DRUG FREE AUSTRALIA

THE EVIDENCE HAS LONG BEEN IN

AMA Position Paper on drug policy unaware of evidence making many of its positions outdated and obsolete

1. **All AMA drug policy positions should uniformly address the fact that surveys show almost all Australians do not approve of illicit drug use. Australians want less drugs, not more, and the AMA should discard policies that increase use/do not work**
2. **Decriminalisation characteristically creates increased drug use, not less. Portugal's decriminalisation experiment has seen increasing illicit drug use**
3. **Decriminalisation has been specifically used as an incremental step towards drug legalisation, which in the US has markedly increased cannabis use and associated social problems**
4. **The most recent Cochrane Collaboration review on methadone found it does not reduce overdose mortality or criminality, the very things it was employed to reduce**
5. **The world's most authoritative review of needle programs by the US IOM, which has historically been sympathetic to these programs, shows no protective effect**
6. **The science on injecting rooms shows no success across a broad range of outcomes**
7. **The only studies on ecstasy deaths in Australia indicate that ecstasy itself causes almost every pill death, while pill testing does in fact promote ecstasy use – the very substance causing almost all deaths**

Central Issues
&
Compiled Evidence

DRUG FREE AUSTRALIA

EVIDENCE CONTRADICTING AMA POLICY POSITIONS

Executive Summary

1. **All AMA drug policy positions should uniformly address the fact that surveys show almost all Australians do not approve of illicit drug use. Australians want less drugs, not more, and the AMA should discard policies that increase use/do not work**

   Almost all Australians, according to the 2019 National Drug Strategy Household Survey of around 25,000 Australians, do not approve of illicit drug use. 99% do not give approval to the regular use of heroin or speed/ice, cocaine (97%), ecstasy (96%) or cannabis (80%).

   Australian drug policy positions should be designed for the MAJORITY of Australians, not the minority 1.0% that use heroin, or the 1.3% that use speed and ice, or the 4.2% that use cocaine, or the 3% that use ecstasy, or the 11.6% using cannabis. Policies assuming user rights must be scrapped for policies that prioritise prevention

   The AMA is not a political party which can installed or removed for its drug policies by the vote of an Australian public. While some AMA positions reflect Australian attitudes, for which the AMA deserves due praise, others contradict them. AMA policies should uniformly reflect Australian attitudes to drug use unless medically countermanded

2. **Decriminalisation characteristically creates increased drug use, not less, something Australian clearly do not want. Portugal's decriminalisation experiment has seen increasing illicit drug use in contrast to Australia's 1998-2007 Tough on Drugs policy which saw Australian drug use decrease by 42% across comparable drugs types as those measured in Portugal**

   Decriminalisation has always been associated with increases in drug use. This is true for the Netherlands, various states in the USA that decriminalised cannabis in the 1970s, Australian States that decriminalised

cannabis in the 1980s and 1990s, as well as for Portugal which decriminalised all illicit drugs in 2001

3. **Decriminalisation has been specifically used as an incremental step towards drug legalisation, which in the US has markedly increased cannabis use and associated social problems**

   According to the US SAMHSA household survey, those reporting they had used cannabis in the last month before survey increased by 245,000 between 2010 (when medical cannabis was commercialised) and 2015. This 43% increase in regular cannabis users creates a vast new population susceptible to the multitude of harms presented by cannabis - psychosis, depression, suicide, driving and work accidents, amotivational syndrome, immunosuppression, permanent harms to the unborn, as well as cardio and pulmonary conditions.

   Colorado and Washington were the first states to legalise recreational use, having previously legalised medical cannabis. Within a year of legalisation in 2013 cannabis use by those aged 12-17 had risen 20% against decreases of 4% for all other states, rising 17% for college age young people against 2% for other states – all despite cannabis being illegal for all under age 21. Adult use rose 63% against 21% nationally.

   When comparing three year averages before and after legalisation, cannabis-related traffic deaths rose 62%. Hospitalisations related to cannabis went from 6,715 in 2012 to 11,439 in 2014. Notably, black market criminals found new sanctuary in Colorado, attracted by lower risks of enforcement. In 2018, Governor Hickenlooper introduced House Bill 1221 to address the 380% rise in arrests for black market grows between 2014 and 2016.

4. **The most recent Cochrane Collaboration review on methadone found it does not reduce overdose mortality OR criminality, the very things it was employed to reduce**

5. **The world's most authoritative review of needle programs by the US IOM, which has historically been sympathetic to these programs, shows no protective effect**

   Most of the rigorous studies on the effectiveness of needle exchanges in preventing blood-borne diseases were done between 1995 and 2005. The most authoritative 2006 review by the prestigious US Institute of Medicine found no success in preventing HIV and

Hepatitis C for stand-alone needle and syringe programs.

6. **The science on injecting rooms shows no success across a broad range of outcomes**

   The most rigorous review on injecting rooms to date found reductions in overdoses, ambulance callouts and in crime. However, Drug Free Australia has irrefutably demonstrated that the Vancouver study conclusions cited for overdose reductions is contradicted by official statistics as well as the then Police Commander. The study on reduced ambulance callouts failed to note that there were superior reductions at night when the injecting facility was closed, thus discrediting its conclusions. The study finding reduced crime in Vancouver falls to the same criticisms levelled at the study on reduced overdoses. No positive outcomes have been demonstrated for injecting rooms in rigorous scientific studies

   The recent June 2020 review of the Melbourne MSIR shows that the facility failed against all legislated outcomes, while simultaneously increasing crime in the North Richmond area.

7. **The only studies on ecstasy deaths in Australia indicate that ecstasy itself caused almost every pill death, while pill testing does in fact promote ecstasy use – the very substance causing almost all deaths**

   Pill testing doesn't address the causes of ecstasy deaths:

   1. **It cannot identify individual vulnerabilities to ecstasy that cause deaths**
   2. **It doesn't identify other co-used drugs such as alcohol or amphetamines which make ecstasy deadly**
   3. **It can't identify which ecstasy user will have an ecstasy-fuelled accident (mostly car accidents)**

The evidence supporting each of the seven central issues nominated here is found in the following pages

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EVIDENCE CONTRADICTING AMA POLICY POSITIONS - 1

All AMA drug policy positions should uniformly address the fact that surveys show almost all Australians do not approve of illicit drug use. Australians want less drugs, not more, and the AMA should discard policies that increase use/do not work

Almost all Australians, according to the 2019 National Drug Strategy Household Survey of around 25,000 Australians, do not approve of illicit drug use. 99% do not give approval to the regular use of heroin or speed/ice, cocaine (97%), ecstasy (96%) or cannabis (80%).

Australian drug policy positions should be designed for the MAJORITY of Australians, not the minority 1.0% that use heroin, or the 1.3% that use speed and ice, or the 4.2% that use cocaine, or the 3% that use ecstasy, or the 11.6% using cannabis. Policies assuming user rights must be scrapped for policies that prioritise prevention

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Almost all Australians do not approve of illicit drug use

The Australian Government's Australian Institute of Health and Welfare (AIHW) conducts the National Drug Strategy Household Survey every 3 years, surveying close to 25,000 Australians each time. The very large sample gives this survey a great deal of validity.

The last survey was in 2019, and Table 9.17 from its statistical data https://www.aihw.gov.au/reports/illicit-use-of-drugs/national-drug-strategy-household-survey-2019/data indicates Australian approval or disapproval of the regular use of various illicit drugs.

					Persons
Drug	**2007**	**2010**	**2013**	**2016**	**2019**
Alcohol	45.2	45.1	45.1	46.0	45.4
Tobacco	14.3	15.3	14.7	15.7	15.4
Illicit drugs (excluding pharmaceuticals)					
Marijuana/cannabis	6.6	8.1	9.8	14.5	19.6#
Ecstasy	2.0	2.3	2.4	2.9	3.8#
Meth/amphetamine[(b)]	1.2	1.2	1.4	1.2	1.2
Cocaine/crack	1.4	1.7	1.6	1.7	2.3#
Hallucinogens	1.7	2.4	3.1	3.7	5.6#
Inhalants	0.8	1.0	0.9	1.0	1.0
Heroin	1.0	1.2	1.2	1.1	1.1
Pharmaceuticals					
Over-the-counter pain-killers/pain-relievers[(b)]	n.a.	14.3	14.5	19.1	n.a.
Prescription pain-killers/pain-relievers[(b)]	n.a.	13.0	12.6	12.7	12.4
Tranquilisers, sleeping pills[(b)]	4.1	6.4	8.2	9.3	9.3
Steroids[(b)]	1.6	2.2	2.2	2.4	2.4
Methadone or buprenorphine[(b)]	1.0	1.2	1.3	1.3	1.5

Australians want less drugs, not more

With 96-99% of all Australians not giving their approval to the use of heroin, cocaine, speed/ice and ecstasy, and 80% not giving their approval to the regular use of cannabis, it is clear that Australians do not want these drugs being used in their society.

Drug policy should not pander to tiny user minorities

The percentages of Australians using the main illicit drugs are very, very small. Heroin, speed and ice is used by 1% or less of Australians, while ecstasy (3%), cocaine (4%) and cannabis (12%) are used by only tiny to small minorities. As such there is no reason for government or the AMA to pander to user rights ideologies – and most importantly, there is no United Nations right to use illicit drugs. In fact UN policy is precisely the opposite, with the 1961 Single Convention on Narcotic Drugs finding international agreement against illicit drug use since that date, confirming other Conventions in place since 1912.

Below is Table 4.6 from the same 2019 Australian survey, this time for drug use in the past 12 months before survey.

Table 4.6: Recent[a] illicit use of drugs, people aged 14 and over, 2001 to 2019 (per cent)

	Proportion						
Drug/behaviour	**2001**	**2004**	**2007**	**2010**	**2013**	**2016**	**2019**
Illicit drugs (excluding pharmaceuticals)							
Marijuana/cannabis[b]	12.9	11.3	9.1	10.3	10.2	10.4	11.6#
Ecstasy[c]	2.9	3.4	3.5	3.0	2.5	2.2	3.0#
Meth/amphetamine[d]	3.4	3.2	2.3	2.1	2.1	1.4	1.3
Cocaine	1.3	1.0	1.6	2.1	2.1	2.5	4.2#
Hallucinogens	1.1	0.7	0.6	1.4	1.3	1.0	1.6#
Inhalants	0.4	0.4	0.4	0.6	0.8	1.0	1.4#
Heroin	0.2	0.2	0.2	0.2	0.1	0.2	*<0.1
Ketamine	n.a.	0.3	0.2	0.2	0.3	0.4	0.9#
GHB	n.a.	0.1	*0.1	0.1	*<0.1	*0.1	*0.1
Synthetic Cannabinoids	n.a.	n.a.	n.a.	n.a.	1.2	0.3	0.2
New and Emerging Psychoactive Substances	n.a.	n.a.	n.a.	n.a.	0.4	0.3	*0.1#
Injected drugs	0.6	0.4	0.5	0.4	0.3	0.3	0.3
Any illicit[e] excluding pharmaceuticals	14.2	12.6	10.8	12.0	12.0	12.6	14.1#
Non-medical use of pharmaceuticals							
Pain-killers/pain-relievers and opioids[d,f]	n.a.	n.a.	n.a.	n.a.	n.a.	3.6	2.7#
Tranquillisers/sleeping pills[d]	1.1	1.0	1.4	1.5	1.6	1.6	1.8
Steroids[d]	0.2	*<0.1	*0.1	0.1	*0.1	*0.1	0.2
Methadone or Buprenorphine[d,g]	0.1	*<0.1	*<0.1	0.2	0.2	0.1	0.1
Non-medical use of pharmaceuticals[f,h]	n.a.	n.a.	n.a.	n.a.	n.a.	4.8	4.2#
Illicit use of any drug							
Any opioid[i]	n.a.	n.a.	n.a.	n.a.	n.a.	3.7	2.8#
Any illicit[j]	16.7	15.3	13.4	14.7	15.0	15.6	16.4

AMA has some excellent drug prevention policy positions

Some of the AMA's current drug policy positions reflect Australian attitudes to drugs, with prevention being highlighted, and state-of-the-art education models such as that being used in Iceland being given prominence. For this Drug Free Australia commends the AMA. However there are a whole range of positions which are contrary to the Australian desire for less drug use.

The AMA is not a political party which can be installed or removed from government at the whim of the Australian people, thus making it even more necessary that the AMA reflect Australian attitudes to drug use in their communities.

Australians have every right to expect their elected governments to enact the will of the people, and populist, rather than elitist governments, make a priority of enacting that will. Unless medically countermanded, there is no rationale that would support the AMA taking drug policy positions which are contrary to the current scientific evidence. **Unfortunately, the main harm reduction measures funded by Australian governments have an evidence-base indicating failure rather than a protective effect.**

A number of AMA positions contrary to the current science

The 2017 iteration of the AMA's drug policy positions contain a number of drug policy positions which directly contradict the current science on various drug interventions. This document will outline, in documented detail, the science which is at odds with AMA positions.

EVIDENCE CONTRADICTING AMA POLICY POSITIONS - 2

Decriminalisation characteristically creates increased drug use, not less, something Australian clearly do not want. Portugal's decriminalisation experiment has seen increasing illicit drug use, in contrast to Australia's 1998-2007 Tough on Drugs policy which saw Australian drug use decrease by 42% across comparable drugs types as those measured in Portugal

Decriminalisation has always been associated with increases in drug use. This is true for the Netherlands, various states in the USA that decriminalised cannabis in the 1970s, Australian States that decriminalised cannabis in the 1980s and 1990s, as well as for Portugal which decriminalised all illicit drugs in 2001.

Soft policies in the Netherlands increased use

In 1976 the Netherlands took a liberal approach to what they called the 'soft' drug cannabis but by the late 1990s **the Netherlands had the highest levels of hard' drug use in Europe**, outside of the drug-liberal United Kingdom/Ireland.

The Table (below) from the EMCDDA 2000 Annual Report Annex, http://www.emcdda.europa.eu/html.cfm/index37279EN.html shows **student drug use higher than all but the drug-liberal UK/Ireland** (all European countries where English was a second language arguably had a lesser level of penetration by US and UK musicians and artists who promoted illicit drug use). Over the last decade the country has become more politically conservative, bringing a tightening of drug policy with a greater majority of cannabis cafes closed and recently made unavailable to foreigners. Since 2004 the government has concentrated on anti-cannabis campaigns highlighting its harms, with some success.

