 856[a][1]). Prior case law has noted that *purpose* and *knowledge* are distinct elements.[52] An SCS could argue that allowing drug use is not the *purpose* of the SCS, but the means to achieve other purposes (e.g., reduced overdose deaths, reduced blood-borne diseases), just as the purpose of using morphine in a hospital is not the use of morphine but the relief of pain. If the mere knowledge that drugs will be used on the premises is enough to establish that drug use is the purpose of the defendant, then the purpose element adds nothing to the state-of-mind requirement that is not already captured in the element of *knowingly*.[53] Interpreting the statute without distinguishing the two terms violates the canon of construction of surplusage—that is, where one reading of a statute would make one or more parts of the statute redundant and another reading would avoid the redundancy, the second option is preferred. As an analogy, one might look to previous issues with SEPs. Drug paraphernalia laws generally prohibit the distribution of any item with knowledge that it will be used for the purpose of illegal drug consumption. In some states, local governments took the position that SEPs did not violate the paraphernalia laws in the first place because the *purpose* was not illegal drug consumption, but the betterment of public health.[54] However, these cases generally involved conflicts between local and state law, rather than (hypothetical) state and federal law.

Other provisions of the CSA could also be used to counter an argument that an SCS violates Section 856.[55] For instance, Section 1101 provides that

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[52] *United States v. Chen.*

[53] Look at the example of nuisance laws; in general, these laws prohibit activity that involves a property being used for unlawful conduct—e.g., N.Y. Penal Law Section 240.45 (New York State, 2008). If unauthorized by the state, an SCS would almost certainly be subject to this provision. However, if the SCS was state-authorized, the employees and clients would not be engaging in "unlawful conduct," nor would the premises be maintained for the purpose of engaging in unlawful conduct. Similarly, state authorization should give SCS operators a reasonable claim of "lawfulness" against a federal statute like Section 856 that is predicated on knowingly maintaining a place for the purpose of unlawful drug activity.

[54] See, for example, *Spokane County Health District v. Brockett.* This holds that

> the needles at issue in this case are 'drug paraphernalia.' Those distributing the needles know they will be used to inject controlled substances unlawfully. Nevertheless, plaintiffs argue, the needle exchange program is authorized under the Washington Constitution, statutes granting broad powers to local health officials, and the omnibus AIDS act. Therefore, they conclude, the drug paraphernalia act, which is aimed at criminal conduct, simply does not apply to their actions. We agree.

[55] As this report was going to press, Kreit (forthcoming) published an article proposing

> a novel solution to the conflict between cities and the federal government over safe injection sites in the form of an obscure provision of the Controlled Substances Act that immunizes officials who are engaged in the enforcement of state and local laws relating to controlled substances. Although the CSA's immunity provision was likely written with undercover police officers in mind, the plain language of the law seems to apply to a government-run safe injection site. A handful of courts have already relied on the statute to immunize government officials who were engaged in

> Control of drug abuse requires the development of a comprehensive, coordinated long-term Federal strategy that encompasses both effective law enforcement against illegal drug traffic and *effective health programs to rehabilitate victims of drug abuse. . . . Local governments with high concentrations of drug abuse should be actively involved in the planning and coordination of efforts to combat drug abuse.* (21 U.S.C. 1101; emphasis added)

It is possible to argue that opening an SCS in an area with high concentrations of drug use (a descriptor that applies to most of the areas that are considering opening a facility at the moment) is part of that area's plan to address drug use. Relatedly, Section 801a states that "nothing in the Convention will interfere with ethical medical practice in this country as determined by the Secretary of Health and Human Services on the basis of a consensus of the views of the American medical and scientific community" (21 U.S.C. 801a). The American Medical Association (2017) called for SCS pilot studies. Although the association does not dictate the policy of the U.S. Department of Health and Human Services, it is a strong signal from the medical community.

Legal Issues for Medical Staff

SCS medical staff commonly supervise and educate clients about safe and hygienic injection techniques but do not assist them with injection. This decreases their likelihood of liability; however, professional medical staff may rightly worry about losing their professional licensing or prescribing privileges. States could reassure doctors and nurses in this regard by introducing explicit statutory language making the SCS staff roles fully compliant with state law and endorsing their responsibilities in an SCS as *good* medical practice, not medical practice that poses a threat to public health, safety, or welfare (see, for example, Fitzgerald, Abel, and Bates, 2017). Medical staff might also worry about malpractice lawsuits because malpractice insurance generally excludes "criminal activity" from coverage, or courts might disallow insurance payouts in SCS cases as contrary to public policy.

Staff could have clients sign liability waivers. Although waivers would not protect doctors in instances of gross negligence or worse, having a signed waiver might deter lawsuits. Complicating that protection is the question of whether someone with OUD can give informed consent. It is generally clear that acute intoxication can lead to decisional impairment, and it is suggested that acute withdrawal may be similarly incapacitating (National Bioethics Advisory Commission, 1998, p. 9). The diagnosis of a substance use disorder does not indicate that decisionmaking capacity is necessarily impaired, but it is possible that there may be some

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> the enforcement of state medical marijuana laws. The logic of those decisions supports immunizing the operators of government-run safe injection sites. To be sure, there is other precedent that points toward a narrower reading of the immunity provision and so the case for applying it to safe injection sites is not open-and-shut. But if courts were to agree with the interpretation of the immunity provision outlined in this article, cities would be free to open safe injection sites without putting their employees at risk of federal prosecution.

We look forward to thinking more about this argument and seeing it discussed by legal scholars and those participating in SCS debates.

impairment even outside the two acute circumstances described above. However, it seems unlikely that, in the case of an SCS, the argument that users were unable to give informed consent to a liability waiver because of a drug craving or a state of withdrawal would succeed. Because the SCS is not providing the drugs, there is no coercive inducement for users to sign the waiver. Clients are exchanging their ability to sue for the increased safety of sterile supplies, staff who can assist in case of an overdose, and perhaps even the opportunity to test their drugs. Anyone who did not want to sign a waiver at an SCS would be free to leave and to engage in the same actions they did prior to the opening of the SCS.

Tort Liability

If a client of an SCS leaves while under the influence and causes harm (e.g., falls asleep at the wheel on the way home), the client would certainly be individually liable for the damages. Would the SCS itself face any liability? Commercial providers of intoxicants have been liable under dram shop laws, but social hosts have been subject to a different legal framework (see, for example, Coppock, 2009). Under the common law, social hosts did not have a legal duty of care, but courts have more recently been inclined to find a legal duty. A case might be made that operators of SCSs should face the same type of liability as a social host at a "bring your own beer" party.[56]

Insights from Interviews and Focus Groups

Key informants were invited to comment on whether they thought that SCSs could help improve outcomes for PWUO and whether they believed that SCSs would be acceptable to the community.[57] Table 4.3 lists all themes that emerged and their frequency (i.e., low, medium, high, or very high frequency is indicated if the theme emerged in 1–25 percent, 26–50 percent, 51–75 percent, or 76–100 percent of all transcripts, respectively) that respond to these two questions. We include the indicator of the relative frequency with which the themes emerged to show how the emergence of themes differed between professionals and PWUO. Key findings pertaining to SCS based on insights from interviews and focus groups are discussed after the table.

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[56] The question of whether liability attaches to a social host is contingent on the five elements of a prima facie negligence case: the existence of a legal duty, breach of that duty, factual cause, proximate cause, and physical harm.

[57] The definition of *SCSs* that interviewers and focus group facilitators used to describe the intervention to key informants who were not familiar with SCSs is listed in Chapter 2 and in the interview and study protocols in Appendixes A–C of Ober et al. (2018).

Table 4.3. SCS Themes Cited by Key Informants (Professionals and PWUO)

Theme	Frequency	
	Professionals[a] *N* = 80	PWUO[b] *N* = 79
Could SCS Help Improve Outcomes for PWUO?		
Reasons SCS could help improve outcomes		
SCSs could help prevent overdose deaths	Medium	Very high
SCSs could help link PWUO to treatment and other resources	Medium	High
SCSs could provide PWUO with a safe, nonjudgmental place to use	Low	Medium
SCSs could provide clean needles and information to prevent HIV, hepatitis C, and abscesses	Low	Medium
SCSs could provide drug composition testing	Low	Medium
Reasons SCSs might not help improve outcomes		
PWUO would view it as a law enforcement trap	Medium	High
SCSs would be stigmatizing for PWUO	Medium	Medium
PWUO would be reluctant to travel to an SCS after purchasing drugs; they want to use immediately	Low	High
SCSs would enable or perpetuate opioid use	Medium	Very high
SCSs would create a forum for drug dealers	Low	Medium
PWUO do not want to be monitored while using	Low	Low
SCSs increases risks for PWUO	Low	Low
Not sure if SCSs would help improve outcomes		
Need to see more evidence	Medium	Low
Would SCS Be Acceptable to the Community?		
SCS implementation would be impeded by community values and local culture	Very high	Medium
Community members would believe that an SCS enables or perpetuates use	Medium	Low
Community would say "not in my backyard" (NIMBY)	Medium	Low
Stigma against PWUO would impede implementation	Medium	Medium
An SCS is not a priority in the community right now	Medium	Low
There might be more buy-in for SCSs in "less rural" areas	Low	N/A
Rural communities do not have the resources to implement SCSs	Low	N/A
Community members would believe that an SCS normalizes opioid use	Low	Low
SCSs would affect neighborhoods and community resources	Low	Low
SCSs would "clean up" the streets and reduce strain on police and emergency medical services	Low	Low

NOTES: N/A: Theme did not arise in any transcript; Low frequency: Theme arose in 1–25% of transcripts; Medium frequency: Theme arose in 26–50% of transcripts; High frequency: Theme arose in 51–75% of transcripts; Very high frequency: Theme arose in 76–100% of transcripts.

[a] Professionals include all non-PWUO key informants who participated in an interview (*N* = 44) or focus group (*N* = 5 groups and 36 providers) who were invited to participate based on their current profession. We are mindful that at least some of consulted PWUO may also be professionals. The use of *professional* in this report is not a comment on any individual's job status; rather, it is meant to capture the fact that we invited one group of key informants to inform the research project on the grounds of their occupations.

[b] PWUO who participated in ten focus groups.