Lifetime prevalence of use of different illegal drugs among 15- to 16- year-

	SCHOOL Surveys Lifetime prev				
	Year	Sample	All illegal drugs	Cannabis	Sc
Austria	1994	2250	9.9%	9.5%	
Belgium (Fle.) (1)	1996	2391	-	19.6%	
Belgium (Fle.) (2)	1998	9211	-	23.7%	
Denmark (1)	1995	2571	-	18.0%	
Denmark (2)	1999	1557	-	24.4%	
Finland (1)	1995	2300	5.5%	5.2%	
Finland (2)	1999	Preliminar	-	(10%)	
France (1)	1993	12391	15.3%	11.9%	
France (2)	1997	9919	27.5%	23.0%	
Greece (1)	1993	10543	4.5%	3.0%	
Greece (2)	1998	8557	11.4%	10.2%	
Ireland	1995	1849	37.0%	37.0%	
Italy (1)	1995	1641	21.0%	19.0%	
Italy (2)	1999	20000	-	19.0%	
Luxembourg	1998	660		18.5%	
Netherlands	1996	10455	31.7%	31.1%	
Portugal	1995	4767	4.7%	3.8%	
Spain (1)	1996	19191	29.6%	24.3%	
Spain (2)	1998	18348	33.9%	28.0%	
Sweden (1)	1997	5683	7.6%	6.8%	
Sweden (2)	1998	5455	7.7%	7.2%	
United Kingdom (1)	1995	7722	42.0%	41.0%	
United Kingdom (2)	1997	28756	39.8%	37.5%	

Decriminalisation in the USA increased use

Alaska legalised cannabis in 1975. A study in 1988 found that **72%** of year 12 students had tried it.[1] They recriminalised shortly thereafter.

California decriminalised cannabis on January 1, 1975. 10 months after cannabis use by 18 - 29 year olds was up **15%**.[2]

Oregon decriminalised cannabis in 1973. 12 months after cannabis use by 18 - 29 year olds was up **12%.**[3]

If tobacco smoking rose by 12-15% in 12 months for young people in this country, we would be horrified.

By contrast, increases in US cannabis use overall from 1973-76 were **negligible**, as per the US Household Surveys (below) found in https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1508375/pdf/amjph00013-0029.pdf. WE note that the reducing use from the US 1980s 'Just Say No' campaign is also evident, something drug law reformers try to deny.

Table 2.1. Trends in Prevalence of Lifetime and Last Year Marijuana Use by Age[1] (NHSDA 1974-1996)

	1974	1976	1977	1979	1982	1985	1988	1990	1991	1992	1993	1994	1995	1996
	%	%	%	%	%	%	%	%	%	%	%	%	%	%
Lifetime														
12-17 years	23.0	22.4	28.0	26.7	23.2	20.1	15.0	12.7	11.1	9.1	9.9	13.6	16.2	16.8
18-25 years	52.7	52.9	59.9	66.1	61.3	57.6	54.6	50.4	48.8	46.6	45.7	41.9	41.4	44.0
26-34 years	-	-	-	45.0	51.5	54.1	57.6	56.5	55.2	54.3	54.9	52.7	51.8	50.5
26 + years	9.9	12.9	15.3	-	-	-	-	-	-	-	-	-	-	-
35 + years	-	-	-	9.0	10.4	13.9	17.6	19.6	21.1	22.2	23.8	25.4	25.3	27.0
Last Year														
12-17 years	18.5	18.4	22.3	21.3	17.7	16.7	10.7	9.6	8.5	6.9	8.5	11.4	14.2	13.0
18-25 years	34.2	35.0	38.7	44.2	37.4	34.0	26.1	23.0	22.9	21.2	21.4	21.4	21.8	23.8
26-34 years	-	-	-	20.5	21.4	20.2	14.2	14.4	11.6	11.5	11.1	11.5	11.8	11.3
26+ years	3.8	5.4	6.4	-	-	-	-	-	-	-	-	-	-	-
35 + years	-	-	-	4.3	6.2	4.3	3.7	4.2	4.6	3.8	4.6	4.1	3.4	3.8

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1508375/pdf/amjph00013-0029.pdf

[1] Olsson O, Liberalization of drug policies – an overview of research and studies concerning a restrictive drug policy. Swedish National Institute of Public Health, Stockholm 1996 pp 33-4

[2] Ibid pp 32,3

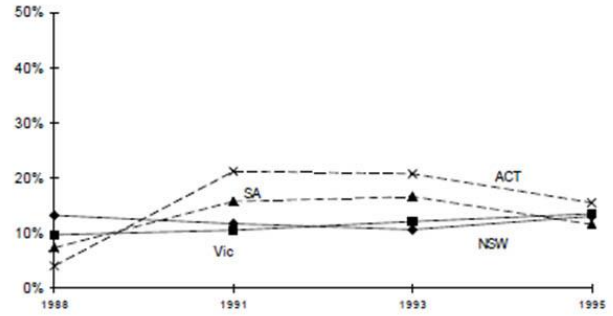
[3] Ibid, pp 31,2

Decriminalisation in Australia increased use

South Australia decriminalised cannabis in 1987, followed by the **ACT** in 1993. The graphs below from NDS Household Surveys show sharp rises in cannabis use for both jurisdictions before equalling the use of NSW and Victoria, States with previously entrenched cannabis problems.

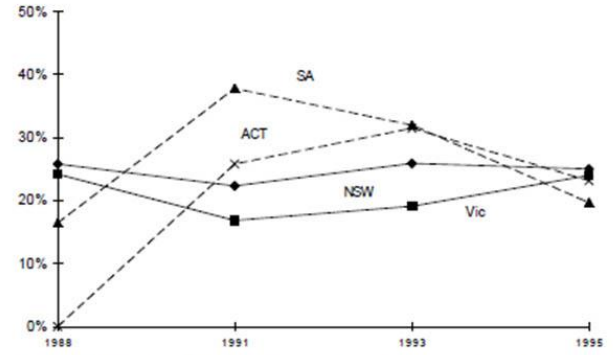
SA offences went from 6,231 in '87/'88 to 17,425 in '93/'94 and when researchers asked users about the increases, many said "We thought cannabis was now legal."

Figure 4.1: Used in the past 12 months for four jurisdictions



Source: NDS 1988, 1991, 1993, 1995

Figure 4.2: Use marijuana monthly or more often for four juridictions, 1988–1996



Source: NDS 1988, 1991, 1993, 1995; those who have never tried marijuana are excluded

http://www.health.gov.au/internet/main/publishing.nsf/Content/phd-drugs-mono31-cnt.htm

The truth on Portugal's decriminalisation

Portugal decriminalised all illicit drug use as of July 2001 and since that time drug decriminalisation/legalisation activists have inundated politicians and the media with glowing reports of Portugal's touted 'success'.

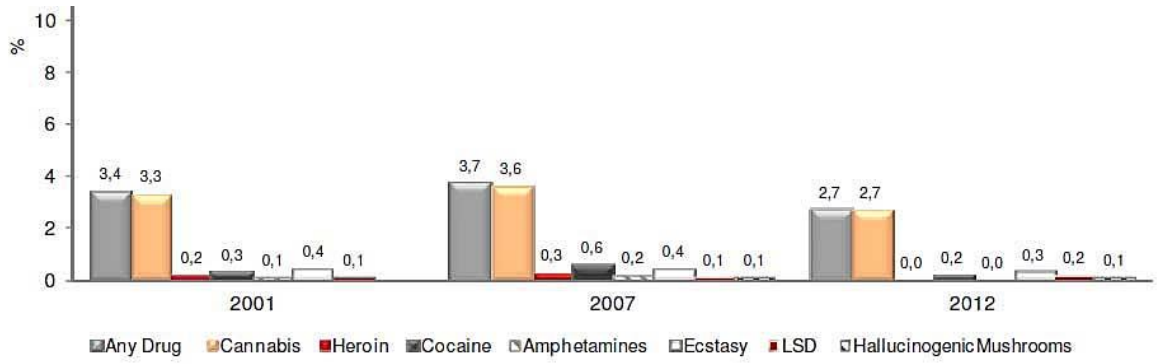
But below is the graphic reality, using their own official data and graphs sent to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the

same statistics used for the yearly United Nations World Drug Report drug use tables.

Portugal's drug use rose after decriminalisation

Since the implementation of decriminalisation in 2001 drug use for all age-groups in Portugal rose through to 2007 - compare the grey bars in its official REITOX 2014 annual report to the European Monitoring Centre http://www.emcdda.europa.eu/system/files/publications/996/2014_NATIONAL_REPORT.pdf graphed below. While cannabis use increased marginally for all aged groups, cocaine use doubled as did use of speed and ice.

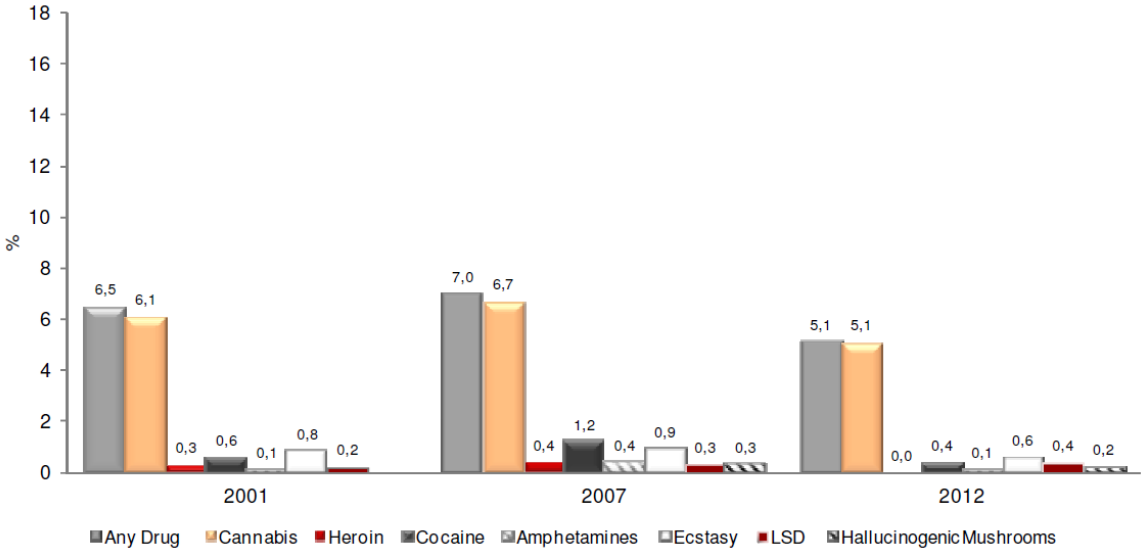
Any drug	Up 9%
Cannabis	Up 9%
Heroin	Up 50%
Cocaine	Doubled
Speed/Ice	Doubled
Ecstasy	No change
LSD	No change
Magic Mushrooms	Up from negligible to 0.1%



Graph 3 – General Population, Portugal – Total (15-64), last 12 months prevalence, by type of drug (%) (SICAD2013)

Drug use by young people aged 15-34, as graphed by the REITOX report (below), saw greater increases.

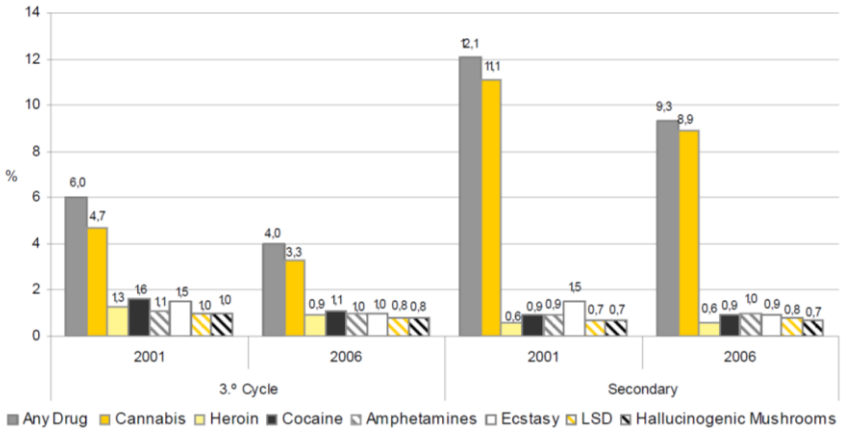
Any drug	Up 8%
Cannabis	Up 10%
Heroin	Up 33%
Cocaine	Doubled
Speed/Ice	Quadrupled
Ecstasy	Up 13%
LSD	Up 50%
Magic Mushrooms	Up from negligible to 0.3%



Graph 4 – General Population, Portugal – Young Adult Population (15-34 years), last 12 months prevalence, by type of drug (%) (SICAD2013)

Although high-school student use fell from 2001 to 2006

The dominant given by activists about Portugal is that decriminalisation did not cause increases in drug use. High-school student use did in fact fall by 33% for 3rd Cycle students (typically aged 13-15) and by 23% for secondary students (aged 16-18). A Cato Institute report promoting the "success" of decriminalisation made much of these decreases while downplaying the increases for the greater part of the population already seen in the graphs above.



Graph 7 - School Population – 3rd Cycle and Secondary: Last Month Prevalence, by type of Drug

http://www.emcdda.europa.eu/system/files/publications/522/NR_2008_PT_168550.pdf

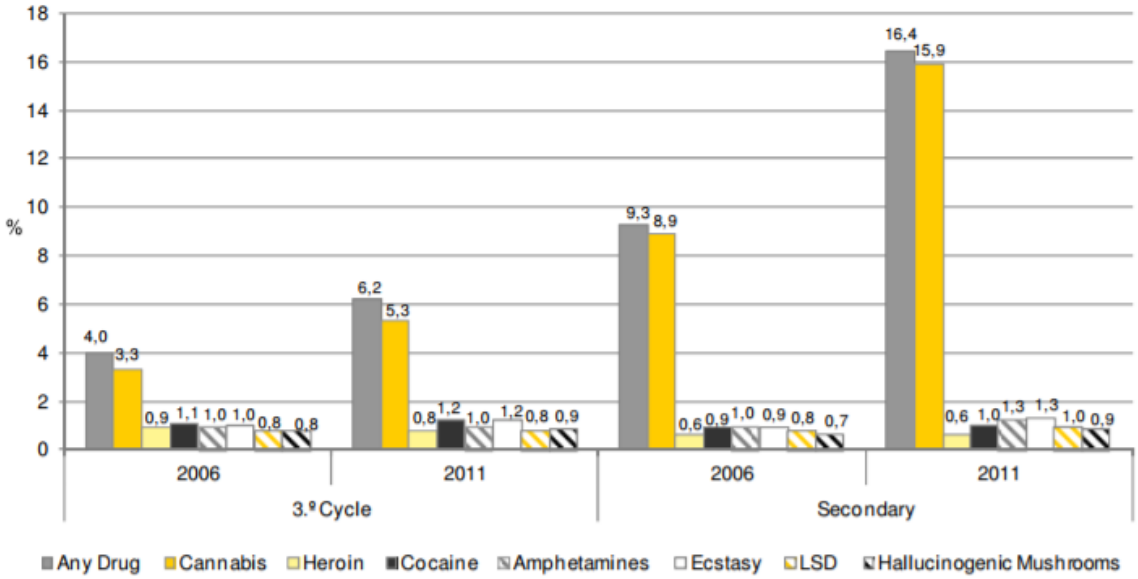
Overall drug use fell from 2007 to 2012 in Portugal but . . .

Between 2007 and 2012 drug use in Portugal for all age groups declined in line with general decreases across various European countries. Compare the figures in the first column for earlier years than those in the final column.