Overall, there were four key insights about SCSs. First, key informants noted harm-reduction benefits to SCSs but also perceived drawbacks, such as that SCS may enable or perpetuate opioid use, and practical barriers, including PWUO's unwillingness to travel far to an SCS after purchasing opioids. Among the main benefits noted were preventing overdose and disease, offering links to treatment, providing a safe, judgment-free place for PWUO to use, and supporting drug composition testing. Some professionals and PWUO also thought that SCSs would enable or perpetuate opioid use. PWUO in all focus groups, rural and urban, saw an SCS as impractical because of the time needed to travel to an SCS after purchasing drugs, with rural

PWUO emphasizing its impracticality because of overall transportation challenges. PWUO and professionals also worried that an SCS would be a law enforcement trap for PWUO. Some PWUO currently receiving MT noted that an SCS could provide a safe place to use while waiting to get into treatment.

Second, despite supporting the benefits of SCSs, interviewees and focus group participants generally believed that their communities as a whole likely would not currently accept an SCS as a viable strategy for helping address the opioid crisis because of cultural, resource, and practical barriers. Although this view was particularly salient among informants from the rural counties—neither of which currently has an SEP or adequate naloxone distribution, detoxification services, treatment provision, or sober living facilities—even urban informants who supported the concept felt that an SCS in their communities was not the current priority for addressing the opioid crisis. Key informants generally believed that putting funding into evidence-based programs that already have gained traction with community members would be a more prudent investment of limited available resources. Moreover, key informants cited multiple reasons that SCSs likely might not be acceptable to community members, including conservative political and cultural landscapes, lack of endorsement of a harm-reduction approach to OUD, long-standing stigma and fear around addiction, and general "NIMBYism" around placing such facilities in areas that would be accessible to PWUO.

Third, despite cultural and policy-related barriers, implementation may be more feasible in urban communities with existing (and perhaps more long-standing) harm-reduction programs, greater treatment resources, and adequate transportation, particularly if there is evidence to support it. Although some interviewees and focus group participants had reservations about SCSs and believed that their communities have other, more-pressing priorities, professional interviewees in the two urban communities were more inclined to believe that with education, evidence, and time, SCSs could eventually be accepted by community members, as SEP and MT have been accepted, at least by key stakeholders and policymakers. This was particularly the case in Cuyahoga County, where there has been an SEP since 1995, first authorized only through local emergency orders, and then legalized statewide in 2013.

Fourth, as with HAT, publication of evidence on SCSs and community education were seen as essential in fostering community acceptance of SCSs. A number of key informants expressed belief that more education around SCSs and published evidence would facilitate acceptance and generate potential community buy-in, on the assumption that there is adequate evidence of SCS effectiveness. This call for evidence was also made by key informants who were skeptical of SCSs or expressed reservations about the SCS model. Among other steps that could help address community concerns toward SCS were integrating the service with an existing medical facility and introducing a mobile supervision service, with the perceived dual benefit of reaching PWUO who might not come to a fixed SCS and of minimizing neighborhood concerns associated with a fixed SCS location. However, neither of these steps was fully endorsed as adequate for addressing community concerns.

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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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References

Albertson, T.E., Derlet, R.W., Van Hoozen, B.E., 1999. Methamphetamine and the expanding complications of amphetamines. West. J. Med. 170, 214–219.

Australian Institute of Health Welfare, 2008. 2007 National Drug Strategy Household Survey: First Results. Drug Statistics Series No. 20. AIHW, Canberra, AIHW cat. no. PHE 66.

Bailey, D.N., Shaw, R.F., 1989. Cocaine- and methamphetamine-related deaths in San Diego County (1987): homicides and accidental overdoses. J. Forensic Sci. 34, 407–422.

Baylen, C., Rosenberg, H., 2006. A review of the acute subjective effects of MDMA/ecstasy. Addiction 101, 933–947.

Burgess, C., O'Donohoe, A., Gill, M., 2000. Agony and ecstasy: a review of MDMA effects and toxicity. Eur. Psychiatry 15, 287–294.

Coffin, P.O., Galea, S., Ahern, J., Leon, A.C., Vlahov, D., Tardiff, K., 2003. Opiates, cocaine and alcohol combinations in accidental drug overdose deaths in New York City, 1990–98. Addiction 98, 739–747.

Cohen, R.S., 1996. Adverse symptomatology and suicide associated with the use of methylenedioxymethamphetamine (MDMA; "Ecstasy"). Biol. Psychiatry 39, 819–820.

Darke, S., Degenhardt, L., Mattick, R., 2007. Mortality amongst Illicit Drug Users. Cambridge University Press, Cambridge.

Darke, S., Kaye, S., Duflou, J., 2005. Cocaine-related fatalities in New South Wales, Australia 1993–2002. Drug Alcohol Depend. 77, 107–114.

Degenhardt, L., Dunn, M., 2007. Ecstasy. In: Ross, J. (Ed.), Illicit Drug use in Australia: Epidemiology, Use Patterns and Associated Harm, 2nd edition. Commonwealth of Australia, Canberra, pp. 37–44.

Degenhardt, L., Roxburgh, A., 2007a. 2005 Cocaine and Methamphetamine related Drug-induced Deaths in Australia. National Drug and Alcohol Research Centre, Sydney.

Degenhardt, L., Roxburgh, A., 2007b. Accidental Drug-induced Deaths due to Opioids in Australia, 2005. National Drug and Alcohol Research Centre, Sydney.

Duflou, J., Mark, A., 2000. Aortic dissection after ingestion of "ecstasy" (MDMA). Am. J. Forensic Med. Pathol. 21, 261–263.

Gable, R.S., 2004. Acute toxic effects of club drugs. J. Psychoactive Drugs 36, 303–313.

Gill, J., Hayes, J., deSouza, I., Marker, E., Stajic, M., 2002. Ecstasy (MDMA) deaths in New York City: a case series and review of the literature. J. Forensic Sci. 47, 121–126.

Gouzoulis-Mayfrank, E., Daumann, J., 2006. The confounding problem of polydrug use in recreational ecstasy/MDMA users: a brief overview. J. Psychopharmacol. (Oxf.) 20, 188–193.

Gowing, L., Henry-Edwards, S., Irvine, R., Ali, R., 2002. The health effects of ecstasy: a literature review. Drug Alcohol Rev. 21, 53–63.

Hall, A.P., Henry, J.A., 2006. Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management. Br. J. Anaesth. 96, 678–685.

Kalant, H., 2001. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. CMAJ 165, 917–928.

Kalant, H., Kalant, O.J., 1975. Death in amphetamine users: causes and rates. Can. Med. Assoc. J. 112, 299–304.

Karch, S.B., 2002. Karch's Pathology of Drug Abuse. CRC Press, Boca Raton.

Karch, S.B., Stephens, B.G., Ho, C.H., 1999. Methamphetamine-related deaths in San Francisco: demographic, pathologic, and toxicological profiles. J. Forensic Sci. 44, 359–368.

Kaye, S., Darke, S., 2004. Non-fatal cocaine overdose among injecting and non-injecting cocaine users in Sydney, Australia [see comment]. Addiction 99, 1315–1322.

Kaye, S., Darke, S., Duflou, J., McKetin, R., 2008. Methamphetamine-related fatalities in Australia: demographics, circumstances, toxicology and major organ pathology. Addiction 103, 1353–1360.

Kaye, S., McKetin, R., Duflou, J., Darke, S., 2007. Methamphetamine and cardiovascular pathology: a review of the evidence. Addiction 102, 1204–1211.

Lai, T., Hwang, J., Fang, C., Chen, W., 2003. Methylene 3,4 dioxymethamphetamine-induced acute myocardial infarction. Ann. Emerg. Med. 42, 759–762.

Lester, S., Baggott, M., Welm, S., Schiller, N., Jones, R., Foster, E., 2000. Cardiovascular effects of 3,4-methylenedioxymethamphetamine. Ann. Intern. Med. 133, 969–973.

Libiseller, K., Pavlic, M., Grubwieser, P., Rabl, W., 2005. Ecstasy—deadly risk even outside rave parties. Forensic Sci. Int. 153, 227–230.

Liechti, M., Kunz, I., Kupferschmidt, H., 2005. Acute medical problems due to Ecstasy use. Swiss Med. Weekly 135, 652–657.

Logan, B., Fligner, C.L., Haddix, T., 1998. Cause and manner of death in fatalities involving methamphetamine. J. Forensic Sci. 43, 28–34.

Lora-Tamayo, C., Tena, T., Rodriguez, A., 1997. Amphetamine derivative related deaths. Forensic Sci. Int. 85, 149–157.

Mendelson, J., Jones, R.T., Upton, R., Jacob, P., 1995. Methamphetamine and ethanol interactions in humans. Clin. Pharmacol. Ther. 57, 559–568.

Milroy, C., Clark, J., Forrest, A., 1996. Pathology of deaths associated with "ecstasy" and "eve" misuse. J. Clin. Pathol. 49, 149–153.

Patel, M., Belson, M., Wright, D., Lu, H., Heninger, M., Miller, M., 2005a. Methylenedioxymethamphetamine (ecstasy)-related myocardial hypertrophy: an autopsy study. Resuscitation 66, 197–202.

Patel, M., Wright, D., Ratcliff, J., Miller, M., 2004. Shedding new light on the "safe" club drug: methylenedioxymethamphetamine (ecstasy)-related fatalities. Acad. Emerg. Med. 11, 208–210.

Patel, M.M., Belson, M.G., Longwater, A.B., Olson, K.R., Miller, M.A., 2005b. Methylenedioxymethamphetamine (ecstasy)-related hyperthermia. J. Emerg. Med. 29, 451–454.

Petitti, D., Sidney, S., Quesenberry, C., Bernstein, A., 1998. Stroke and cocaine or amphetamine use. Epidemiology 9, 596–600.

Qasim, A., Townend, J., Davies, M., 2001. Ecstasy induced acute myocardial infarction. Heart 85, e10.

Quinn, C., Breen, C., White, B., 2004, June. Illicit Tablet Market in Victoria. Party Drug Trends Bulletin. National Drug and Alcohol Research Centre, Sydney.

Raikos, N., Tsoukali, H., Psaroulis, D., Vassiliadis, N., Tsoungas, M., Njau, S., 2002. Amphetamine derivative related deaths in northern Greece. Forensic Sci. Int. 128, 31–34.

Rosenson, J., Smollin, C., Sporer, K., Blanc, P., Olson, K., 2007. Patterns of ecstasy-associated hyponatremia in California. Ann. Emerg. Med. 49, 164–171.