Italy - Opiates	0.8% (2005)	0.48% (2011)
Spain - Opiates	0.6% (2000)	0.29% (2012)
Switzerland - Opiates	0.61% (2000)	0.1% (2011)
Italy - Cocaine	1.1% (2001)	0.6% (2012)
Italy - Speed/Ice	0.4% (2005)	0.09% (2012)
Austria - Speed/Ice	0.8% (2004)	0.5% (2012)

. . . high school use rose steeply from 2006 to 2011

Use of any illicit drug by high-school students rose markedly between 2006 and 2011. The graph below is again copied directly from the 2014 REITOX report to the EMCDDA http://www.emcdda.europa.eu/system/files/publications/996/2014_NATIONAL_REPORT.pdf. From 2001, when decriminalisation commenced, Secondary School drug use was 36% higher and 76% higher than in 2006.



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

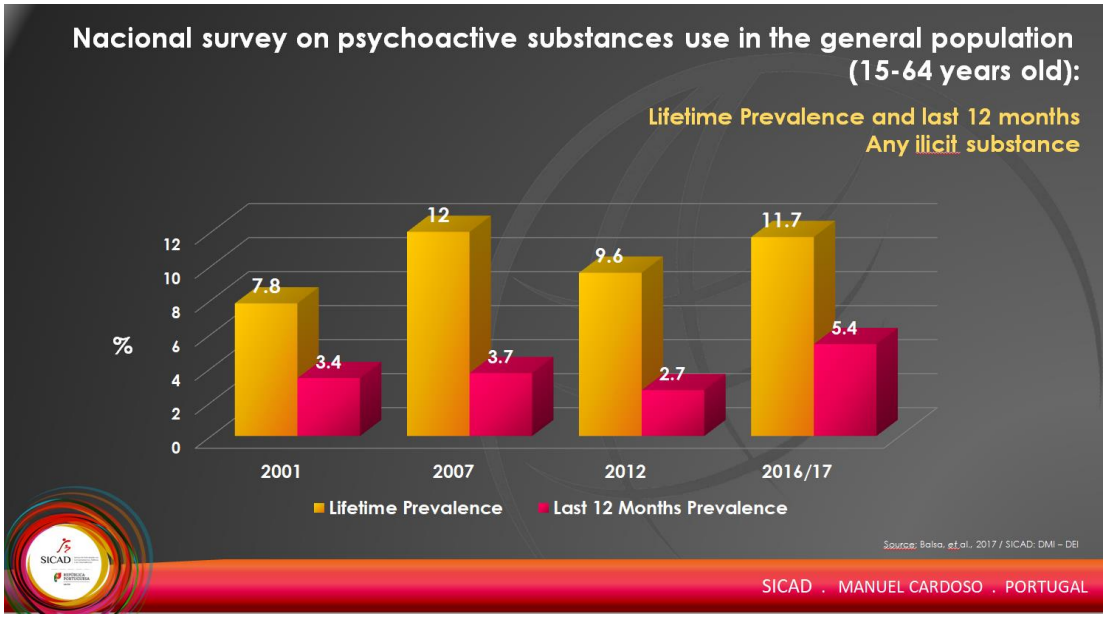
By 2017 drug use was 59% higher than in 2001

While Portugal has not yet reproduced the results of its 2016-17 survey in the usual REITOX National Report which would give a breakdown of use for each drug type, the figures for overall illicit drug use are available from a presentation by Manuel Cardoso, the Deputy General-Director of SICAD, Portugal's agency responsible for monitoring the country's drug use. This presentation can be accessed at https://drugfree.org.au/index.php/resources/library/9-drug-information/182-portugal.html using the link Integrated Drug Policy Manuel Cardoso SICAD (zip file).

Copied below from Cardoso's Powerpoint presentation at the June 2018 Sydney conference run by the Network of Alcohol and other Drug Agencies (NADA) are both the lifetime prevalence and last 12 month figures for Portugal for 2016/17. The figures for use in the last 12 months before survey are as follows:

Use in the last 12 months

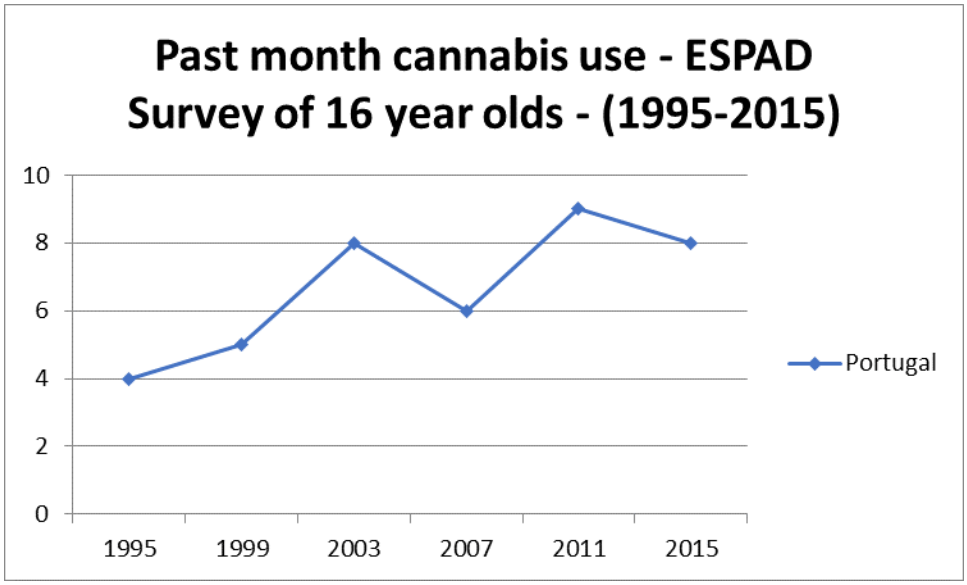
2001	3.4
2007	3.7
2012	2.7
2017	**5.4**



Note that Portugal's drug use in 2017 for those aged 15-64 was 59% higher than in 2001. This would be an alarming outcome for any country, demonstrating that Portugal's drug policy fails to deter rising drug use.

High School cannabis use 60% higher in 2015 than in 2001

The ESPAD survey of cannabis use (last 30 days before survey) for 16 year old high-school students shows increases in use of the drug from 1999, a couple of years before decriminalisation, through to 2015. The increases are substantial - 60% higher than in 1999. See Appendix C for the actual ESPAD statistics.



Drug deaths in Portugal increased

Claims that there were significant decreases in drug-related deaths in Portugal immediately following decriminalisation are based on two errors.

First, false claims that there were more than 75 drug-related deaths in 2001 which more than halved to 34 deaths in 2002 use a figure for 2001 for which there is no substantiation. Official drug-related deaths for Portugal, taken from the latest 2018 EMCDDA Statistical Bulletin are copied below. Notice that there is no such figure recorded for 2001.

Overdose deaths > Trends > EMCDDA 'Selection B'

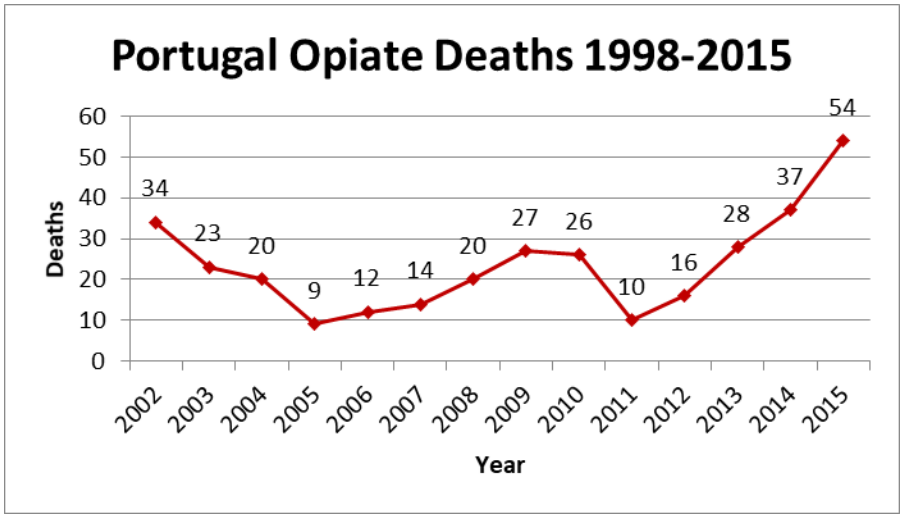
Download as Excel file (.xlsx)

Search:

Country	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000
Poland	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
Portugal	:	54	37	28	16	10	26	27	20	14	12	9	20	23	34	:	:
Romania *	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:

http://www.emcdda.europa.eu/data/stats2018/drd_en

Second, there is no way of knowing what the real number of drug related deaths before 2002 was. Up until 2009 Portugal counted all deaths where any illicit drug was detected, whether the death was caused by that illicit drug or not. Portugal later changed its definition for Selection B drug-induced deaths to only those that were caused by overdose or poisoning, and in 2009 reanalysed their data back to 2002. This leaves no comparison to the years before decriminalisation. The official figures yield the following graph.



Early decreases between 2002 and 2005 are part of the same decreasing trend in opiate use, as noted previously, which **predated** decriminalisation with reductions from 0.9% in 1998, to 0.7% in 2000. These decreases were not due to decriminalisation because they were not a part of it. Decriminalisation was introduced July 2001 and appears to be the beneficiary of whatever dynamic was driving opiate use and deaths down. However these early decreases in deaths are matched by an increasing trend between 2005 and 2010, which is followed by sharper rises in drug deaths from 2011 to 2015, the latest year for which data is currently available.

Portugal's graph should be compared with Australia's Tough on Drugs results recorded below. While Australia maintained criminal penalties for use of most drugs, it saw sharply decreased drug deaths that were then maintained at those lower levels throughout the tenure of Tough on Drugs.

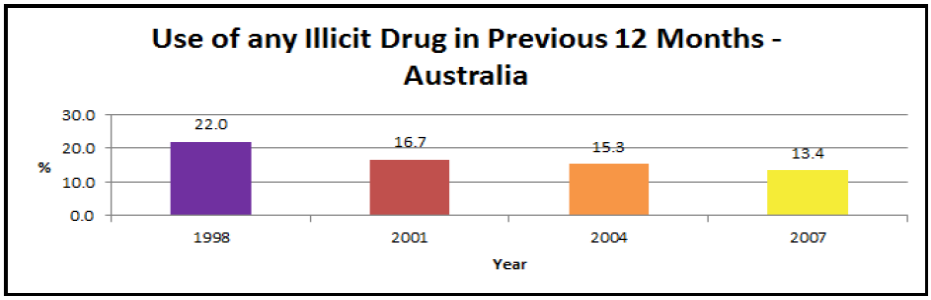
Portugal's increasing trend in deaths since 2011 undoubtedly reflects rising drug use, in light of drug overdose deaths usually closely correlated to levels of rising opiate use. This is because there is a reasonably inelastic relationship between opiate use and opiate deaths, where typically 1% of opiate users fatally overdose each year. Portugal's increasing trend in overdose deaths should be indicate similar increases in opiate use.

Now compare Australia's Tough on Drugs results

Compare the results of Australia's 'Tough on Drugs' between 1998 and 2007. This approach was with use of most illicits still a criminal offence. Use of all illicit drugs declined by 39%. Portugal's decriminalisation has never approached the success of Tough on Drugs.

Table 2.1: Summary of recent[a] drug use, people aged 14 years or older, 1993 to 2010 (per cent)

Drug/behaviour	1993	1995	1998	2001	2004	2007	2010
Illicit drugs (excluding pharmaceuticals)							
Cannabis	12.7	13.1	17.9	12.9	11.3	9.1	10.3
Ecstasy[b]	1.2	0.9	2.4	2.9	3.4	3.5	3.0
Meth/amphetamines[c]	2.0	2.1	3.7	3.4	3.2	2.3	2.1
Cocaine	0.5	1.0	1.4	1.3	1.0	1.6	2.1
Hallucinogens	1.3	1.9	3.0	1.1	0.7	0.6	1.4
Inhalants	0.6	0.4	0.9	0.4	0.4	0.4	0.6
Heroin	0.2	0.4	0.8	0.2	0.2	0.2	0.2
Ketamine	n.a.	n.a.	n.a.	n.a.	0.3	0.2	0.2
GHB	n.a.	n.a.	n.a.	n.a.	0.1	0.1	0.1
Injectable drugs	0.5	0.5	0.8	0.6	0.4	0.5	0.4
Any illicit[d][g]	**14.0**	**16.7**	**22.0**	**16.7**	**15.3**	**13.4**	**14.7**



It is important to recognize that Australia's drug use statistics, graphed from the final line of Table 2.1 above, include a wide variety of drugs, whereas Portugal's statistics are based on only a handful of drugs. When Australian drug use decreases are compared with Portugal on a drug by drug comparison, Australian decreased its drug use by 42% in comparison to Portugal's increases.

Decriminalisation increases use – something Australians don't want

Australians surveyed on their attitudes to decriminalisation are largely in favour, but Drug Free Australia contends that the Australian media's dereliction of its duty to inform the public of these statistics above is wholly responsible. Drug Free Australia has sent all the above information to a wide variety of Australian media, which shows no interest in publicising them.

Given Australians high disapproval ratings of illicit drug use, there can be no question that there attitudes to decriminalisation would change dramatically if they were given the truth about decriminalisation.

Drug Free Australia contends that the AMA's advocacy for decriminalisation needs to be cognisant of real data as well as Australian attitudes to drug use.

EVIDENCE CONTRADICTING AMA POLICY POSITIONS - 3

Decriminalisation has been specifically used as an incremental step towards drug legalisation, which in the US has markedly increased cannabis use and associated social problems

According to the US SAMHSA household survey, those reporting they had used cannabis in the last month before survey increased by 245,000 between 2010 (when medical cannabis was commercialised) and 2015. This 43% increase in regular cannabis users creates a vast new population susceptible to the multitude of harms presented by cannabis - psychosis, depression, suicide, driving and work accidents, amotivational syndrome, immunosuppression, permanent harms to the unborn, as well as cardio and pulmonary conditions.

Colorado and Washington were the first states to legalise recreational use, having previously legalised medical cannabis. Within a year of legalisation in 2013 cannabis use by those aged 12-17 had risen 20% against decreases of 4% for all other states, rising 17% for college age young people against 2% for other states – all despite cannabis being illegal for all under age 21. Adult use rose 63% against 21% nationally.

When comparing three year averages before and after legalisation, cannabis-related traffic deaths rose 62%. Hospitalisations related to cannabis went from 6,715 in 2012 to 11,439 in 2014. Notably, black market criminals found new sanctuary in Colorado, attracted by lower risks of enforcement. In 2018, Governor Hickenlooper introduced House Bill 1221 to address the 380% rise in arrests for black market grows between 2014 and 2016.

Australians do not want drugs legalised

The last National Drug Strategy Household Survey of 25,000+ Australians which asked attitudes to the legalisation of any illicit drug gave the results facsimiled below. While 2 in every 3 Australians do not want cannabis legalised, only 5-10% of Australians support the legalisation of heroin, ice, speed, cocaine and ecstasy.

Table 9.25: Support[a] for the legalisation of selected illicit drugs, people aged 14 and over, by drug use, 2010 to 2019 (per cent)

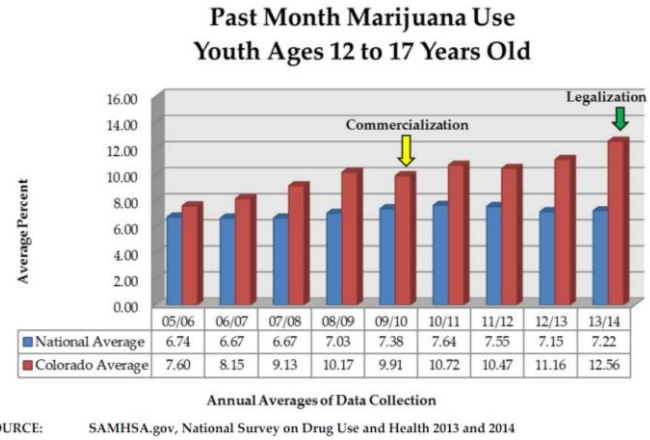
Proportion

	Never used				Ex-user[b]				Recent user[c]				Persons			
Drug	2010	2013	2016	2019	2010	2013	2016	2019	2010	2013	2016	2019	2010	2013	2016	2019
Cannabis	13.6	14.1	21.3	24.8#	32.5	33.5	47.8	56.6#	69.5	76.8	85.7	88.2	24.8	26.0	35.4	41.1#
Heroin[d]	5.7	5.3	5.4	5.3	26.6	27.8	26.3	25.2	49.3	48.0	57.9	59.2	6.0	5.7	5.8	5.6
Meth/amphetamines	4.6	4.2	4.2	3.9	7.1	7.7	8.7	9.7	17.4	22.5	26.9	33.3	5.0	4.8	4.8	4.6
Cocaine	5.3	4.8	5.3	5.3	14.3	15.0	19.7	19.6	27.2	31.7	30.0	42.0#	6.3	6.2	7.0	8.0#
Ecstasy	5.3	5.3	5.5	5.8	14.0	14.6	22.2	24.5	30.4	40.3	52.1	60.1	6.8	7.3	8.2	9.5#

The AMA should recognise that decriminalisation is an incremental step in an endgame that Australians simply do not want.

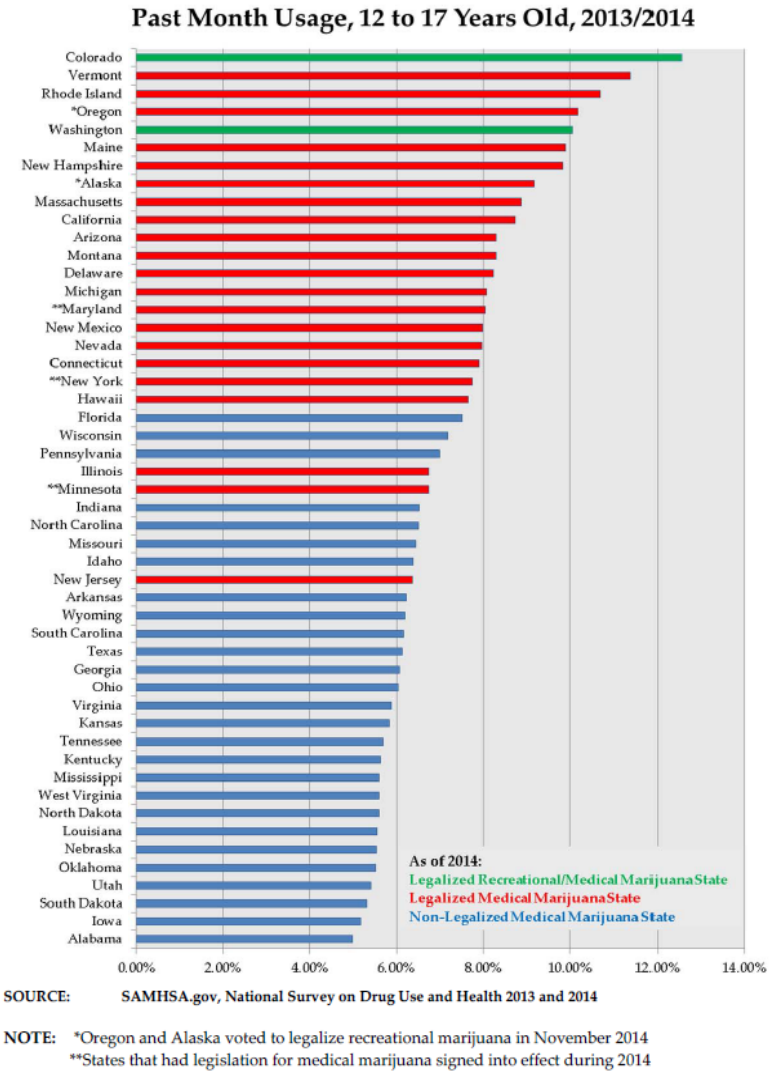
Use of cannabis by those aged 12-17 rose 20% in first year

The legalisation of recreational use of cannabis in Colorado and Washington in 2013 has led to increasing drug use in those states. It is illegal for any under the age of 21 to use cannabis, especially given the effect of cannabis on the developing adolescent brain. But use in Colorado by those aged 12-17 rose substantially against decreases of 4% in other states, despite use already being elevated by the legalisation of medical cannabis.



SOURCE: SAMHSA.gov, National Survey on Drug Use and Health 2013 and 2014

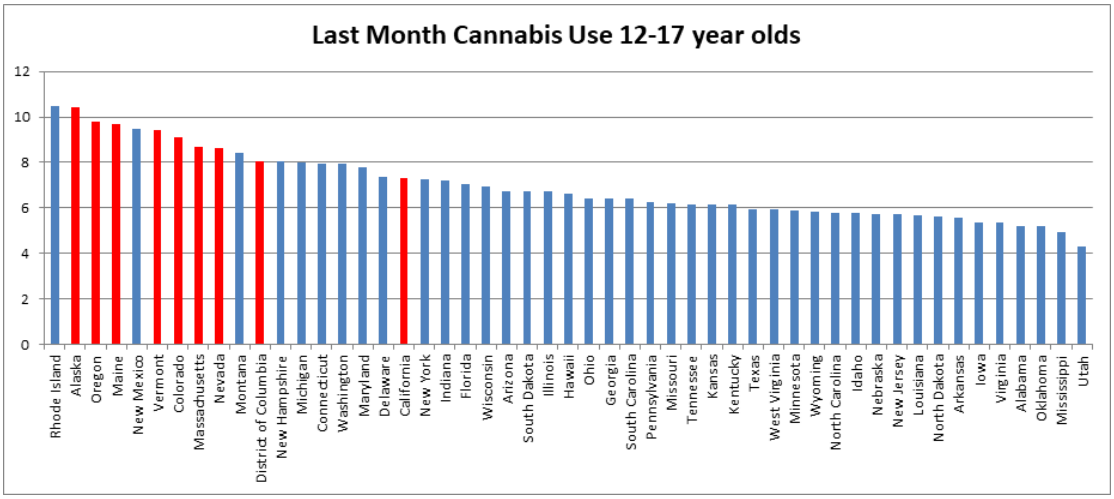
In 2013/14 Colorado youth ranked #1 for cannabis use in the United States, up from #4 in 2011/12 and from #14 in 2005/6. In the graph below states with legalised medical cannabis are marked red, and green for recreational use.



SOURCE: SAMHSA.gov, National Survey on Drug Use and Health 2013 and 2014

NOTE: *Oregon and Alaska voted to legalize recreational marijuana in November 2014
**States that had legislation for medical marijuana signed into effect during 2014

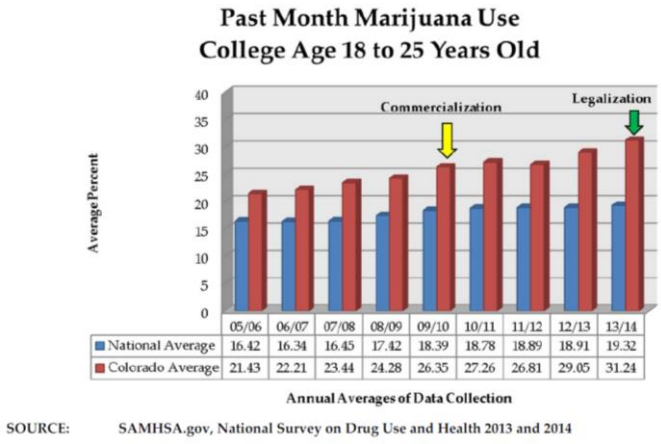
In the following 2 year period, drug use fell such that Colorado recent use for this age group fell to 7th in the nation. This was because other states had legalised cannabis in the intervening years, and Colorado was passed by states most of which had legalised cannabis use or were in the process of doing so. Below is the graph for all states with those states that had legalised cannabis by 2016 in red, or where legalisation legislation was already in process.



The most likely explanation for the marked decreases for this age-group is that they are under the institutional control of schools, whereas older age-groups are not subject to those institutional controls.

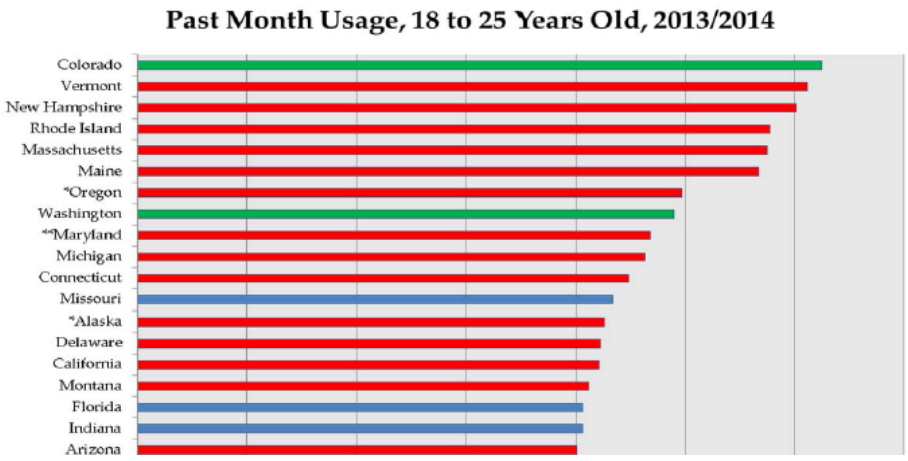
College-age use rose by 17%

Against increases of 2% nationally, use of cannabis by those of college age rose by 17% within the first year of legalised cannabis use.

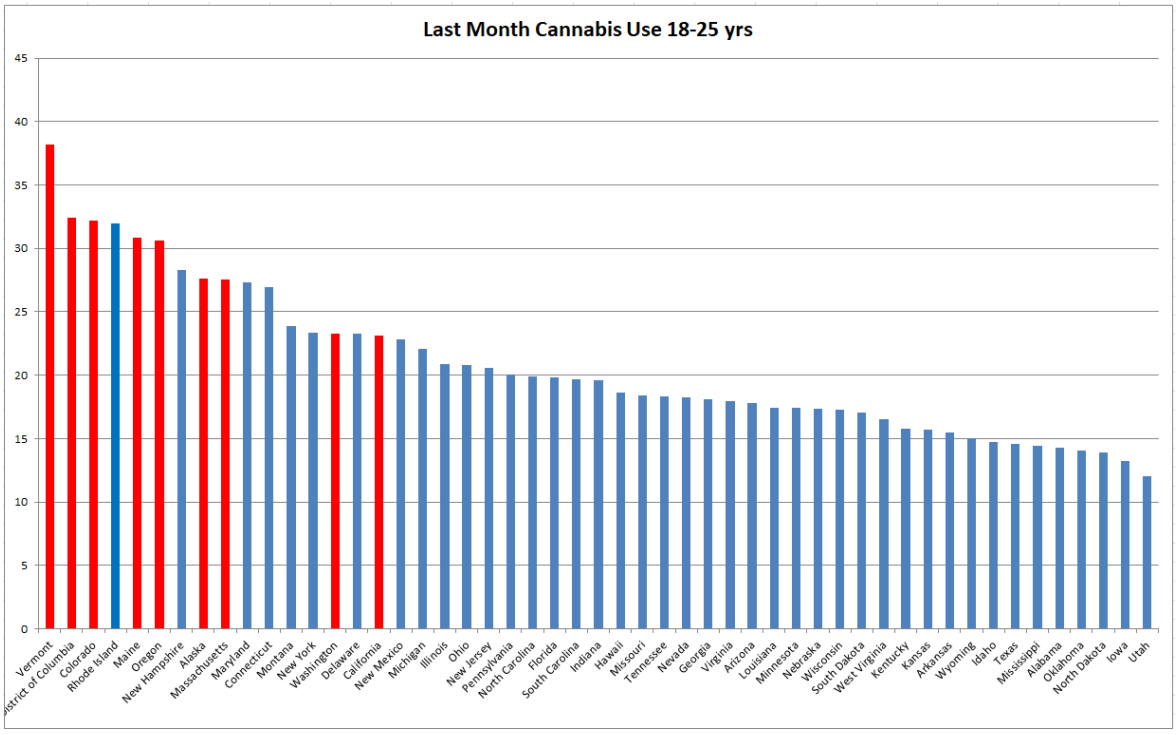


SOURCE: SAMHSA.gov, National Survey on Drug Use and Health 2013 and 2014

In 2013/14 Colorado college-age students ranked #1 for cannabis use in the United States, up from #3 in 2011/12 and from #8 in 2005/6.

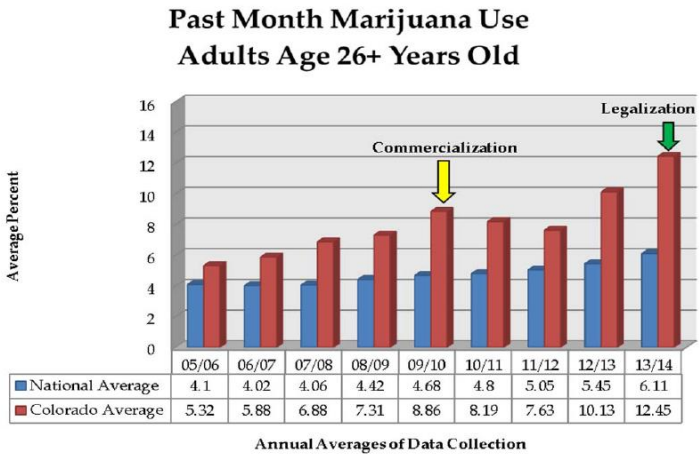


In 2015/16 against increases of 6% nationally, use of cannabis by those of college age rose by 3% (from 31.24% to 32.20%) between 2013/2014 and 2015/2016. In 2015/2016 Colorado college-age students ranked #3 for cannabis use in the United States. States ranking #1 (Vermont) and #2 (District of Columbia) were states that had legalised cannabis or were in the process of legalising (denoted by red below).