Schifano, F., 2004. A bitter pill. Overview of ecstasy (MDMA, MDA) related fatalities. Psychopharmacology 173, 242–248.

Schifano, F., Corkery, J., Deluca, P., Oyefeso, A., Ghodse, A., 2006. Ecstasy (MDMA, MDA, MDEA, MBDB) consumption, seizures, related offences, prices, dosage levels and deaths in the UK (1994–2003) (United kingdom). J. Psychopharmacol. (Oxf.) 20, 456–463.

Schifano, F., Oyefeso, A., Corkery, J., Cobain, K., Jambert-Gray, R., Martinotti, G., Ghodse, A., 2003a. Death rates from ecstasy (MDMA, MDA) and polydrug use in England and Wales 1996–2002. Hum. Psychopharmacol. 18, 519–524.

Schifano, F., Oyefeso, A., Webb, L., Pollard, M., Corkery, J., Ghodse, A., 2003b. Review of deaths related to taking ecstasy, England and Wales, 1997–2000. BMJ 326, 80–81.

SPSS Inc., 2006. SPSS for Windows, Rel. 14.0.2. SPSS Inc., Chicago.

Stafford, J., Sindicich, N., Burns, L., 2008, December. An overview of the 2008 EDRS: the regular ecstasy user survey findings. In: EDRS Drug Trends Bulletin. National Drug and Alcohol Research Centre, Sydney.

Tardiff, K., Marzuk, P.M., Leon, A.C., Portera, L., Hartwell, N., Hirsch, C.S., Stajic, M., 1996. Accidental fatal drug overdoses in New York City: 1990–1992. Am. J. Drug Alcohol Abuse 22, 135–146.

Topp, L., Hando, J., Dillion, P., Roche, A., Solowij, N., 1999. Ecstasy use in Australia: patterns of use and associated harm. Drug Alcohol Depend. 55, 105–115.

Westover, A.N., McBride, S., Haley, R.W., 2007. Stroke in young adults who abuse amphetamines or cocaine. Arch. Gen. Psychiatry 64, 495–502.

Wetli, C.V., Wright, R.K., 1979. Death caused by recreational cocaine use. JAMA 241, 2519–2522.

Zhu, B.L., Oritani, S., Shimotouge, K., Ishida, K., Quan, L., Fujita, M.Q., Ogawa, M., Maeda, H., 2000. Methamphetamine-related fatalities in forensic autopsy during 5 years in the southern half of Osaka city and surrounding areas. Forensic Sci. Int. 113, 443–447.

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REVIEW ARTICLE

Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management

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Since the late 1980s 'Ecstasy' (3,4-methylenedioxymethamphetamine, MDMA) has become established as a popular recreational drug in western Europe. The UK National Criminal Intelligence Service estimates that 0.5–2 million tablets are consumed weekly in Britain. It has been reported that 4.5% of young adults (15–34 yr) in the UK have used MDMA in the previous 12 months. Clinically important toxic effects have been reported, including fatalities. While the phenomenon of hyperpyrexia and multi-organ failure is now relatively well known, other serious effects have become apparent more recently. Patients with acute MDMA toxicity may present to doctors working in Anaesthesia, Intensive Care and Emergency Medicine. A broad knowledge of these pathologies and their treatment is necessary for anyone working in an acute medical speciality. An overview of MDMA pharmacology and acute toxicity will be given followed by a plan for clinical management.

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Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) has been described as 'the love drug' and is also known under a number of other names including 'XTC', 'Adam' or simply 'E'. It became established as a dance drug, popular at 'rave' parties and is taken for its mood-enhancing properties, principally the 3 Es; energy, empathy and euphoria.[14] According to the British Crime Survey for 2000, 5% of 16–19-yr-olds use Ecstasy.[34] In England during 1995–6 there were 18 deaths related to Ecstasy.[19] From 1997 to 2000 there were 81 Ecstasy-related deaths in England and Wales.[59] The risk of death for first-time users has been estimated to be between 1 in 2000 to 1 in 50 000.[19]

The immediate effects of Ecstasy vary from almost universal minor symptoms to those that are rare but potentially life-threatening. Minor side-effects include trismus, tachycardia and bruxism. Delayed effects include midweek 'lows' and a prolonged 'hangover' that may last up to 5 days.[11 52] Severe effects include sudden death, hyperpyrexia, rhabdomyolysis and multi-organ failure, the serotonin syndrome, isolated liver failure, an acute panic disorder and hyponatraemia with cerebral oedema (Table 1). An additional association and possible causation in morbidity and mortality related to trauma is hard to quantify. It has been reported that recreational drugs have become a major associated factor in fatal road traffic accidents.[61]

Pharmacology and pharmacokinetics

Over 16 'Ecstasy'-related compounds have been identified. These include its 'sister' drug 3,4-methylenedioxyethamphetamine, MDEA, 'Eve' and their common metabolite 3,4-methylenedioxyamphetamine, MDA, 'Ice' (Fig. 1). Tablets sold as Ecstasy may contain varying amounts of MDMA (typically 30–150 mg) or none at all. Other MDMA-related compounds may be sold as Ecstasy, and 'Ecstasy' tablets have also been found to contain a variety of other drugs including amphetamine, methamphetamine, caffeine, ketamine and acetaminophen.[76]

MDMA causes the release of serotonin (5-hydroxytryptamine; 5-HT), dopamine and norepinephrine in the

Table 1 Major acute syndromes related to MDMA

Sudden death
Exertional hyperpyrexia leading to rhabdomyolysis and multi-organ failure
Serotonin syndrome
Hyponatraemia and cerebral oedema
Isolated acute liver failure
Cerebrovascular accidents
Acute anxiety and panic disorder

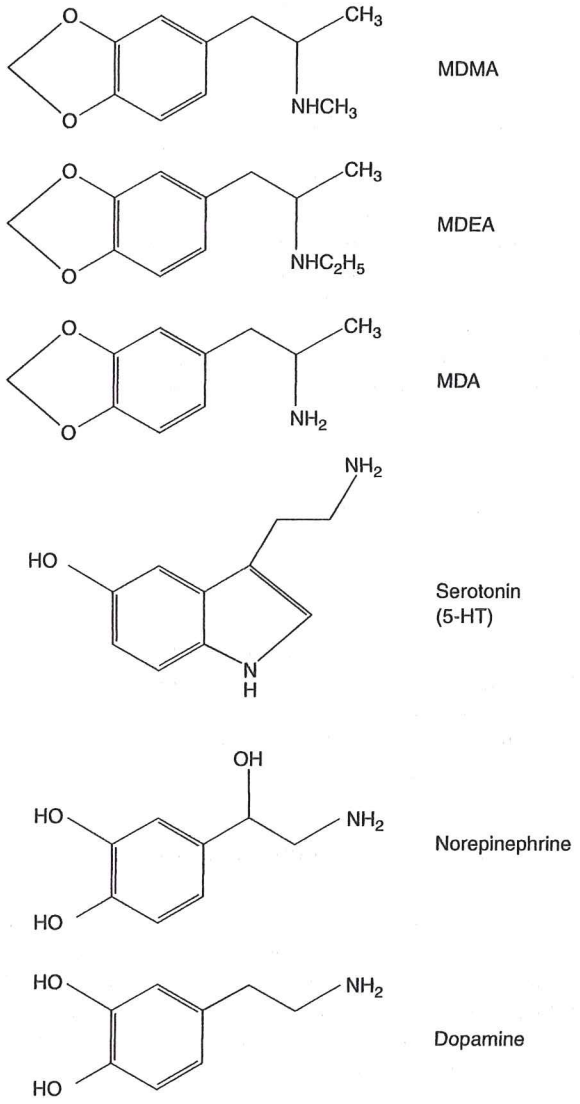

Fig 1 Chemical structures of MDMA (Ecstasy), MDEA, MDA, serotonin (5-HT), norepinephrine, and dopamine.

central nervous system. MDMA has also been shown to bind and inhibit their reuptake transporters at the synapse, principally with 5-HT.[20 44 68] There is thus an acute increase in the intra-synaptic concentration of these transmitters, followed by a period of depletion. The chemical structures of these important neurotransmitters are also shown in Figure 1. These compounds are involved in the control of mood but are also central to the mechanisms of thermoregulation and control of sleep, appetite, reward and the autonomic nervous system.[20 44] Additionally, after MDMA administration, there is an increase in blood levels of cortisol, prolactin, adrenocorticotropic hormone (ACTH), dehydro-epiandrosterone and antidiuretic hormone (ADH).[29 68] It has been suggested that the increase in prolactin may be responsible for the feeling of emotional closeness and may mimic the post-orgasmic state;[41 50] MDMA has slight monoamine oxidase (MAO) inhibiting activity and some direct activity at several receptor types (5-HT_2, M_1-muscarinic, H_1-histamine and α_2-adrenergic), the significance of which is not known.[68] MDMA has a plasma half-life of 7.6 h. Typically, after oral ingestion (75–150 mg), desired effects begin within 1 h and last 4–6 h.[68] Blood levels in asymptomatic users and those with serious side-effects are often similar, suggesting that adverse reactions are likely to relate to the circumstances in which the drug is taken, and that there may also be an idiosyncratic component.[28] A number of fatalities have been reported with blood levels of 0.1–2.1 mg $litre^{-1}$.[31] However, a case of a deliberate overdose of MDMA in which the blood level reached 4.3 mg $litre^{-1}$ with no more than mild sinus tachycardia and a degree of somnolence has been reported.[54] Another analytically documented overdose resulted in a plasma MDMA of 7.72 mg $litre^{-1}$, the highest recorded in a surviving patient, with just a 'hangover', tachycardia and hypertension.[31] The highest level reported in association with multi-organ failure in a subsequent survivor was 7 mg $litre^{-1}$.[6]

MDMA metabolism involves two main pathways. In one, *O*-demethylenation is followed by catechol-*O*-methyltransferase (COMT)-catalysed methylation and/or glucuronide or sulphate conjugation. In the other, *N*-dealkylation, deamination and oxidation is followed by conjugation with glycine. The cytochrome P450 isoenzyme CYP2D6 partially regulates the *O*-demethylenation pathway. As CYP2D6 displays genetic polymorphism in human subjects, it might be suspected that slow metabolizers are at a higher risk of acute MDMA toxicity. However, the formation of an enzyme–metabolite complex results in auto-inhibition that renders all subjects, regardless of genotype, phenotypically poor metabolizers after two consecutive doses. This limits the effect of CYP2D6 pharmacogenetic variation on the acute toxicity of MDMA.[58 68] COMT activity is also subject to genetic variation. This enzyme converts 3,4-dihydroxymethamphetame (HHMA) to 4-hydroxy-3-methoxymethamphetamine (HMMA). *In vitro* studies have shown that HMMA is even more potent than MDMA in releasing ADH. COMT polymorphism may thus contribute to inter-individual differences in ADH release after MDMA (see below).