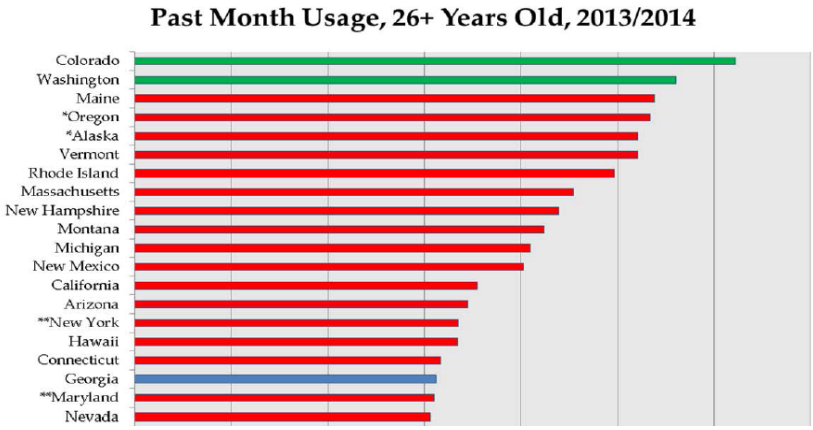
Adult use rose by 63%

Adult use increased by 63% in the first year after legalisation against increases of 21% nationally.

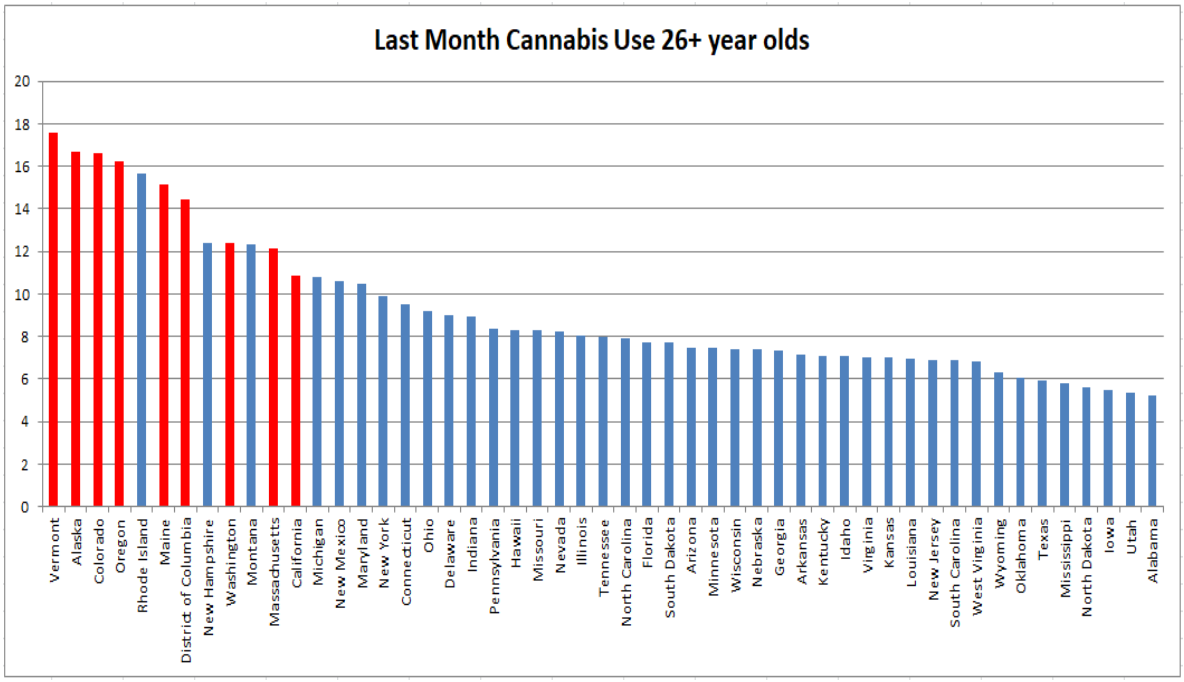


SOURCE: SAMHSA.gov, National Survey on Drug Use and Health 2013 and 2014.

In 2013/14 Colorado adults ranked #1 for cannabis use in the United States, up from #7 in 2011/12 and from #8 in 2005/6. States marked red are those states that had legalised cannabis for medical use.



In 2015/16 adult use increased by 33% (from 12.45% - 16.62%) against increases of 49% nationally. In 2015/2016 Colorado adults ranked #3 in the United States. The impact of various states legalising cannabis can be seen on the United States skyrocketing consumption. States ranking #1 (Vermont) and #2 (Alaska) ahead of Colorado were states which had legalised cannabis or were in the process of legalising (denoted by red below).



Cannabis legalisation, as has been graphically shown, creates considerably more use, not less use as Australians want.

Cannabis-related road fatalities rose by 62%

Road fatalities related to cannabis use rose by 62%, from 71 to 115 persons since 2013 when recreational cannabis use was legalised.

Traffic Deaths Related to Marijuana*			
Crash Year	Total Statewide Fatalities	Fatalities with Operators Testing Positive for Marijuana	Percentage Total Fatalities (Marijuana)
2006	535	37	6.92%
2007	554	39	7.04%
2008	548	43	7.85%
2009	465	47	10.10%
2010	450	49	10.89%
2011	447	63	14.09%
2012	472	78	16.53%
2013	481	71	14.76%
2014	488	94	19.26%
2015	547	115	21.02%

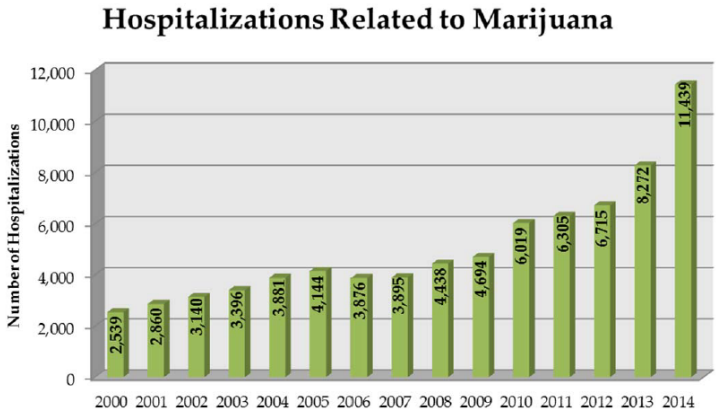
*Fatalities Involving Operators Testing Positive for Marijuana

SOURCE: National Highway Traffic Safety Administration, Fatality Analysis Reporting System (FARS)

Hospitalisations related to cannabis use rose markedly

The number of hospitalisations likely related to cannabis increased 32% in the two year average (2013-14) since Colorado legalised recreational marijuana compared to the two-year average prior to legalisation (2011-2012).

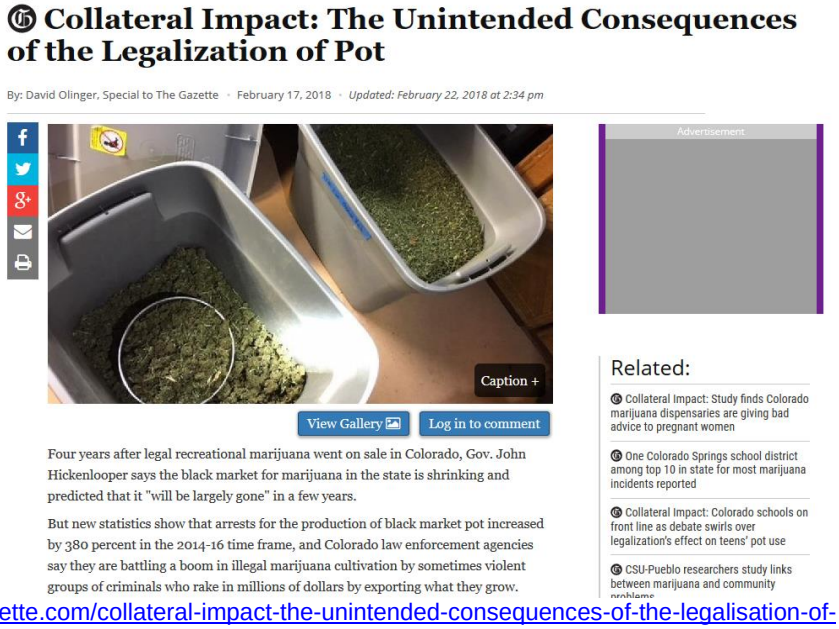
Hospitalisations moved from 6,715 to 11,439 since 2013.



SOURCE: Colorado Hospital Association, Hospital Discharge Dataset. Statistics prepared by the Health Statist and Evaluation Branch, Colorado Department of Public Health and Environment

Legislation introduced to cut black market criminality

Governor Hickenlooper last year introduced House Bill 1221 to address the 380% rise in arrests for black market grows between 2014 and 2016.



Collateral Impact: The Unintended Consequences of the Legalization of Pot

By: David Olinger, Special to The Gazette · February 17, 2018 · *Updated: February 22, 2018 at 2:34 pm*

Caption +

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Four years after legal recreational marijuana went on sale in Colorado, Gov. John Hickenlooper says the black market for marijuana in the state is shrinking and predicted that it "will be largely gone" in a few years.

But new statistics show that arrests for the production of black market pot increased by 380 percent in the 2014-16 time frame, and Colorado law enforcement agencies say they are battling a boom in illegal marijuana cultivation by sometimes violent groups of criminals who rake in millions of dollars by exporting what they grow.

Advertisement

Related:

- Collateral Impact: Study finds Colorado marijuana dispensaries are giving bad advice to pregnant women
- One Colorado Springs school district among top 10 in state for most marijuana incidents reported
- Collateral Impact: Colorado schools on front line as debate swirls over legalization's effect on teens' pot use
- CSU-Pueblo researchers study links between marijuana and community problems

http://gazette.com/collateral-impact-the-unintended-consequences-of-the-legalisation-of-pot/article/1621232

House Bill 1220 would aid law enforcement in detecting black market operations and might eliminate Colorado's dubious distinction as the best place in North America to produce pot for widespread distribution. It would limit grows on residential property to 12 plants, with an exception for medical marijuana patients or primary caregivers in compliance with local laws that allow exceptions.

House Bill 1221 would establish an annual $6 million grant program to reimburse local governments for training, education and enforcement related to black market grows. These bills may not go far enough, and the $6 million in HB 1221 does not approach what local authorities need. But the two bills are a good start in what should be an urgent effort to stop the unseemly and dangerous proliferation of black market pot.

http://gazette.com/editorial-pass-bills-to-curb-black-market-marijuana-in-colorado/article/1598339

Colorado added 245,000 extra cannabis users in 5 years

From 2010, when Colorado introduced the commercialisation of medical cannabis (with an explosion of medical cannabis user numbers) to 2015, the state added 245,000 extra frequent cannabis users. This is a 43% increase in cannabis use during those years for all surveyed age-groups.

Year	Population	Frequent Users
2010	5,029,196	573,919
2015	5,448,055	819,179
Change		245,260

245,000 extra users became susceptible to these cannabis harms

While the harms of cannabis have not been studied for as many years as the harms of tobacco and alcohol, it is already well-established that cannabis combines the harms of intoxication from alcohol with the particulate damage of tobacco. Cannabis presents a wide variety of additional harms.

- Cannabis is an established gateway to other dangerous drugs, adding an additional gateway beyond the two existing legal drugs
- Cannabis users are 50% more likely to develop alcohol use disorder
- Cannabis use is associated with a doubling the chance of psychosis
- Cannabis use is associated with a 4 times greater chance of depression
- Cannabis is associated with Amotivational Syndrome
- Cannabis use is associated with a 3 fold risk of suicidal ideation

- The immune system of cannabis users is adversely affected
- VIOLENCE AND AGGRESSION are a documented part of its withdrawal syndrome
- Brain Function
    - Verbal learning is adversely affected
    - Organisational skills are adversely affected
    - Cannabis causes loss of coordination
    - Associated memory loss can become permanent
    - Cannabis is associated with attention problems
- Drivers are 16 times more likely to hit obstacles
- Miscarriage is elevated with cannabis use
- Fertility is adversely affected
- Newborns are adversely affected with appearance, weight, size, hormonal function, cognition and motor function adversely affected through to adulthood
- Cannabis use causes COPD & bronchitis
- Cannabis is also associated with cardio-vascular stroke and heart attack, with chance of myocardial infarction 5 times higher after one joint

EVIDENCE CONTRADICTING AMA POLICY POSITIONS - 4

The most recent Cochrane Collaboration review on methadone found it does not reduce overdose mortality OR criminality, the very things it was employed to reduce

Gold standard review - methadone does not reduce overdose or criminality

The most important outcome for methadone maintenance (which undoubtedly falls under the AMA title 'treatment') is its ability to save lives from opiate overdose, as well as reducing the need for users to commit criminal acts to buy heroin.

Yet the most authoritative review of well-designed journal studies by the Cochrane Collaboration (full study at Appendix A) found no such effectiveness for methadone maintenance. It is notable that the lead researcher for this review is Richard Mattick, former head of the Australian National Drug and Alcohol Research Centre (NDARC) at NSW University, who is an ardent harm reductionist.

From the Abstract of the Cochrane review itself:

Main results

Eleven studies met the criteria for inclusion in this review, all were randomised clinical trials, two were double-blind. There were a total number of 1969 participants. The sequence generation was inadequate in one study, adequate in five studies and unclear in the remaining studies. The allocation of concealment was adequate in three studies and unclear in the remaining studies. Methadone appeared statistically significantly more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use as measured by self report and urine/hair analysis (6 RCTs, RR = 0.66 95% CI 0.56-0.78), but not statistically different in criminal activity (3 RCTs, RR=0.39; 95%CI: 0.12-1.25) or mortality (4 RCTs, RR=0.48; 95%CI: 0.10-2.39).

Authors' conclusions

Methadone is an effective maintenance therapy intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilise opioid replacement therapy. It does not show a statistically significant superior effect on criminal activity or mortality.

A substantial percentage of methadone users still use heroin

From the Cochrane review by Mattick et al, the relevant studies show that a varying percentage of methadone patients still use heroin, with one study finding 73% still using the substance.

Analysis 1.3. Comparison 1 Methadone maintenance treatment vs No methadone maintenance treatment, Outcome 3 Self reported heroin use.

Review: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

Comparison: 1 Methadone maintenance treatment vs No methadone maintenance treatment

Outcome: 3 Self reported heroin use

Study or subgroup	Methadone MT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Dolan 2003	41/129	92/124		0.43 [0.33, 0.56]
Dole 1969	2/12	15/15		0.20 [0.06, 0.61]
Gruber 2008	30/41	15/24		1.17 [0.82, 1.68]
Gunne 1981	5/17	12/17		0.42 [0.19, 0.93]
Kinlock 2007	28/70	39/64		0.66 [0.46, 0.93]
Yancovitz 1991	21/75	83/94		0.32 [0.22, 0.46]

EVIDENCE CONTRADICTING AMA POLICY POSITIONS - 5

The world's most authoritative review of needle programs by the US IOM, which has historically been sympathetic to these programs, shows no protective effect

Most of the rigorous studies on the effectiveness of needle exchanges in preventing blood-borne diseases were done between 1995 and 2005. The most authoritative 2006 review by the prestigious US Institute of Medicine found no success in preventing HIV and Hepatitis C for stand-alone needle and syringe programs.

Needle programs have no demonstrated positive effect

In 2006 the prestigious US Institute of Medicine (IOM), with its extensive panel of 24 scientists, medical practitioners, and reviewers did a comprehensive review of the literature on needle exchanges.

In their late 1997 review of needle exchanges, the IOM had noted the poor design and lack of rigour in most of the studies on the effectiveness of NEPs to that time, but nevertheless advocated for their implementation in the United States, *indicating that they were sympathetic to the intervention even before the evidence was in*. This bias toward harm reduction makes their later conclusions against the effectiveness of NSP important.

Almost all rigorous studies on Needle and Syringe Programs have been done between 1995 and 2005, which allowed the IOM to better review NSP effectiveness in reducing HIV and HCV (Hepatitis C) in their 2005 Geneva Conference.

The result of all their deliberations were published in 2006, and the chapter reviewing studies on NSP is appended (Appendix B).

While the IOM report found that multi-component programs which contained needle exchanges were effective in reducing self-reported risk behaviours, the IOM review, when considering the effectiveness of NSPs alone found (page 149) that:

> "evidence regarding the effect of needle and syringe exchange on HIV incidence *is limited and inconclusive*"
>
> "ecological studies monitor populations rather than individuals, and therefore *cannot establish causality" for NSPs*
>
> "multiple studies show that (needle exchanges) *do not reduce transmission* of (Hepatitis C)."

Conclusion 3-5: Moderate evidence indicates that multi-component HIV prevention programs that include needle and syringe exchange reduce intermediate HIV risk behavior. However, evidence regarding the effect of needle and syringe exchange on HIV incidence is limited and inconclusive.

Conclusion 3-6: Five studies provide moderate evidence that HIV prevention programs that include needle and syringe exchange have significantly less impact on transmission and acquisition of hepatitis C virus than on HIV, although one case-control study shows a dramatic decrease in HCV and HBV acquisition.

https://www.nap.edu/login.php?record_id=11731&page=https%3A%2F%2Fwww.nap.edu%2Fdownload%2F11731 p 149

It is abundantly clear that if NSPs are ineffective with HCV, where there is a large pool of infected users transmitting Hep C via shared needles and equipment, then the failure of NSPs to stop the high rates of shared needles and equipment is as ineffective against HIV as it is against HCV.

The fact that Australia has low rates of HIV transmission can be easily explained by the initial small pool of infected users, by the success of Australia's Grim Reaper television advertising campaign, and to high rates of freely available HIV testing.

In fact, Dr Alex Wodak, the doctor responsible for introducing NSPs within Australia lamented the ineffectiveness of NSPs with HCV in this country, where rates are little different to other countries of the world with no NSPs. His 1997 MJA article http://www.mja.com.au/public/issues/mar17/wodak/wodak.html titled "Hepatitis C: Waiting for the Grim Reaper" made the following telling points:

> "Despite the success of the harm reduction/public health approach in controlling the HIV epidemic and slowing the spread of hepatitis B among IDUs in Australia, it appears not to have reduced the incidence of hepatitis C."
>
> "Until Australia embarks on a major national awareness-raising exercise, such as a "Grim Reaper"-style public education campaign, the band will continue to play on for hepatitis C as it once did for HIV."

The MJA article says it all and the AMA is advised to remove support from this failed harm reduction approach.

EMCDDA review does not supersede the IOM review

A 2010 'review of reviews' by Norah Palmateer et al. in Addiction (105) pages 844-859 studying the effectiveness of needle exchanges found that "there is insufficient evidence to conclude that any of the interventions are effective in preventing HCV (Hepatitis C) transmission." This is a somewhat more optimistic outcome than that of the US IOM. Palmateer also concludes that there is "tentative evidence to support the effectiveness of NSP in preventing HIV transmission." Again, this is a more optimistic outcome.

However the 2010 Palmateer study makes a critical error in its 'review of reviews', failing to adequately look into the primary studies guiding those reviews, as well as uncritically accepting the conclusions of the three reviews. The three reviews included the 2004 Wodak/Cooney study completed for the World Health Organisation (WHO) and the 2006 Tilson et al. study representing the work of the prestigious US Institute of Medicine we have already outlined with its extensive panel of 24 scientists, medical practitioners and reviewers. The third study was the 2001 Gibson et al. study for which the Palmateer reviewers concluded that "their (Gibson's) conclusions were apparently inconsistent with the HIV studies reviewed" (p 851).

The more optimistic HIV conclusion of the 2010 Palmateer study, as compared to the formidable US Institute of Medicine 2006 'inconclusive' finding lies visibly in a specific lack of scrutiny by the Palmateer reviewers of the 2004 Wodak/Cooney review. On pages 845-6, the Palmateer 'review of reviews' reports its

methodology whereby, “(f)rom each review, we extracted reviewers’ assessment of the evidence and the number, design and findings of relevant primary studies. Information on primary studies was extracted from the reviews; in the case where reviews reported discrepant study findings, the primary studies were consulted.” Notably though, the Palmateer ‘review of reviews’ failed to check whether the 2004 Wodak/Cooney review’s classification of 5 primary studies as ‘positive’ accorded with the internal conclusions of those five studies, or whether each had entirely defensible methodologies. This is something that the 2006 US Institute of Medicine review in fact did.

In their December 2005 Geneva Conference convened to study the effectiveness of needle exchange on HIV transmission, the US IOM had Australia’s Dr Alex Wodak present the findings of his 2004 WHO study, followed by Sweden’s Dr Kerstin Käll (a Drug Free Australia Fellow) who clearly demonstrated that three of the five ‘positive’ studies for needle exchange effectiveness cited by the 2004 WHO review were either invalid or were in fact inconclusive.

The ‘positive’ 1993 Heimer et al study did not measure HIV prevalence among IDUs but only in returned needles, which, she stated, cannot be directly translated into a population and therefore should not have been included in the WHO review. The ‘positive’ 2000 study by Monterosso and co-workers was misclassified as positive for NEP, whereas in fact the result was clearly statistically non-significant and should have been labeled inconclusive. The purportedly ‘positive’ 1991 Ljungberg et al study had found HIV seroprevalence in Sweden’s Lund, a city with needle exchange, to be maintained at -1% in contrast to 60% in Stockholm, but ignored the authors’ own comment that incidence in Stockholm had been reduced to 1% by the time of the study without the implementation of needle exchanges, therefore she maintained that this study should have been moved to the inconclusive table.

The Palmateer ‘review of reviews’, while uncritically accepting the ‘positive’ classifications wrongly attributed by the 2004 WHO review, did look at the strength or otherwise of the described design of the studies cited therein, noting, to their own credit, that "(f)our of the five positive findings were generated by studies with weaker designs.”

Drug Free Australia again alerts the AMA to the fact that there is insufficient evidence to conclude that NSPs are effective in preventing HCV (Hepatitis C) transmission, and that the evidence supporting the effectiveness of NSPs in preventing HIV transmission still remains inconclusive.

The science contradicts two Australian studies on NSP

Two well-known Australian studies which calculated the cost-benefit for needle and syringe programs are thereby based on a falsehood, where they assumed that there was scientific support for the effectiveness of needle and syringe programs when there was none.

The first 2002 study, Return on Investment which was the kind of ecological study panned by the Institute of Medicine review but widely publicised in the media, calculated that to that date there had been 25,000 less cases of HIV and 21,000 less cases of Hepatitis C (HCV) as a result of Australian government investment in needle and syringe programs. The second 2009 report Return on Investment 2 calculated a staggering 32,050 cases of HIV and 96,667 cases of

HCV avoided between 2000 and 2009 which created a net saving, at lowest estimate of $1.03 billion from an investment of $243 million.

In neither of these reports was there any presentation of defensible data or statistically derived evidence on needle and syringe programs from rigorous studies (ecological studies cannot infer outcomes), supporting any alleged success of such programs in averting HCV transmission, and where the evidence on the alleged success on HIV has in fact been scientifically inconclusive.

The one conclusion that can be well defended is that NSPs are ineffective in controlling HCV, and by their failure to control needle sharing, the very practice it was designed to remove, it cannot have ever been effective in decreasing HIV transmissions.

Drug Free Australia urges the AMA to reflect the current science in its drug policy positions.

EVIDENCE CONTRADICTING AMA POLICY POSITIONS – 6

The science on injecting rooms shows no success across a broad range of outcomes

The most rigorous review on injecting rooms to date found reductions in overdoses, ambulance callouts and in crime. However, Drug Free Australia has irrefutably demonstrated that the Vancouver study conclusions cited for overdose reductions is contradicted by official statistics as well as the then Police Commander. The study on reduced ambulance callouts failed to note that there were superior reductions at night when the injecting facility was closed, thus discrediting its conclusions. The study finding reduced crime in Vancouver falls to the same criticisms levelled at the study on reduced overdoses. No positive outcomes have been demonstrated for injecting rooms in rigorous scientific studies

The recent June 2020 review of the Melbourne MSIR shows that the facility failed against all legislated outcomes, while simultaneously increasing crime in the North Richmond area.

The failure of injecting rooms

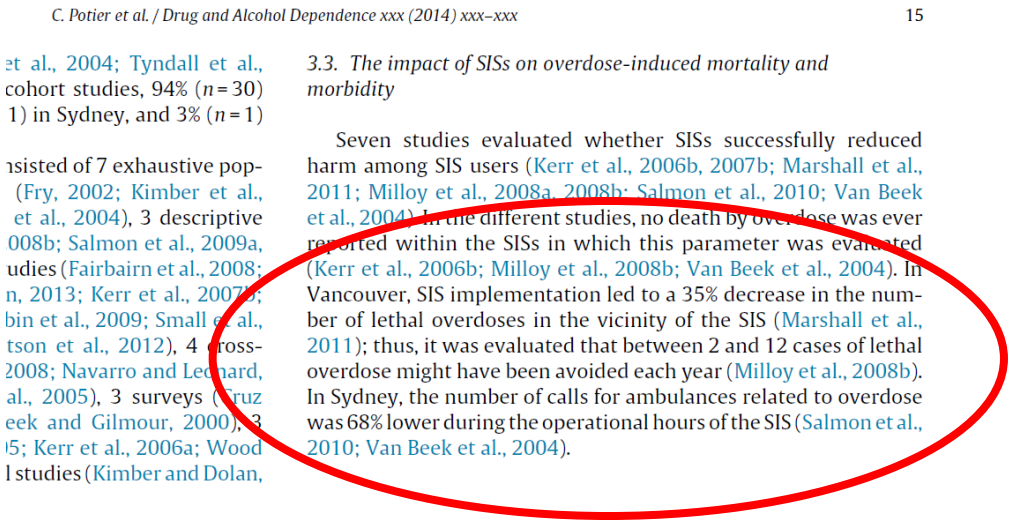
Reviews of scientific evaluations of SIFs (Kerr et al., 2007; McNeil and Small, 2014; Potier et al., 2014; Garcia, 2015; Kennedy, Karamouzian, and Kerr, 2017; May et al., 2018 (retracted); Kilmer et al., 2018), have reported positive outcomes across a range of evaluated criteria, **but most have used studies which methodologically fail to demonstrate the effectiveness of SIFs to alter individual or population-level outcomes**. Just two reviews, May et al. 2018 and Kilmer et al. 2018 (RAND Corporation) included only studies with a quasi-experimental design using control groups/areas, with May et al. subsequently being retracted because of "methodological weaknesses linked to the pooling of diverse outcomes into a single composite measure" (International Journal of Drug Policy, 2018) but not for its selection criteria of high-quality studies on SIF effectiveness.

The RAND Corporation similarly identified nine studies with quasi-experimental design, noting that four of the earlier studies had been superseded by others within the remaining five which studied the same outcomes with longer time series in the same locations. This effectively reduced the available number of reviewed studies to just five which are limited to overdose-related outcomes, discarded injecting equipment and crime. These studies examined SIFs in only three cities – Sydney, Vancouver and Barcelona.

Of these five studies, Marshall et al. found a 35% reduction in opiate overdose fatalities in the immediate area surrounding Vancouver' s Insite, while Salmon et al. 2010 found a greater reduction in ambulance callouts for overdose in the Kings Cross postcode housing the Sydney MSIC than for the rest of New South Wales. Donnelly and Mahoney found a null effect of the Sydney MSIC on crime in the Kings Cross neighbourhood, while Myer and Belisle found a significant reduction in property and violent crime in the area surrounding Insite immediately after its opening. Espelt et al. 2017 had conflicting results regarding discarded injecting equipment. These results led to the Rand Corporation review delivering a largely positive report concerning the possibility of implementing SIFs in the United States where no such facilities currently exist.

RAND review relied on two discredited studies

The main two studies demonstrating the supposed effectiveness of a Medically Supervised Injecting Centre in reducing overdose mortality (Marshall et al. Lancet 2011) and ambulance overdose callout reductions (Salmon et al. Addiction 2010) *both demonstrate either incompetence on the part of the researchers or possibly fraudulent intent*, and yet likewise form the centre of the other major literature review to that date (see the 2014 review by Potier, C., et al., Supervised injection services: What has been demonstrated? A systematic literature review. Drug Alcohol Depend. (2014), http://dx.doi.org/10.1016/j.drugalcdep.2014.10.012 below).