There is considerable scope for interaction between Ecstasy and other drugs that affect these pathways.

Table 2 Minor clinical symptoms and signs seen with MDMA

Tachycardia	Elevated mood
Hypertension	Confusion
Mydriasis	Ataxia
Dry mouth	Nystagmus
Sweating	Bruxism (jaw clenching)

HIV-1 protease inhibitors (antiretrovirals) such as ritonavir are potent inhibitors of CYP2D6 and prolonged effects of a small dose of MDMA have been reported.[2 30]

Adverse effects

A number of minor clinical symptoms and signs in Ecstasy users relate to a disturbance in the central and autonomic nervous systems. The principal features are shown in Table 2.

An increased risk of trauma, particularly from road traffic accidents, is self-evident. This is particularly likely as most recreational drug users travel to venues, often by car because of late finishing times. They may combine Ecstasy use with that of other agents that may impair judgement, principally alcohol, marijuana and cocaine.[9]

An association between Ecstasy use and cerebral haemorrhage, cerebral venous sinus thrombosis, and aplastic anaemia has been reported.[18 26 33 37 56] There have also been a number of reports of pneumothorax and pneumomediastinum in Ecstasy users.[3 39 53] In one report, two cases occurred on the same evening among a group of friends.[55] It is thought that the mechanism of injury here relates to sustained physical activity with a closed glottis, a form of Valsalva manoeuvre. This can lead to alveolar rupture and subsequent tracking of air along the perivascular space. However, in one case, a small oesophageal tear was found.[55] All subjects reported recovered with conservative management, but most involved several days in hospital. They were investigated with chest radiographs and contrast swallow and treated with i.v. antibiotics when oesophageal injury was proven or suspected.

MDMA and sudden death

Little is known about the aetiology of sudden death in individuals who had taken MDMA. It seems likely that the sympathomimetic effects of the drug may precipitate a dysrhythmic catastrophe. This may occur in an otherwise perfectly healthy individual. However, undiagnosed cardiomyopathy, hypertension or viral myocarditis may be involved. A number of other congenital cardiac conduction abnormalities may go undiagnosed in young people (such as Wolff–Parkinson–White, Romano–Ward, Brugada, and Jervell and Lange–Nielsen Syndromes). These individuals are evidently at risk of sudden death from excessive sympathetic stimulation.[8 60 74] Furthermore, a long QT interval has been reported in association with MDMA toxicity.[27]

Hyperpyrexia, rhabdomyolysis and multi-organ failure

The syndrome of hyperpyrexia together with rhabdomyolysis and multi-organ failure is well described.[31] Most cases appear to be associated with excessive exertion with inadequate fluid replacement to facilitate thermoregulation. Some of these effects may be explained by the euphoric effects of the drug, accentuated by repetitive music and a crowded environment. It is known that both 5-HT and dopamine are involved in central control of thermoregulation and that MDMA effects lead to the activation of mechanisms that both conserve and generate heat. The serotonin syndrome is probably the most extreme of these effects. The occurrence of gross hyperpyrexia and its consequences in predominantly nightclub-going UK users, led to the suggestion that the circumstances in which the drug is taken is pivotal to the occurrence of this complication.[28] Users who spend the night dancing energetically in a warm environment predispose themselves to the development of exertional hyperpyrexia. There is an excess of deaths in relation to parties in the summer and at New Year.[59] Interestingly, laboratory studies with rats have shown that MDMA-induced hyperthermia in males is increased significantly in a warm environment, with overcrowding ('aggregation toxicity')[22] and by social interaction with a female.[7] A switching effect has been demonstrated whereby rats fail to show a hyperthermic response to MDMA if housed below 20°C.[22]

Patients present with hyperpyrexia, muscle rigidity, hyper-reflexia and are often subsequently found to have rhabdomyolysis. Impaired consciousness, disseminated intravascular coagulation (DIC) and multi-organ failure rapidly follow. Five organ-system failure is not unusual; some of these cases have survived after prompt treatment in an intensive care environment.[24] The height and duration of hyperpyrexia are indicators of the risk of mortality. There are few survivors if the peak core temperature exceeds 42°C, though the highest recorded value in a survivor reached 42.9°C.[36] Rhabdomyolysis can be pronounced, with peak creatine phosphokinase (CPK) levels in the region of 30 000–100 000 u litre^{-1}. The highest recorded peak CPK in a survivor is 555 000 u litre^{-1}.[25]

Denborough and Hopkinson[12] suggested that there might be a direct effect of Ecstasy on muscle. They showed some augmentation of the halothane and caffeine induced muscle contraction produced *in vitro* while testing muscle biopsy specimens in the investigation of possible malignant hyperthermia (MH). However, this work has been criticized for using concentrations of MDMA up to 2000 times greater than that found in the plasma of Ecstasy-related fatalities.[23] More recent work, in a rat model, suggests that MDMA uncouples skeletal muscle mitochondria *in vivo*, but that this is the result of an indirect mechanism.[57]

The overlap in clinical features between MDMA-induced hyperthermia and severe heat stroke, neuroleptic malignant

syndrome, serotonergic syndrome and MH cannot be ignored. It may be that these pathological entities ultimately share a final common pathway associated with the consequences of extreme hyperthermia. All would agree, that rapid cooling measures are essential along with the support of failing organ systems. Dantrolene has been used in the treatment of Ecstasy-related hyperpyrexia. While of established benefit in MH, its use in these other conditions remains controversial. It has been suggested that dantrolene treats the effects and not the cause of hyperpyrexia and that it may be better to direct treatment at central mechanisms of thermoregulation.[48] It is, of course, difficult to perform a proper controlled trial when cases present *in extremis* and require urgent management. This is particularly so when they occur sporadically, across a variety of centres. However, this is not always the case with heatstroke. The use of dantrolene in the treatment of heatstroke has been investigated by the Heatstroke Centre in Makkah, Saudi Arabia. An experienced unit, they were able to study 52 patients over a 4 day period in a randomized double blind controlled trial.[5] Dantrolene made no difference to the rate of cooling. This group is, however, well-practised and has equipment for patient cooling not usually available in other countries, where severe heatstrokes occur less commonly.

A review of case reports over the initial 10 yr of widespread use of MDMA lends some support to the use of dantrolene. While an entirely arbitrary period, it allows for a reasonable number of cases to be considered. Cases described beyond this time have been excluded because dantrolene had become well established on the basis of anecdotal evidence and withholding the drug might suggest inadequate care on a number of levels. Cases reported over this period have been broken down into those with peak temperatures in the ranges 41–41.9°C and 40–40.9°C. Patients with a peak temperature of 42°C or more are considerably less likely to survive irrespective of treatment, while those with a peak of less than 40°C might not be expected to develop rhabdomyolysis and multi-organ failure. Peak temperatures in the range 41–41.9°C have been associated with 4/4 survivors in the dantrolene treated group and 2/5 in the non-dantrolene treated group.[6 25 31 45 62 72 77] In the lower range 40–40.9°C, there were 6/6 survivors with dantrolene and 4/5 without it.[4 15 31 46 62 64 66 72 73] Overall, considering cases in the range 40–41.9°C, there were 10/10 survivors with dantrolene treatment and 6/10 without. It has been noted that more rapid control of temperature was achieved in cases where dantrolene was used.[35 64] In most centres, where a patient is *in extremis*, requiring intubation, ventilation, transfer to intensive care facilities and the establishment of invasive monitoring and support, any aid to cooling at this critical time may be of benefit. Once hyperthermia occurs, the calcium requirement for excitation–contraction coupling is reduced, so that hyperthermia alone can cause a degree of muscle contraction with a consequent increase in heat production and metabolic demand. This added complication can be counteracted by the administration of dantrolene, which raises the calcium requirement for excitation–contraction coupling in skeletal muscle. This may be the reason why dantrolene appears to make a difference in survival for patients presenting with very high body temperatures. Possible reasons for hyperthermia associated with MDMA are summarized in Table 3.

Table 3 Aetiology of hyperthermia associated with MDMA

- Prolonged exertion
- Warm environment

Amphetamine-like effects
- Promotion of repetitive activity (dancing)
- Disregard for body signals (thirst, exhaustion)

Mood-enhancing effects
- Euphoria
- Energy

Serotonin effects
- Increased muscle tone
- Heat production

Secondary effects of hyperthermia
- Increased muscle tone
- Further heat production

Serotonin syndrome

MDMA is one of the many pharmacological triggers of the serotonin syndrome. This syndrome is characterized by a rapid onset, with confusion, diaphoresis, diarrhoea and cardiovascular instability. Increased muscle tone and rigidity are accompanied by shivering, tremor, heightened deep tendon reflexes and myoclonus.[17] The excessive muscle contraction may lead to hyperthermia and death, and this condition has a mortality rate of 10–15%. Serotonin syndrome clearly shows great similarity to the acute hyperthermia and multi-organ failure seen with MDMA toxicity, and also MH and neuroleptic malignant syndrome.[71] An overlap of these conditions seems likely with both being part of the same clinical spectrum. Other drugs known to cause the serotonin syndrome include amphetamines, cocaine and various anti-depressant agents. There is particularly a risk with the combination of MAO inhibitor (MAOI) and any serotonin reuptake inhibitor (SRI). A number of agents commonly used in anaesthesia and critical care also display these characteristics. The phenylpiperidine series opioids, pethidine (meperidine), tramadol, methadone, dextromethorphan and propoxyphene all have a weak SRI effect and linezolid and isoniazid have MAOI properties.[17 47]

The serotonin syndrome may cause severe hyperthermia in MDMA users that have not engaged in significant physical exertion. Mild cases may resolve spontaneously, but should be monitored closely. In severe cases, deep sedation, paralysis and ventilation should be undertaken. As the production of heat is secondary to muscle contraction, and hyperthermia arises because heat production exceeds the body's capacity to lose heat, paralysis immediately cuts heat production and body temperature should decrease rapidly without any further active cooling measures.