C. Potier et al. / Drug and Alcohol Dependence xxx (2014) xxx–xxx 15

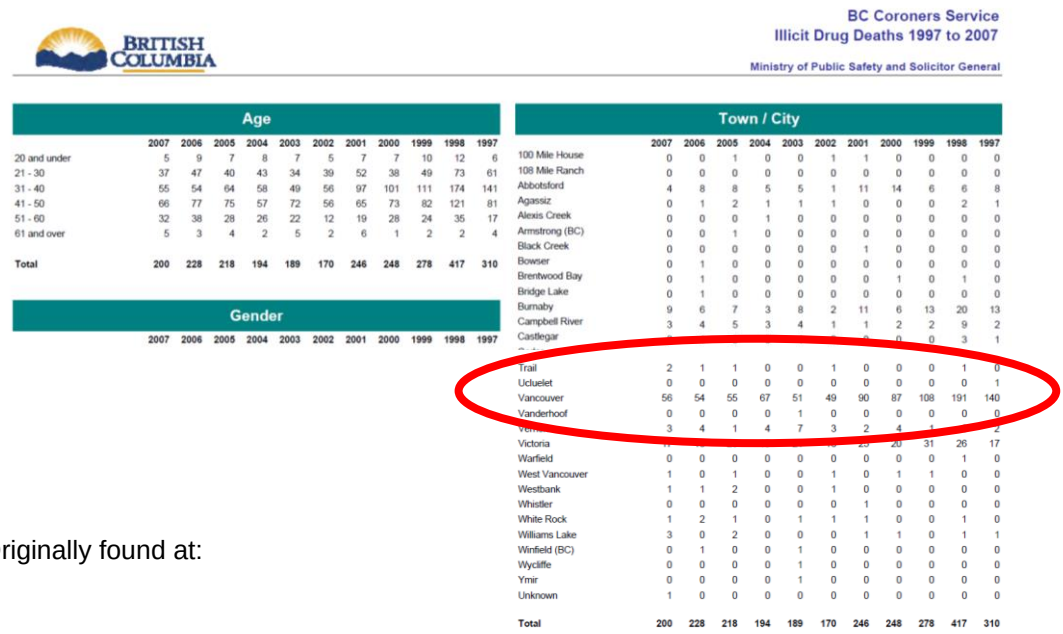
et al., 2004; Tyndall et al., cohort studies, 94% ($n = 30$) 1) in Sydney, and 3% ($n = 1$)

nsisted of 7 exhaustive pop- (Fry, 2002; Kimber et al., et al., 2004), 3 descriptive 008b; Salmon et al., 2009a, udies (Fairbairn et al., 2008; n, 2013; Kerr et al., 2007b; bin et al., 2009; Small et al., tson et al., 2012), 4 cross- 2008; Navarro and Lechard, al., 2005), 3 surveys (Cruz eek and Gilmour, 2000), 3 05; Kerr et al., 2006a; Wood l studies (Kimber and Dolan,

3.3. The impact of SISs on overdose-induced mortality and morbidity

Seven studies evaluated whether SISs successfully reduced harm among SIS users (Kerr et al., 2006b, 2007b; Marshall et al., 2011; Milloy et al., 2008a, 2008b; Salmon et al., 2010; Van Beek et al., 2004). In the different studies, no death by overdose was ever reported within the SISs in which this parameter was evaluated (Kerr et al., 2006b; Milloy et al., 2008b; Van Beek et al., 2004). In Vancouver, SIS implementation led to a 35% decrease in the number of lethal overdoses in the vicinity of the SIS (Marshall et al., 2011); thus, it was evaluated that between 2 and 12 cases of lethal overdose might have been avoided each year (Milloy et al., 2008b). In Sydney, the number of calls for ambulances related to overdose was 68% lower during the operational hours of the SIS (Salmon et al., 2010; Van Beek et al., 2004).

The 2011 Marshall et al. Lancet study so central to these positive reviews spuriously claimed that Insite likely reduced overdoses in Vancouver by 9% despite official BC Coroners' stats clearly showing only increases in ODs for Vancouver after Insite's 2003 opening as per screenshot of their document immediately below. Drug Free Australia corrected Lancet on these statistics in a full page letter printed by Lancet in its January 2012 issue (See Appendix C).



BC Coroners Service
Illicit Drug Deaths 1997 to 2007
Ministry of Public Safety and Solicitor General

Age

	2007	2006	2005	2004	2003	2002	2001	2000	1999	1998	1997
20 and under	5	9	7	8	7	5	7	7	10	12	6
21 - 30	37	47	40	43	34	39	52	38	49	73	61
31 - 40	55	54	64	58	49	56	97	101	111	174	141
41 - 50	66	77	75	57	72	56	65	73	82	121	81
51 - 60	32	38	28	26	22	12	19	28	24	35	17
61 and over	5	3	4	2	5	2	6	1	2	2	4
Total	**200**	**228**	**218**	**194**	**189**	**170**	**246**	**248**	**278**	**417**	**310**

Gender

	2007	2006	2005	2004	2003	2002	2001	2000	1999	1998	1997

Town / City

	2007	2006	2005	2004	2003	2002	2001	2000	1999	1998	1997
100 Mile House	0	0	1	0	0	1	1	0	0	0	0
108 Mile Ranch	0	0	0	0	0	0	0	0	0	0	0
Abbotsford	4	8	8	5	5	1	11	14	6	6	8
Agassiz	0	1	2	1	1	1	0	0	0	2	1
Alexis Creek	0	0	0	1	0	0	0	0	0	0	0
Armstrong (BC)	0	0	1	0	0	0	0	0	0	0	0
Black Creek	0	0	0	0	0	0	1	0	0	0	0
Bowser	0	1	0	0	0	0	0	0	0	0	0
Brentwood Bay	0	1	0	0	0	0	0	1	0	1	0
Bridge Lake	0	1	0	0	0	0	0	0	0	0	0
Burnaby	9	6	7	3	8	2	11	6	13	20	13
Campbell River	3	4	5	3	4	1	1	2	2	9	2
Castlegar	[illegible]								0	3	1
Trail	2	1	1	0	0	1	0	0	0	1	0
Ucluelet	0	0	0	0	0	0	0	0	0	0	1
Vancouver	56	54	55	67	51	49	90	87	108	191	140
Vanderhoof	0	0	0	0	1	0	0	0	0	0	0
[illegible]	3	4	1	4	7	3	2	4	1		2
Victoria	[illegible]								20	31	26	17
Warfield	0	0	0	0	0	0	0	0	0	1	0
West Vancouver	1	0	1	0	0	1	0	1	1	0	0
Westbank	1	1	2	0	0	1	0	0	0	0	0
Whistler	0	0	0	0	0	0	1	0	0	0	0
White Rock	1	2	1	0	1	1	1	0	0	1	0
Williams Lake	3	0	2	0	0	0	1	1	0	1	1
Winfield (BC)	0	1	0	0	1	0	0	0	0	0	0
Wycliffe	0	0	0	0	1	0	0	0	0	0	0
Ymir	0	0	0	0	1	0	0	0	0	0	0
Unknown	1	0	0	0	0	0	0	0	0	0	0
Total	**200**	**228**	**218**	**194**	**189**	**170**	**246**	**248**	**278**	**417**	**310**

Originally found at:

http://www.pssg.gov.bc.ca/coroners/publications/docs/stats-illicitdrugdeaths-1997-2007.pdf now at https://web.archive.org/web/20120321162004/http://www.pssg.gov.bc.ca/coroners/publications/docs/stats-illicitdrugdeaths-1997-2007.pdf

The same study also claimed overdose reductions by 35% in the area immediately surrounding Vancouver's Insite. Drug Free Australia's Australian/Canadian team of epidemiologists and addiction specialists demonstrated in 2012 that Marshall et al. **had concealed the tripling of police numbers around Insite in 2003**,[4] falsely claiming that this was temporary when in fact it was permanent,[5] as attested by the DTES Area Commander at that time, John McKay (See Appendix D). Such policing served to disperse drug dealers away from the area around Insite, reducing crime and loitering, and of course ODs as users purchased their drugs elsewhere. Policing alone was shown to be demonstrably capable of reducing overdoses around Insite by 35%.[6] **This then collapses the Vancouver study describing reduced crime around Insite, the result of tripled policing which changed from a philosophy of containment to one of zero tolerance 6 months before Insite opened.**

The 2010 Salmon et al. Addiction study, which claimed a **31%** greater reduction in overdose ambulance callouts for Kings Cross (80%) than for the rest of NSW (61%) when Australia's heroin drought ensued, failed to note that there were proportionately greater reductions in ambulance callouts during nighttime hours, where Kings Cross, at 71% reductions was **a full 70% better** than the rest of NSW (42% reductions) when the injecting room *was closed*.[7] This can be clearly seen in the ringed cells on the spreadsheet below.

[4] https://drugfree.org.au/images/13Books-FP/pdf/Lancet_2011_Insite_Analysis.pdf, https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(12)60054-3.pdf?code=lancet-site
[5] https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(12)60055-5.pdf
[6] https://drugfree.org.au/images/13Books-FP/pdf/Lancet_2011_Insite_Analysis.pdf
[7] https://www.drugfree.org.au/images/13Books-FP/pdf/2017InjectingRoom.pdf

	AMBULANCE CALLOUTS BEFORE MSIC OVER 36 MONTHS					
	During Op hours	Average per month	Outside Op hours	Average per month	Total all hours	Average per month
Postcode 2011 - Kings Cross	626	17.4	922	25.6	1548	43.0
Postcode 2010 - Darlinghurst	338	9.4	311	8.6	649	18.0
Rest of NSW	6779	188.3	2901	80.6	9680	268.9
	AMBULANCE CALLOUTS AFTER MSIC OVER 60 MONTHS					
	During Op hours	Average per month	Outside Op hours	Average per month	Total all hours	Average per month
Postcode 2011 - Kings Cross	210	3.5	440	7.3	650	10.8
Postcode 2010 - Darlinghurst	311	5.2	383	6.4	694	11.6
Rest of NSW	4382	73.0	2806	46.8	7188	119.8
	PERCENTAGE REDUCTION IN AMBULANCE CALLOUTS					
		During Op hours		Outside Op hours		Total all hours
Postcode 2011 - Kings Cross		80%		71%		75%
Postcode 2010 - Darlinghurst		45%		26%		36%
Rest of NSW		61%		42%		55%

This irrefutably indicates reductions were not due to the MSIC, and suggests it was rather due to sniffer dog policing introduced one month after the MSIC opened, where sniffer dog use was even more extensive at night. Any null effect of the MSIC on crime in the area can be slated to changed policing, just as was the case for Vancouver's Insite.

Thus five studies on SIS impacts on crime in the immediate area around an SIS are voided due to the effect of increased police operations.[8] The upshot is that there is no science which supports injecting rooms.

Latest MSIR review well-illustrates the failure

The recently released review of the North Richmond Medically Supervised Injecting Room (MSIR) evaluated the performance of the facility against its six legislated objectives, with the review's own data and comments demonstrating failure on five of the six objectives, despite rosier media reports indicating otherwise. The facility has also been associated with increases in drug-related crime.

The review records the following regarding its six objectives (please note the verbatim comments by the MSIR reviewers within the quotation marks):

1. **Reduce discarded needles on streets** - "Local people record no difference in seeing discarded injecting equipment" (p 76 of the review)

2. **Improve public amenity** - "significantly fewer residents and business respondents reported feeling safe walking alone during the day and after dark due to concerns about violence and crime . . . " (p 85)

3. **Reduce the spread of blood-borne viruses** - "There is not a significant difference between MSIR service users and other people who inject drugs in reporting that they had injected with someone's used needle/syringe in the previous month." (p 100)

4. **Referrals to treatment and other services** - "in the first year of operation (the MSIR) has not demonstrated higher levels of service

[8] Wood et al. 2004; Fitzgerald et al. 2010; Milloy et al. 2009; Wood et al. 2006[a]; Freeman et al. 2005

take-up for MSIR users as compared with other people who use drugs." (p 48).

5. **Reduce heroin deaths** - Figure 17 on p 45 of the review shows that there were 12 heroin deaths within 1 km of the MSIR the year before it opened, and 13 the year after. Figure 19 on p 47 shows that for the top 5 Local Government Areas for heroin deaths in Melbourne there was a cumulative 65 deaths before the MSIR opened and 67 in its first year. Clearly there is no observable reduction in heroin deaths in Melbourne or North Richmond in its first year of operation. Furthermore, had the 112,831 heroin injections in the MSIR over 18 months happened on the *streets* of North Richmond, there would, according to Australian statistics, have been only *one* death to be expected, indicating that the MSIR spent $6 million to save only one life, an extremely expensive failure.

6. **Reduce ambulance and hospital attendances** - On the streets of Melbourne, 112,831 opiate injections would have produced 26 overdoses, (25 non-fatal and 1 fatal) according to an important Australian study (see p 59). Of these 19 would likely have been attended by an ambulance. Comparing 18 months before and after, the MSIR would therefore have reduced ambulance callouts by just 5%. Yet the review egregiously claims reductions of 36%, which were clearly due to heightened police operations arresting drug dealers in the vicinity of the MSIR, sending drug dealers elsewhere to ply their trade. Because users most often overdose near where they bought their drugs (p 83), ambulance callouts were clearly the result of policing, which nullifies (see footnote on p 67) the review's spurious claims regarding callouts. Additionally, analysis of heroin OD presentations at nearby St Vincent's Hospital "found that the number of heroin overdose cases did not change significantly after the facility opened." (p 74)

Adding to the failure against objectives listed above, police complained of increasing crime around the MSIR, and residents of a honey-pot effect where drug dealers were drawn to the streets outside the MSIR.

Drug Free Australia urges the AMA to fully review the science on injecting rooms before promoting them as part of its drug policy positions. Clearly, the science does not favour injecting rooms.

EVIDENCE CONTRADICTING AMA POLICY POSITIONS - 7

The only studies on ecstasy deaths in Australia indicate that ecstasy itself caused almost every pill death, while pill testing does in fact promote ecstasy use – the very substance causing almost all deaths

Pill testing doesn't address the causes of ecstasy deaths:

1. **It cannot identify individual vulnerabilities to ecstasy that cause deaths**
2. **It doesn't identify other co-used drugs such as alcohol or amphetamines which make ecstasy deadly**
3. **It can't identify which ecstasy user will have an ecstasy-fuelled accident (mostly car accidents)**

Two Australian studies show ecstasy itself causal of most deaths

In January 2020 data on 392 ecstasy-related deaths between July 2000 and November 2018 was published in the International Journal of Drug Policy (see Appendix E). This study extended the data beyond the MDMA-related deaths from July 2000 and December 2005 examined in the only other Australian study https://pubmed.ncbi.nlm.nih.gov/19604654/ of ecstasy deaths.

There were three main causes of deaths. 14% of deaths were caused by ecstasy alone, often due to individual vulnerabilities to the drug. Anna Wood took an ecstasy pill from the same batch as four friends, but only she died, no doubt from an individual vulnerability. It was not an overdose because the science clearly shows that ecstasy overdose is in fact rare. 48% of deaths were from ecstasy being co-consumed with other legal or illegal drugs such as alcohol, amphetamines or cocaine which create deadly synergies. A further 29% were from accidents due to ecstasy/other drug intoxication, mostly car accidents.

Very few deaths from adulterant drugs mixed with ecstasy

No more than 5% of Australian ecstasy-related deaths, according to the above study, were from other exotic drugs mixed into ecstasy pills. Obviously, it is not clear at autopsy whether these other exotic drugs caused the death, or whether it was the ecstasy in the pill.

Very few deaths from party drugs other than ecstasy

Drug Free Australia has identified a handful of MDMA-related deaths that lie outside of the years 2000 to 2018, with 6 PMA deaths in South Australia in the mid-1990s.

Again there are a handful of deaths from party drugs other than ecstasy, with a number of NBOMe deaths identified by Google search between 2012 and 2016, where evidence indicates the deceased users knew what they were taking. Notably, three Melbourne deaths in January 2017 were caused by pills containing NBOMe and 4-FA but it is questionable whether these drugs would have been delineated by the Bruker Alphas used for the Canberra pill testing trials simply because this mobile equipment often fails in identification where there are multiple drugs in a pill (Written advice from toxicologist Dr Andrew Leibie as contained in DFA document "Why-have-pill-testing-when-most-ecstasy-deaths-are-from-normal-doses-of-MDMA).

Pill testing does not address the real causes of MDMA deaths

With at least 95% of Australian deaths caused or co-caused by ecstasy itself, pill testing fails to address the causes of most MDMA-related deaths.