Hyponatraemia and cerebral oedema

Awareness of the danger of hyperthermia among users of MDMA led to the practice of drinking large volumes of water to prevent the compounding effect of dehydration. Clubs have been encouraged to provide 'chill-out' areas with free/cheap drinking water available. However, a number of deaths in Ecstasy users have been reported resulting from dilutional hyponatraemia and consequent cerebral oedema.[27 38] Patients generally present with confusion, and convulsions, delirium, or both, and can rapidly progress to coma and death as a result of 'coning' (cerebral oedema, hypoxia and uncal herniation). The practice of drinking large amounts of water, sugared/carbonated drinks, or both, appears to be a major contributory factor. In one case associated with recreational use of MDMA, an elevated level of ADH was reported.[32] In order to examine this phenomenon, Henry and colleagues[29] administered a modest dose of MDMA, 40 mg, to eight healthy volunteers. They showed a marked increase in plasma levels of ADH that would not have been expected at that time of day and were not matched by increases in ACTH (as might be expected if part of a stress response). MDMA thus promotes ADH release in humans. Additionally, as is described above, some genetic polymorphism in relation to COMT may result in a greater release of ADH in some individuals. However, it is clear once again that the circumstances in which the drug is taken affects the incidence of a significant complication, in this case, fluid consumption which exceeds the body's requirements. It is likely that many users who hydrate themselves vigorously would have some degree of hyponatraemia, but only those who consume excessive quantities of fluids achieve clinically significant levels (generally Na <125 mmol litre^{-1}). There may be some benefit if users of MDMA rehydrate with electrolyte-containing fluids.

Conventional management of dilutional hyponatraemia is with fluid restriction, and this is adequate in the great majority of cases of MDMA-associated hyponatraemia. Distinction should be made between the treatment of chronic hyponatraemia and the management of MDMA-associated hyponatraemia, where an acute derangement has occurred. In chronic hyponatraemia, correction should be no faster than 6–8 mmol litre^{-1} per day in order to avoid the osmotic demyelination syndrome.[65] This would be unlikely in the case of an acute hyponatraemia. However, the patient with mild to moderate MDMA-associated hyponatraemia will usually correct automatically by producing a diuresis within hours. The more severely ill patient may not be sufficiently stable to allow such a conservative approach and the use of hypertonic saline solution may be required. There is little evidence concerning the effectiveness of diuretics or mannitol in this situation. In cases of MDMA-related hyponatraemia, other complications may coexist including cardiovascular instability.[24] A more rapid volume correction may be required. Isotonic saline may be most appropriate in this circumstance. Possible reasons for hyponatraemia associated with MDMA are summarized in Table 4.

Table 4 Aetiology of hyponatraemia associated with MDMA

- 'Harm reduction' message to drink fluids

Amphetamine-like effects

- Dry mouth and throat
- Repetitive behaviour—may include compulsively drinking water

Mood-enhancing effect

- Reduced inhibitions and impaired judgement possibly leading to excessive water intake

Serotonergic effects

- Excess ADH production leading to reduced renal response to water load (SIADH)

Liver failure

Hepatic failure has been reported as part of a picture of multi-organ failure attributable to hyperpyrexia. Isolated liver damage of varying severity has also been reported. In the former, liver histology generally shows a picture of centrilobular necrosis and microvascular steatosis, a picture consistent with heatstroke.[42] In isolated liver failure, the histology has been reported to be characteristic of an acute cholestatic hepatitis. The presence of eosinophils and histiocytes constitute strong evidence for a hypersensitivity reaction.[1 13 16] Patients commonly present with jaundice, abdominal pain, raised serum transaminases, hypoglycaemia and elevated prothrombin time. Encephalopathy may occur and presentation can be fulminant. Andreu and colleagues[1] reported that 31% of drug-related hepatotoxicity was attributable to MDMA, second only to that after anti-tuberculous chemotherapy. It represented 20% of all liver failure and 36% of non-viral liver failure in patients <25 yr of age. Treatment is primarily supportive and most patients survive. It is interesting that recurrence has been reported on re-exposure to the drug, which along with the eosinophilic infiltration may suggest an immunologically mediated mechanism.[16] Patients with end-stage liver failure after MDMA use have undergone successful liver transplantation.[1 13]

Acute severe anxiety/panic disorder

Though anxiety is often seen as a minor side-effect of MDMA use, there have been a number of reports of more severe reaction with an acute panic disorder.[40 49 75] This has been reported in subjects without prior personal or family history of an anxiety disorder and where a modest dose of Ecstasy was taken. In one report, another user from the same source reacted similarly[75] though this has not been seen elsewhere. Prior and subsequent Ecstasy use has been reported without similar effect. Though most anxiety and panic reactions settle within hours, there have been reports of a persisting condition lasting several months.[40 49] Benzodiazepines have been found to be acutely effective. Longer-term therapy has been recorded with a

Table 5 The management of acute MDMA toxicity

- Activated charcoal 50 g po ng^{-1} if <1 h post-ingestion

Monitor
- Observe for at least 4 h
- Pulse, blood pressure, ECG, core temperature

Check
- Blood for urea, electrolytes, creatinine, liver function, CPK; consider clotting profile and arterial blood gases
- 12-lead ECG
- Urine drug screen (a positive result for methamphethamine helps to confirm MDMA consumption; specific tests are also available)

Treat
- *Anxiety or agitation*—diazepam (0.1–0.3 mg kg^{-1}) po or i.v.
- *Seizures*—diazepam (0.1–0.3 mg kg^{-1}) i.v. or per rectum (pr)
- *Hyponatraemia*—fluid restrict, consider hypertonic saline if severe
- *Metabolic acidosis*—correct (especially if QT interval prolonged) using sodium bicarbonate
- *Severe hypertension*—consider labetalol
- *Hypotension*—intravascular volume expansion, consider need for central venous access, cardiac output monitoring, etc.
- *Hyperthermia*—simple cooling methods. If temperature >39°C after initial measures, give dantrolene; intubation and ventilation are likely to be required
- *Organ-system failure*—conventional support; promote diuresis of 1–2 ml $kg^{-1}h^{-1}$ with mannitol or furosemide

number of agents including benzodiazepines and SSRI antidepressants.[40 49]

There is good evidence, in a rat model, for a MDMA-induced depletion in central 5-HT levels associated with anxiety and depression, and that this may be in part attenuated by chronic fluoxetine treatment.[21 67] Depression and anxiety have also been reported in human MDMA users. Though there is some diminution after a period of abstinence, the incidence of problems is related to the number of occasions in which MDMA has been used.[43 51] It has been suggested that some users may either be more vulnerable to the effects of MDMA or have pre-existing mental health problems for which they self medicate by using Ecstasy.[70] The possibility of permanent neuronal damage in human users cannot be excluded.

Management of acute MDMA toxicity

A scheme for the management of patients with acute MDMA-related complications (Table 5) has been adapted from the UK National Poisons Information Service guidelines.[69] The use of activated charcoal is recommended up to 1 h post-ingestion. However, it is unlikely that patients would present with serious adverse effects so soon. Urgent fluid replacement is essential in the patient with marked hypotension and tachycardia attributable to intravascular volume depletion.

Labetalol is preferred for the treatment of tachycardia and hypertension secondary to the sympathomimetic effects of MDMA. It has both β- and α-adrenoceptor blocking effects and is available in an i.v. formulation. Beta-blockers used in isolation may be associated with increased hypertension because of the loss of β-mediated vasodilatation. However, i.v. esmolol may be useful as a short half-life makes it rapidly reversible.

It is important to replace fluid losses and thus enable thermoregulation. Paralysis may be required in order to break the cycle of heat generation. Any patient with a significantly impaired level of consciousness, seizures or hyperpyrexia requiring aggressive cooling and dantrolene, should be sedated, the trachea intubated and lungs ventilated.[24] It should be remembered that dantrolene takes some time to dissolve and prepare. Each vial of dantrolene contains 20 mg along with 3 g of mannitol and sodium hydroxide to give a final pH of 9.5 after the addition of 60 ml sterile water. Alkalinization of urine along with an adequate diuresis may protect the kidneys from failure because of myoglobinuria. The mannitol contained with dantrolene may help to promote the desired diuresis of 1–2 ml kg^{-1} h^{-1}, though this may require supplementation.

Patients with hyponatraemia often have a normal or low temperature and should not be given i.v. fluids, as fluid restriction is usually sufficient. In most cases, treatment is essentially supportive. However, temperature control is important and immediate volume replacement followed by dantrolene and aggressive cooling is likely to be useful with severe hyperthermia. It is important to remember that temperature on arrival may not represent the peak and continued monitoring is required. Conversely, the temperature may have already peaked and significant tissue damage occurred before arrival at hospital.

Paralysis and ventilation is the best management for acute serotonin syndrome.

Consideration should be given to the early establishment of invasive monitoring access and a haemodialysis catheter if multi-organ failure and DIC is expected.

Conclusion

It is clear that despite large-scale consumption of MDMA, serious acute illness remains relatively rare. However, when complications occur, they can be life-threatening, and require the implementation of a clearly thought plan, based on the clinical state and knowledge of the physiological effects and toxicity profile of MDMA. There are still many unanswered questions regarding the pathophysiology and pharmacology of the acute toxic effects of MDMA. It is clear that many different neuroendocrine systems can be affected and that the variety of side-effects may depend upon a multitude of other factors both environmental and pharmacogenetic. Additionally, there still remains the possibility of permanent damage to serotonergic neurological pathways in users of MDMA.[10 20 43 44 51 63 68 70]

References

1 Andreu V, Mas A, Bruguera M, *et al.* Ecstasy: a common cause of severe acute hepatotoxicity. *J Hepatol* 1998; **29**: 394–7

2 Antoniou T, Tseng AL. Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother* 2002; **36**: 1598–613

3 Badaoui R, El Kettani C, Fikri M, Ouendo M, Canova-Bartoli P, Ossart M. Spontaneous cervical and mediastinal air emphysema after Ecstasy abuse. *Anesth Analg* 2002; **95**: 1123

4 Barrett PJ, Taylor GT. 'Ecstasy' ingestion: a case report of severe complications. *J R Soc Med* 1993; **86**: 233–4

5 Bouchama A, Cafege A, Devol EB, Labdi O, El-Assil K, Seraj M. Ineffectiveness of dantrolene sodium in the treatment of heatstroke. *Crit Care Med* 1991; **19**: 176–80

6 Brown C, Osterloh J. Multiple severe complications from recreational ingestion of MDMA ('Ecstasy'). *JAMA* 1987; **258**: 780–1

7 Brown PL, Khatkin EA. Brain hyperthermia induced by MDMA (Ecstasy): modulation by environmental conditions. *Eur J Neurosci* 2004; **20**: 51–8

8 Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. *J Am Coll Cardiol* 1992; **20**: 1391–6

9 Calafat A, Bohrn K, Juan M, *et al.* Night life in Europe and recreational drug use. Valencia: Irefreya and European Commission, 1999

10 Colado MI, O'Shea E, Green AR. Acute and long-term effects of MDMA on cerebral dopamine biochemistry and function. *Psychopharmacol* 2004; **173**: 249–63

11 Curran HV, Travill RA. Mood and cognitive effects of 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy'): weekend 'high' followed by mid-week 'low'. *Addiction* 1997; **92**: 821–31

12 Denborough MA, Hopkinson KC. Dantrolene and 'Ecstasy'. *Med J Aust* 1997; **166**: 165–6

13 Ellis AJ, Wendon JA, Portmann B, Williams R. Acute liver damage and ecstasy ingestion. *Gut* 1996; **38**: 454–8

14 European Monitoring Centre for Drugs and Drug Addiction. *Annual Report on the State of Drugs Problems in the European Union and Norway*. Lisbon: EMCDDA, 2003

15 Fahal IH, Sallomi DF, Yaqoob M, Bell GM. Acute renal failure after ecstasy. *Br Med J* 1992; **305**: 29

16 Fidler H, Dhillon A, Gertner D, Burroughs A. Chronic ecstasy (3,4-methylenedioxymethamphetamine) abuse: a recurrent and unpredictable cause of severe acute hepatitis. *J Hepatol* 1996; **25**: 563–6

17 Gillman PK. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. *Br J Anaesth* 2005; **95**: 434–41

18 Gledhill JA, Moore DF, Bell D, Henry JA. Subarachnoid haemorrhage associated with MDMA use. *J Neurol Neuosurg Psychiatry* 1993; **56**: 1036–7

19 Gore SM. Fatal uncertainty: death rate from use of ecstasy or heroin. *Lancet* 1999; **354**: 1265–6

20 Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy'). *Pharmacol Rev* 2003; **55**: 463–508

21 Green AR, McGregor IS. On the anxiogenic and anxiolytic nature of long-term cerebral 5-HT depletion following MDMA. *Psychopharmacol* 2002; **162**: 448–50

22 Green AR, O'Shea E, Colado MI. A review of the mechanisms involved in the acute MDMA (Ecstasy)-induced hyperthermic response. *Eur J Pharmacol* 2004; **500**: 3–13

23 Hall AP. Dantrolene and 'Ecstasy'. *Med J Aust* 1997; **167**: 506

24 Hall AP. 'Ecstasy' and the anaesthetist. *Br J Anaesth* 1997; **79**: 697–8

25 Hall AP, Lyburn ID, Spears FD, Riley B. An unusual case of Ecstasy poisoning. *Int Care Med* 1996; **22**: 670–1

26 Harries DP, de Silva RN. Ecstasy and intracerebral haemorrhage. *Scot Med J* 1992; **37**: 150–2

27 Hartung TK, Schofield E, Short AI, Parr MJA, Henry JA. Hyponatraemic states following 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') ingestion. *Q J Med* 2002; **95**: 431–7

28 Henry JA. Ecstasy and the dance of death. *Br Med J* 1992; **305**: 5–6

29 Henry JA, Fallon JK, Kicman AT, Hutt AJ, Cowan DA, Forsling M. Low-dose MDMA ('ecstasy') induces vasopressin secretion. *Lancet* 1998; **351**: 1784

30 Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. *Lancet* 1998; **352**: 1751–2

31 Henry JA, Jeffreys KJ, Dawling S. Toxicity and deaths from 3,4-methylenedioxymethamphetamine ('Ecstasy'). *Lancet* 1992; **340**: 384–7

32 Holden R, Jackson MA. Near-fatal hyponatraemic coma due to vasopressin over-secretion after 'ecstasy' (3,4-MDMA). *Lancet* 1996; **347**: 1052

33 Hughes JC, McCabe M, Evans RJ. Intracranial haemorrhage associated with ingestion of 'Ecstasy'. *Arch Emerg Surg* 1993; **10**: 372–4

34 Kershaw C, Budd T, Kinshott G, Mattinson J, Mayhew P, Myhill A. *The 2000 British Crime Survey, England and Wales. Home Office Statistical Bulletin 18/00*. London: British Home Office, 2000

35 Logan AS, Stickle B, O'Keefe N, Hewitson H. Survival following 'Ecstasy' ingestion with a peak temperature of 42°C. *Anaesthesia* 1993; **48**: 1017–18

36 Mallick A, Bodenham AR. MDMA induced hyperthermia: a survivor with an initial body temperature of 42.9°C. *J Accid Emerg Med* 1997; **14**: 336–8

37 Marsh JC, Abboudi ZH, Gibson FM, *et al.* Aplastic anaemia following exposure to 3,4-methylenedioxymethamphetamine ('ecstasy'). *Br J Haematol* 1994; **88**: 281–5

38 Maxwell DL, Polkey MI, Henry JA. Hyponatraemia and catatonic stupor after taking 'ecstasy'. *Br Med J* 1993; **307**: 1399

39 Mazur S, Hitchcock T. Spontaneous pneumomediastinum, pneumothorax and Ecstasy abuse. *Emerg Med* 2001; **13**: 121–3

40 McCann UD, Ricaurte GA. MDMA ('Ecstasy') and panic disorder: induction by a single dose. *Biol Psychiatry* 1992; **32**: 950–3

41 McElrath K. MDMA and sexual behaviour: ecstasy users' perceptions about sexuality and sexual risk. *Subst Use Misuse* 2005; **40**: 1461–77

42 Milroy CM, Clark JC, Forrest ARW. Pathology of deaths associated with 'ecstasy' and 'eve' misuse. *J Clin Pathol* 1996; **49**: 149–53

43 Morgan MJ. Ecstasy (MDMA): a review of its possible persistent psychological effects. *Psychopharmacol* 2000; **152**: 230–48

44 Morton J. Ecstasy: pharmacology and neurotoxicity. *Curr Opin Pharmacol* 2005; **5**: 79–86

45 Murthy BVS, Wilkes RG, Roberts NB. Creatinine kinase isoform changes following ecstasy overdose. *Anaesth Int Care* 1997; **25**: 156–9

46 Nimmo SM, Kennedy BW, Tullett WM, Blyth AS, Dougal JR. Drug-induced hyperthermia. *Anaesthesia* 1993; **48**: 892–5

47 Oesterheld JR, Armstrong SC, Cozza KL. Ecstasy: pharmacodynamic and pharmacokinetic interactions. *Psychosomatics* 2004; **45**: 84–7

48 Padkin A. Treating MDMA ('Ecstasy') toxicity. *Anaesthesia* 1994; **49**: 259

49 Pallanti S, Mazzi D. MDMA (Ecstasy) precipitation of panic disorder. *Biol Psychiatry* 1992; **32**: 91–5

50 Passie T, Hartmann U, Schneider U, Emrich HM, Kruger TH. Ecstasy (MDMA) mimics the post-orgasmic state: impairment of sexual drive and function during acute MDMA-effects may be due to increased prolactin secretion. *Med Hypotheses* 2005; **64**: 899–903

51 Parrott AC, Buchanan T, Scholey AB, Heffernan T, Ling J, Rodgers J. Ecstasy/MDMA attributed problems reported by

novice, moderate and heavy recreational users. *Hum Psychopharmacol* 2002; **17**: 309–12

52 Peroutka SJ, Newman H, Harris H. Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. *Neuropsychopharmacology* 1988; **1**: 273–277

53 Quinn GI, McCarthy GM, Harries DK. Spontaneous pneumomediastinum and Ecstasy abuse. *J Accid Emerg Med* 1999; **16**: 382

54 Regenthal R, Kruger M, Rudolph K, Trauer H, Preiss R. Survival after massive 'ecstasy' (MDMA) ingestion. *Intensive Care Med* 1999; **25**: 640–1

55 Rejali D, Glen P, Odom N. Pneumomediastinum following Ecstasy (methylenedioxymethamphetamine, MDMA) ingestion in two people at the same 'rave'. *J Laryngol Otol* 2002; **116**: 75–6

56 Rothwell PM, Grant R. Cerebral venous sinus thrombosis induced by ecstasy. *J Neurol Neuosurg Psychiatry* 1993; **56**: 1035

57 Rusyniak DE, Tandy SL, Hekmatyar SK, *et al.* The role of mitochondrial uncoupling in 3,4-methylenedioxymethamphetamine-mediated skeletal muscle hyperthermia and rhabdomyolysis. *J Pharmacol Exp Ther* 2005; **313**: 629–39

58 Schifano F. A bitter pill. Overview of ecstasy (MDMA, MDA) related fatalities. *Psychopharmacology* 2004; **173**: 242–8

59 Schifano F, Oyefeso A, Webb L, Pollard M, Corkery J, Ghodse AH. Review of deaths related to taking ecstasy, England and Wales, 1997–2000. *Br Med J* 2003; **326**: 80–1

60 Schwartz J, Periti M, Malliani A. The long Q–T syndrome. *Am Heart J* 1975; **89**: 378–90

61 Scottish Executive. Recreational drug use and driving: a qualitative study. Available from http://www.scotland.gov.uk/cru/kd01/blue/druguse-15.htm

62 Screaton GR, Singer M, Cairns HS, Thrasher A, Sarner M, Cohen SL. Hyperpyrexia and rhabdomyolysis after MDMA ('Ecstasy') abuse. *Lancet* 1992; **339**: 677–8

63 Simantov R. Multiple molecular and neuropharmacological effects of MDMA (Ecstasy). *Life Sci* 2004; **74**: 803–14

64 Singarajah C, Lavies NG. An overdose of ecstasy. *Anaesthesia* 1992; **47**: 686–7

65 Sterns RH. Severe hyponatraemia: the case for conservative management. *Crit Care Med* 1992; **20**: 534–9

66 Tehan B, Hardern R, Bodenham A. Hyperthermia associated with 3,4-methylenedioxyethamphetamine ('Eve'). *Anaesthesia* 1993; **48**: 507–10

67 Thompson MR, Li KM, Clemens KJ, *et al.* Chronic fluoxetine treatment partly attenuates the long-term anxiety and depressive symptoms induced by MDMA ('Ecstasy') in rats. *Neuropsychopharmacology* 2004; **29**: 694–704

68 de la Torre R, Farre M, Roset PN, *et al.* Human pharmacology of MDMA: pharmacokinetics, metabolism and disposition. *Ther Drug Monit* 2004; **26**: 137–44

69 UK National Poisons Information Service Guidelines. Available from http://www.npis.org

70 Verheyden SL, Maidment R, Curran HV. Quitting ecstasy: an investigation of why people stop taking the drug and their subsequent mental health. *J Psychopharmacol* 2003; **17**: 371–8

71 Wappler F, Fiege M, Schulte am Esch F. Pathophysiological role of the serotonin system in malignant hyperthermia. *Br J Anaesth* 2001; **87**: 794–8

72 Watson JD, Ferguson C, Hinds CJ, Skinner R, Coakley JH. Exertional heat stroke induced by amphetamine analogues: does dantrolene have a place? *Anaesthesia* 1993; **48**: 1057–60

73 Webb C, Williams V. Ecstasy intoxication: appreciation of complications and the role of dantrolene. *Anaesthesia* 1993; **48**: 542–3

74 Wellens HJJ, Brugada P, Penn OC. The management of the pre-excitation syndromes. *JAMA* 1987; **257**: 2325–33

75 Whitaker-Azmitia PM, Aronson TA. 'Ecstasy' (MDMA)-induced panic. *Am J Psychol* 1989; **146**: 119

76 Wolff K, Hay AWM, Sherlock K, Conner M. Contents of 'ecstasy'. *Lancet* 1995; **346**: 1100–1

77 Woods JD, Henry JA. Hyperpyrexia induced by 3,4-methylenedioxymethamphetamine ('Ecstasy'). *Lancet* 1992; **340**: 305

PILLS WILL KILL, BUT TESTING

On-site 'labs' checking the content of illegal drugs seem sensible, but the idea is daft

JOHN LEWIS The Australian
JAN 16 2019 PAGE 10

The notion of testing illegal pills to see if they are safe is gaining momentum in the wake of a spate of deaths of young people at music festivals around Australia.

Ross Fitzgerald argued in support of it on this page yesterday.

But it won't work and is fraught with dangers. What if we don't know what we are testing for? New psychoactive compounds are being developed all the time. In any case, is the drug we're testing for consistent throughout the pill? We could easily miss it by scraping a little from the surface. And perhaps the deadly threat lurks in unidentified contaminants.

There is much to be considered — maybe first is the fact no forensic toxicologist I know recommends pill testing or believes it is practical.

Years ago, most people were happy taking amphetamine, cocaine and occasionally LSD in addition to alcohol; in the past few years novel psychoactive substances have become a clinical and forensic nightmare. These drugs include synthetic cannabinoids, such as PB-22, cathinones (stimulants related to the khat plant that mimic the effects of methylamphetamine and cocaine) and a number of synthetic benzodiazepines drugs (related to diazepam).

Consider this: in 2010 there were about a dozen synthetic "spice type" cannabinoids; by 2011 there were about 40; in 2012 there were 60. In 2015 four Australians died from PB-22. By 2016 there were about 125 synthetic cannabinoids, more than 20 cathinones, 20 synthetic benzodiazepines, and by last year about 18 highly potent fentanyl derivatives were found in the US. There have been reported deaths because of the synthetic cathinone MDPV in Italy and carfentanil-laced heroin in Britain. Carfentanil is a fentanyl-like substance 10,000 times as potent as morphine and has been deemed responsible for inadvertent overdoses by regular heroin users. It is estimated that a lethal dose of this drug may be as low as 20 micrograms. Local authorities have already seized shipments of carfentanil. These highly potent substances are mixed with regular benzodiazepines or ecstasy.

Fitzgerald states the risks of pill testing appear to be minimal. That is curious. In a recent toxicology publication, a leading forensic scientist reported there was great concern in the US that these novel illicit substances typically are outside the scope of routine drug testing by hospitals and laboratories or below the sensitivity levels for detection. If major forensic facilities have difficulty in identifying these substances, it stands to reason that on-site pill testing could not adequately identify most of the potentially lethal components in a pill scraping.

In another recent publication, Australian forensic laboratories noted there were about 740 new psychoactive substances reported to the UN Office on Drugs and Crime from 2009 to 2016.

Again, leading Australian forensic institutions using high-resolution mass spectrometry struggle to keep up with ever-increasing variations in synthetic substances.

THEM IS NOT YET THE ANSWER

The issue of pill testing should be decided on forensic science

Pill testing may identify some of these within the time and scope of the on-site facility, but the risk of an adverse or fatal episode remains with several hundred substances not detected.

Fitzgerald reckons there is a strong case from more than two decades of experience in Europe, but that's ignoring the exponential increase in deadly adulterants.

The issue of pill testing should be decided on forensic science. The ability to identify a wide range of components in a compound depends on the ability to test a representative portion of the substances, and that representation is incumbent on the pill being homogeneously mixed when produced. If the pill has not been manufactured to ethical pharmaceutical standards then there is a risk of the pill tester missing the more toxic ingredients of the substances.

If pill testing were trialled, you would need sophisticated instrumentation such as high-resolution mass spectrometry to rapidly analyse the contents of the unknown substance. Such instrumentation is not amenable to on-site music festival venues. Critically, operators of the instrumentation would need to ensure their database of compounds is up to date. As newer synthetic drugs are regularly entering the market, forensic laboratories are struggling to obtain appropriate and expensive analytical reference material to identify unequivocally all ingredients in a pill.

To date, analytically trained experts have yet to explain adequately the complexity of attempting to test pills reliably and quickly at an on-site venue to be reasonably confident they can eliminate minute amounts of potentially lethal ingredients such as the deadly carfentanil.

In any case, the greater difficulty is in figuring out where in the pill, whether purportedly ecstasy or methylamphetamine, might lie the adulterants. Only forensic analysis can determine the concentration of adulterants in pills. For many of these substances, there is no known toxic concentration. When combined with other substances, adverse effects including respiratory depression leading to coma can occur at any level.

Before moving ahead with a policy to trial pill testing, we need some sobering facts. The efficacy of pill testing is best left to forensic scientists, while the value of pill testing as a means of harm reduction is the domain of researchers into behavioural patterns of users and their potential for risk-taking. A 2004 study by the National Drug and Alcohol Research Centre into risk factors and risk perceptions found that those who perceived the possibility of getting caught or being involved in accidents were less likely to drive while impaired. Conversely, the perception of not getting caught or having an adverse reaction contributed to their drug-taking behaviour.

While one cannot draw a direct correlation between drugs and driving and taking of unknown pills at a music festival, it is clear from recent events that many attendees at these events do not perceive the dangers and non-forensic pill testing may well provide attendees with a false sense of security.

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Portugal decriminalised the use of all drugs in July 2001 and the results of their changed drug policy can be compared with Australia's Tough on Drugs policy which was operative from 1998 to 2007.

Australians should not be misled by claims painting a false picture of Portugal's results.

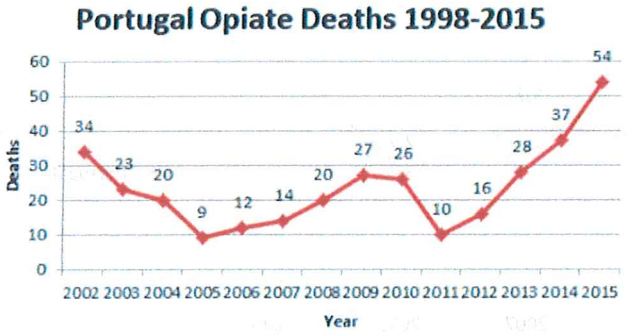
DRUG FREE AUSTRALIA

PORTUGAL versus our TOUGH ON DRUGS

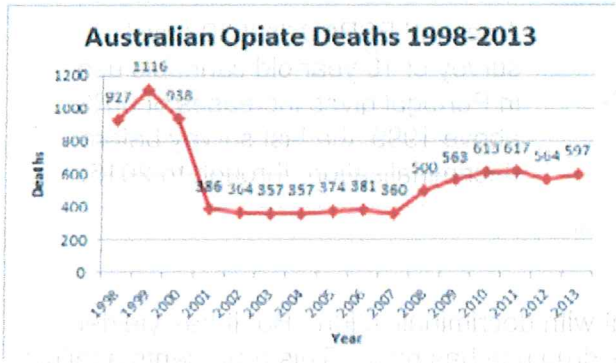
The results of two drug policies compared

Drug deaths

Portugal has no mortality data before 2002 which is comparable with Australia's, but they have lower drug deaths than Australia because opiates are mostly smoked or snorted and not injected as in Australia). Notably, their drug policy has failed to significantly decrease drug deaths since 2001, and steep rises since 2011 normally indicate steep rises in opiate use.



Australia implemented Tough on Drugs in 1998, with criminal penalties intact for use of most drugs. Deaths fell by 67% until it was scrapped by a new Federal government in 2007. Deaths then again rose sharply.

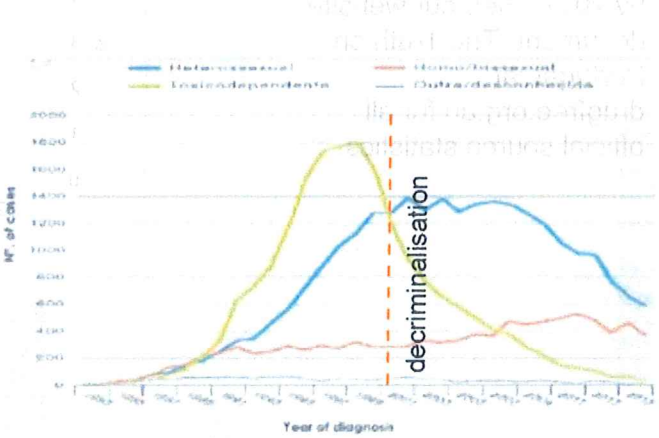


While Portugal has 'dissuasion' programs to encourage drug users to quit and spends liberally on encouraging users into treatment and rehab, decriminalisation appears to have obstructed policies that should otherwise be working.

See www.drugfree.org.au document "The Truth on Portugal" for more detail, citations and graph enlargements

HIV

In 1999 Portugal had the highest HIV levels in Europe, with 45% of drug users infected. Activists claim that Portugal's decriminalisation policy reduced HIV to 5% (green line), but the graph below shows steeper declines before/during 2001.



Clearly, programs were put in place a number of years before July 2001 which were effective and remained so. Decriminalisation was not responsible.

Australia's HIV has always been low, credited to the innovative Grim Reaper television ads of 1987, viewable on Youtube.

False claims on decreasing drug use

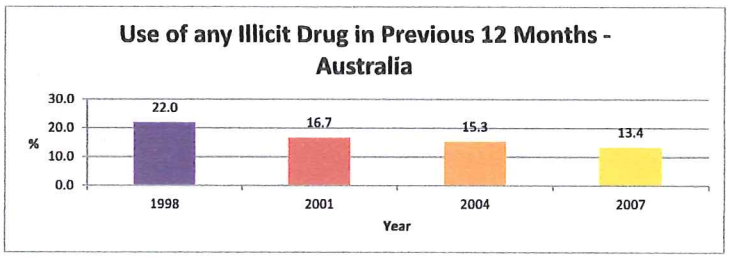
Claims are made that decriminalisation radically reduced Portugal's opiate use. Portugal's opiate use was 0.9% in 1998 but already down to 0.7% by 2000, the year before decriminalisation, indicating already successful demand reduction strategies.

Drug use

Australians do not approve the regular use of illicit drugs, and it is thereby clear that Australians want less drugs, not more.

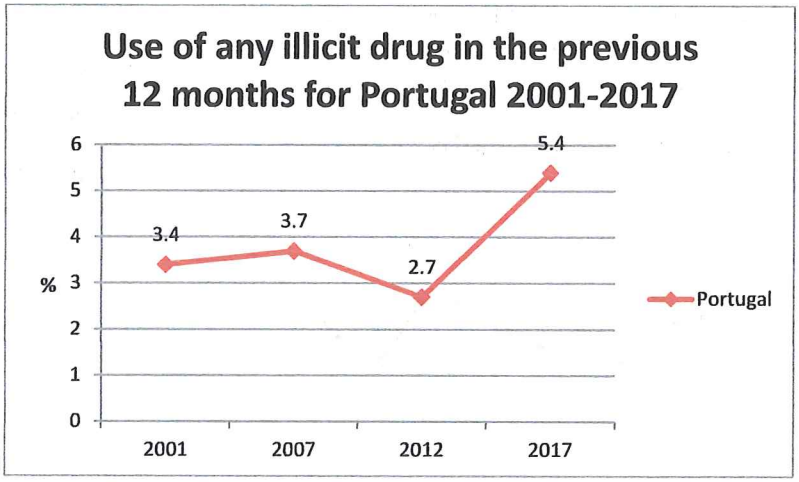
Table 9.7: Personal approval of the regular use by an adult of selected drugs, people aged 14 years or older, 2007 to 2016 (per cent)

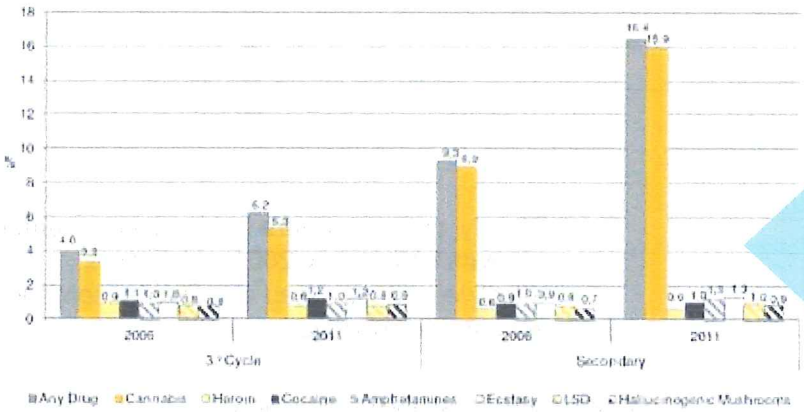
	Persons			
Drug	2007	2010	2013	2016
Tobacco	14.4	15.3	14.7	15.7#
Alcohol	45.3	45.1	45.1	46.0
Cannabis	6.7	8.1	9.8	14.5#
Ecstasy	2.0	2.3	2.4	2.9#
Methamphetamine[a]	1.2	1.2	1.4	1.2
Cocaine/crack	1.4	1.7	1.6	1.7
Hallucinogens	1.7	2.4	3.1	3.7#
Inhalants	0.8	1.0	0.9	1.0
Heroin	1.0	1.2	1.2	1.1
Pharmaceuticals[a]	13.7	22.4	23.2	27.8#
Prescription pain-killers/analgesics[a]	n.a.	13.0	12.6	12.7
Over-the-counter pain-killers/analgesics[a]	n.a.	14.3	14.5	19.1#
Tranquilisers, sleeping pills[a]	4.1	6.4	8.2	9.3#
Steroids[a]	1.7	2.2	2.2	2.4
Methadone or buprenorphine[a]	1.0	1.2	1.3	1.3



Tough on Drugs delivered decreases in overall illicit drug use of 39% between 1998 and 2007.

Portugal's official statistics indicate significantly increased use of any illicit drug which was 59% above 2001 levels by 2017. See our website document "The Truth on Portugal" at drugfree.org.au for all official source statistics.





Graph 15 – School Population – INME (3º Cycle and Secondary): Last 30 Days Prevalence of use, by type of drug (IDT, I.P. 2012)

Teen drug use (left) increased by 43% over 2001 levels by 2011. We do not yet have the 2016 statistics for this national survey.

A second ESPAD 'last 30 days' survey of 16 year old cannabis use in Portugal gives increases of 60% above 1999, the last survey before decriminalisation, through to 2015.

There are many false claims eulogising Portugal's experiment with decriminalisation. But it has yielded increased drug use along with increasing overdose deaths as drug use has risen. This represents a failure in drug policy which should not be emulated in Australia.

AUSTRALIA'S 'TOUGH ON DRUGS' DELIVERED LESS DRUG USE
PORTUGAL'S DRUG POLICY HAS NOT

What Australian drug use would look like by 2031 if replicating Portugal's 'success'

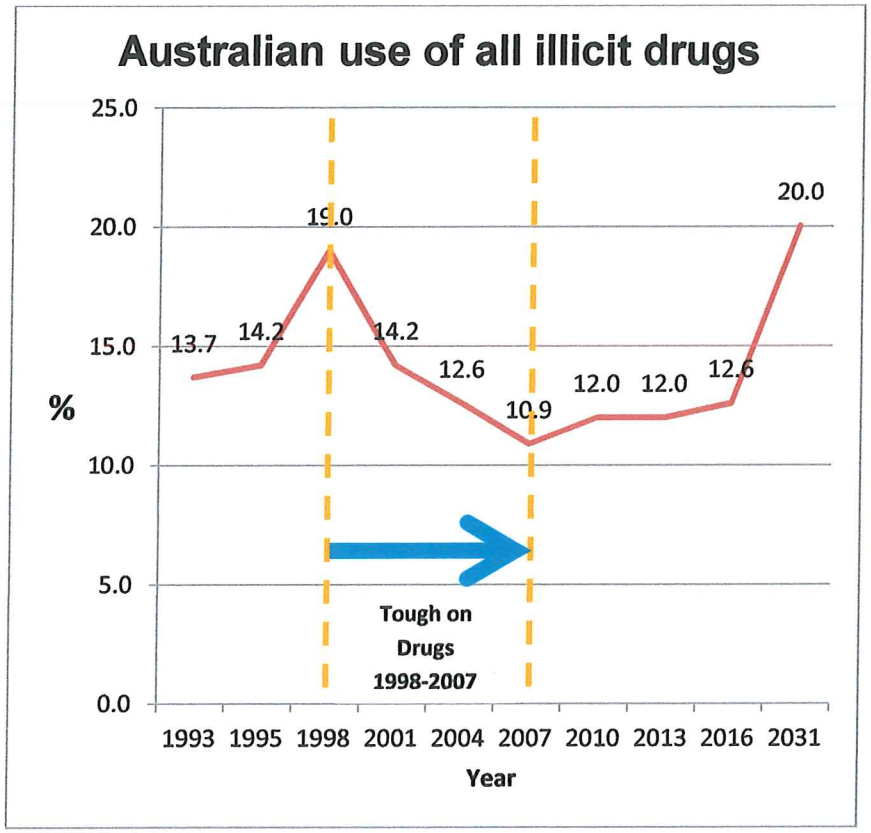


Table 25: Summary of recent[a] drug use, people aged 14 years or older, 1993 to 2016 (per cent)

Drug/behaviour	1993	1995	1998	2001	2004	2007	2010	2013	2016
Illicit drugs (excluding pharmaceuticals)									
Marijuana/cannabis	12.7	13.1	17.9	12.9	11.3	9.1	10.3	10.2	10.4
Ecstasy[b]	1.2	0.9	2.4	2.9	3.4	3.5	3.0	2.5	2.2
Meth/amphetamine[c]	2.0	2.1	3.7	3.4	3.2	2.3	2.1	2.1	1.4#
Cocaine	0.5	1.0	1.4	1.3	1.0	1.6	2.1	2.1	2.5
Hallucinogens	1.3	1.9	3.0	1.1	0.7	0.6	1.4	1.3	1.0#
Inhalants	0.6	0.4	0.9	0.4	0.4	0.4	0.6	0.8	1.0
Heroin	0.2	0.4	0.8	0.2	0.2	0.2	0.2	0.1	0.2
Ketamine	n.a.	n.a.	n.a.	n.a.	0.3	0.2	0.2	0.3	0.4
GHB	n.a.	n.a.	n.a.	n.a.	0.1	0.1	0.1	*<0.1	*0.1
Synthetic Cannabinoids	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a	1.2	0.3#
New and Emerging Psychoactive Substances	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a	0.4	0.3
Injected drugs	0.5	0.5	0.8	0.6	0.4	0.5	0.4	0.3	0.3
Any illicit[d] excluding pharmaceuticals	13.7	14.2	19.0	14.2	12.6	10.9	12.0	12.0	12.6

Source: Australian National Drug Strategy Household Survey 2016