Causes of MDMA-related deaths	Pill testing applicability
Individual vulnerabilities to MDMA	Pill testing cannot test for individual vulnerabilities
MDMA used with alcohol, cocaine etc	Pill testing tests pills, not user blood samples
Accidents, mostly car accidents	Pill testing will not stop MDMA-related accidents

Pill testing might prevent that 5% of deaths, but very good evidence from the second Canberra pill-testing trial indicates that it would do nothing to stop the other 95% of deaths. Worse, pill testing increases the likelihood that the drug responsible for almost all Australian party pill deaths will be taken by those who have purchased it.

Pill testing can't advise an appropriate dose

Pill Testing Australia is now calling for governments to buy them new equipment that can measure the purity and dose in an MDMA pill, saying they need to advise users on how to more safely moderate their doses.

Given that every person metabolises the MDMA in their ecstasy pill differently there will be blood concentrations which will differ tenfold for roughly the same amount of MDMA taken. The graph below from this South Australian study shows the blood MDMA concentrations for 49 ecstasy users, NONE of which died in the study, against the amount of carefully measured MDMA they ingested.

The light blue shaded area in the graph below shows the blood concentration range for 196 of the 392 MDMA-related Australian deaths (the lower 50%)

between 2001 and 2018 (30 - 450 ng/ml – see this and the Roxburgh study previously detailed above for the range). As can be clearly seen, even small doses of MDMA (80-90 mgs) yield blood concentrations well ABOVE the levels which caused 50% of our Australian ecstasy deaths. Notice that ingestion of just 100-115 mg of ecstasy gives blood levels ranging tenfold from 120 – 1040 ng/ml. When it is considered that of 125 – 150 mg of ecstasy can be routinely used for experimental PTSD research with no ethics approval problems, such individual differences against toxic levels makes advice on dose absurd.

Festivals do not need pill testers advising on dose. All that is needed is a large photo of a decedent at each festival captioned – “this ecstasy user died after taking ¼ of a pill”. Messages on what to look for when someone is hyperthermic or toxically affected by ecstasy can be delivered via all sorts of social media and screens at festivals. No need for pill testing at all.

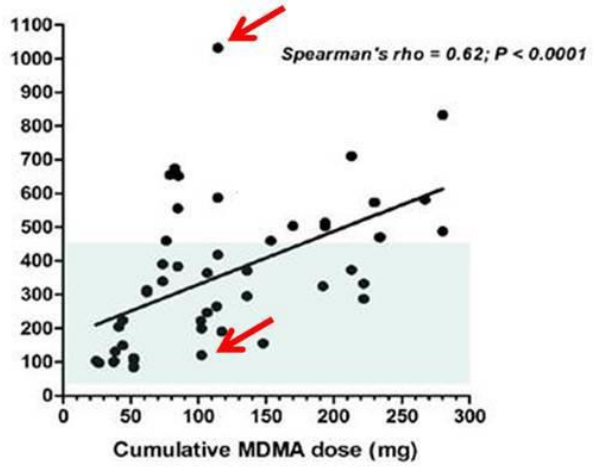


Figure 4 The relationship between maximum plasma 3,4-methylenedioxymethamphetamine (MDMA) concentration (C_{max}) and cumulative MDMA dose consumed by the time of maximum plasma concentration ($n = 49$). Correlation coefficient (Spearman's rho), P-value and line of best fit are shown ($n = 49$ participants where MDMA detectable in plasma)

The clincher - users MORE likely to take ecstasy after pill testing

The Australian National University evaluation of the 2019 Canberra pill testing trial confirms that the methods used by Pill Testing Australia to classify substances they identify is actually increasing the likelihood the user will take that substance.

When pill testing identifies a substance to be what the user thought they had purchased, the substance is given an "all-clear" white card which is displayed on a noticeboard in the pill testing tent, declaring it to not contain substances "associated with increased harm / multiple overdoses / death" (see p 11). If a 'dangerous' drug is identified, it is given a red card.

Yet while the evaluation stated that "most of the patrons had a generally accurate perception of the contents" of their pills before testing, it also states that "**those who received a test result confirming the substance to be what they thought it was were likely to take as much or more than originally intended**" and "**concordance between expectation and identification is associated with stable or increased intention to take a substance**."

When it is considered that 90% of the 158 pills presented in the trial contained ecstasy, the drug found in Dr Amanda Roxburgh's study to be

responsible for almost all of the 392 MDMA-related deaths in Australia between 2000 and 2018, the symbolics of a white card rather than the red card it deserves makes it clear why a user would be more likely to use it after the pill has been tested.

Pill testing clearly sends all the wrong messages which will only increase party drug deaths in Australia.

Pill testing counselling failed to deter use

The same evaluation as described above also confirms that only seven pills were discarded by users after pills were tested, each containing N-ethylpentylone, which would likely come from a batch or batches of 200 or more pills each somewhere in Canberra or Australia which has caused no hospitalisations or deaths.

Pill Testing Australia claims that they tell users of the dangers of ecstasy but there was no evidence of counsellors dissuading any user from taking their tested pill, with not one ecstasy user recorded discarding their pills, evidencing zero behaviour change.

Drug Free Australia asserts that it is too late to be telling ecstasy users that their substance is dangerous saying the horse has bolted once they have spent $100 purchasing it, and the real need is government-funded social media campaigns telling the truth about ecstasy before they make the cash outlay.

Pill testing a failure in England/Wales

Statistics from England and Wales show that the introduction of pill testing did not produce any reduction in deaths as promised, nor did it appear to change the behaviour of users by getting some to quit using ecstasy, as also forecast by its advocates. While European countries have poor to non-existent statistics on ecstasy deaths, the UK keeps up-to-date figures. Pill testing operated by "the Loop" began in 2013 and by 2016 began expanding into 12 music festivals with government assent. In 2013 ecstasy was used by 1.2% of the population, rising significantly to 1.7% by 2017/18 (see Table 1.02). In 2013 there were 43 ecstasy deaths, more than doubling to 92 deaths in 2018. Harm Reduction Australia's specious campaign to establish an intervention that provides little to no protective effect for ecstasy users will continue to mislead young Australians, broaden the pool of novice users and lead to more needless deaths.

Drug Free Australia urges the AMA to consider the science on pill deaths within Australia and to remove its support for an intervention which will only increase ecstasy use and deaths.

APPENDICES

Appendix A	Cochrane Collaboration review of methadone
Appendix B	US IOM review of NSP
Appendix C	DFA letter to Lancet published January 2012
Appendix D	Letter to Lancet by Police Commander John McKay
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Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence (Review)

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[Intervention Review]

Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

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ABSTRACT

Background

Methadone maintenance was the first widely used opioid replacement therapy to treat heroin dependence, and it remains the best-researched treatment for this problem. Despite the widespread use of methadone in maintenance treatment for opioid dependence in many countries, it is a controversial treatment whose effectiveness has been disputed.

Objectives

To evaluate the effects of methadone maintenance treatment (MMT) compared with treatments that did not involve opioid replacement therapy (i.e., detoxification, offer of drug-free rehabilitation, placebo medication, wait-list controls) for opioid dependence.

Search strategy

We searched the following databases up to Dec 2008: the Cochrane Controlled Trials Register, EMBASE, PubMED, CINAHL, Current Contents, Psychlit, CORK [www. state.vt.su/adap/cork], Alcohol and Drug Council of Australia (ADCA) [www.adca.org.au], Australian Drug Foundation (ADF-VIC) [www.adf.org.au], Centre for Education and Information on Drugs and Alcohol (CEIDA) [www.ceida.net.au], Australian Bibliographic Network (ABN), and Library of Congress databases, available NIDA monographs and the College on Problems of Drug Dependence Inc. proceedings, the reference lists of all identified studies and published reviews; authors of identified RCTs were asked about other published or unpublished relevant RCTs.

Selection criteria

All randomised controlled clinical trials of methadone maintenance therapy compared with either placebo maintenance or other non-pharmacological therapy for the treatment of opioid dependence.

Data collection and analysis

Reviewers evaluated the papers separately and independently, rating methodological quality of sequence generation, concealment of allocation and bias. Data were extracted independently for meta-analysis and double-entered.

Main results

Eleven studies met the criteria for inclusion in this review, all were randomised clinical trials, two were double-blind. There were a total number of 1969 participants. The sequence generation was inadequate in one study, adequate in five studies and unclear in the remaining studies. The allocation of concealment was adequate in three studies and unclear in the remaining studies. Methadone appeared statistically significantly more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use as measured by self report and urine/hair analysis (6 RCTs, RR = 0.66 95% CI 0.56-0.78), but not statistically different in criminal activity (3 RCTs, RR=0.39; 95%CI: 0.12-1.25) or mortality (4 RCTs, RR=0.48; 95%CI: 0.10-2.39).

Authors' conclusions

Methadone is an effective maintenance therapy intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilise opioid replacement therapy. It does not show a statistically significant superior effect on criminal activity or mortality.

PLAIN LANGUAGE SUMMARY

Methadone maintenance therapy versus no opioid replacement therapy

Methadone maintenance treatment can keep people who are dependent on heroin in treatment programs and reduce their use of heroin. Methadone is the most widely used replacement for heroin in medically-supported maintenance or detoxification programs. Several non-drug detoxification and rehabilitation methods are also used to try and help people withdraw from heroin. However the review found that people have withdrawn from trials when they are assigned to a drug-free program. Consequently, there are no trials comparing methadone maintenance treatment with drug-free methods other than methadone placebo trials, or comparing methadone maintenance with methadone for detoxification only. These trials show that methadone can reduce the use of heroin in dependent people, and keep them in treatment programs.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Methadone maintenance treatment compared to No methadone maintenance treatment for opioid dependence

Patient or population: patients with opioid dependence
Settings: Prisons, hospitals, community based treatments and research facilities
Intervention: Methadone maintenance treatment
Comparison: No methadone maintenance treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No methadone maintenance treatment	Methadone maintenance treatment				
Retention in treatment - Old studies (pre 2000) objective	**Medium risk population**		**RR 3.05** (1.75 to 5.35)	505 (3)	⊕⊕⊕⊕ **high**[1,2]	
	210 per 1000	**640 per 1000** (368 to 1123)				
Retention in treatment - New studies	**Medium risk population**		**RR 4.44** (3.26 to 6.04)	750 (4)	⊕⊕⊕⊕ **high**[2,3]	
	154 per 1000	**684 per 1000** (502 to 930)				
Morphine positive urine or hair analysis objective	**Medium risk population**		**RR 0.66** (0.56 to 0.78)	1129 (6)	⊕⊕⊕⊕ **high**	

	701 per 1000	**463 per 1000** (393 to 547)			
Criminal activity objective	**Medium risk population**		**RR 0.39** (0.12 to 1.25)	363 (3)	⊕⊕⊕◯ **moderate**[4]
	118 per 1000	**46 per 1000** (14 to 148)			
Mortality objective	**Medium risk population**		**RR 0.48** (0.1 to 2.39)	576 (4)	⊕⊕⊕◯ **moderate**[4]
	17 per 1000	**8 per 1000** (2 to 41)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidance
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] RR 3.05
[2] Other Cochrane review showing dose related effect : Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD002208. DOI: 10.1002/14651858.CD002208
[3] RR 4.4
[4] Too few numbers of events observed

BACKGROUND

Description of the intervention

Currently, the major form of medical therapy for heroin dependence internationally involves orally administered methadone. Methadone is an analgesic medication developed to treat pain in the 1940s. It has been, and is still, prescribed widely for the management of pain in America, Australia and Europe.

It was in New York in the 1960s, during an increase in heroin use and heroin dependence, that researchers (Dole 1965; Dole Nyswander 1967) examined different prescribed opioids to manage heroin dependence, and reported that they found that methadone was most suitable to the task. They believed that long-term heroin use caused a permanent metabolic deficiency in the central nervous system and an associated physiological disease, which required regular administration of opiates to correct the metabolic deficiency (Dole Nyswander 1967). The disorder of opioid dependence has been represented in the International Classification of Disease of the World Health Organisation. It is a chronic or long-term and relapsing disorder, and some believe that it requires ongoing maintenance medication.

How the intervention might work

The aspects of methadone that have led to its use as a substitute drug for heroin include the number of pharmacological features of opioids. At the basis of methadone maintenance treatment (MMT) is the observation that opioid analgesics can be substituted for one another (Jaffe 1990). Methadone at adequate doses (of 20mg to more than 100 mg) prevents or reverses withdrawal symptoms (Ward 1992), and thus reduces the need to use illegal heroin (Jaffe 1990). Methadone remains effective for approximately 24 hours, requiring a single daily dose rather than the more frequent administration of three to four times daily which occurs with the shorter-acting heroin (Jaffe 1990). Methadone can "block" the euphoric effects of heroin, discouraging illicit use and thereby relieving the user of the need or desire to seek heroin (Dole 1969). This allows the opportunity to engage in normative activities, and "rehabilitation" if necessary. Methadone can cause death in overdosage, like other similar medications such as morphine, and for this reason it is a treatment which is dispensed under medical supervision and relatively strict rules. In summary, methadone is a long-acting opioid analgesic with well-understood pharmacological characteristics which make it suitable for stabilising opioid dependent patients in a maintenance treatment approach.

There is evidence that the quality of the therapeutic relationship with staff in methadone clinics plus the intensity of these ancillary services, combined with the dose of methadone prescribed will all act to enhance the outcome for methadone treatment (Ward 1992), although this is not the focus of this review.

Why it is important to do this review

Methadone maintenance treatment remains one of the best researched treatments for opioid dependence (Cooper 1983; Gerstein 1990; Hargreaves 1983; Mattick 1993; Ward 1992). It is the only treatment for opioid dependence which has been clearly demonstrated to reduce illicit opiate use more than either no-treatment (Dole 1969; Yancovitz 1991; Dolan 2003; Schwartz 2006, Kinlock 2007), drug-free treatment (Gunne 1981), placebo medication (Newman 1979; Strain 1993a), or detoxification (Vanichseni 1991; Gruber 2008; Sees 2000) in clinical controlled trials. These trials have been conducted by different research groups, in markedly differing cultural settings, yet have converged to provide similar results.

OBJECTIVES

The present systematic review aimed to provide an evaluation of the effectiveness of methadone maintenance treatment on opioid dependence compared with treatments that did not include an opioid replacement therapy. The focus of the review is on retention in treatment, opioid use as measured by objective urine results and from self-report, as well as criminal activity and patient mortality.

METHODS

Criteria for considering studies for this review

Types of studies

The literature was reviewed for all clinical controlled trials of MMT against another treatment which does not use opioid replacement therapy.

Types of participants

Individuals who were opioid dependent were the target population for this review. No distinction was made between those using heroin and those who have been in methadone treatment prior to entering the research trial treatment. No restrictions were imposed in terms of studies of outpatients, inpatients, those with comorbid states, etc.

Types of interventions

Interventions were included if they used methadone maintenance therapy (MMT). The MMT interventions were included even where they also employed other treatments, such as behavioural therapies or outpatient rehabilitation. The control groups were

treated with placebo medication, withdrawal or detoxification (with or without ancillary medication), drug-free rehabilitation treatment (such as therapeutic communities), and no treatment or wait-list controls.

Types of outcome measures

Primary outcomes

1. retention in treatment
2. mortality
3. proportion of urine or hair analysis results positive for heroin (or morphine)
4. self-reported heroin use
5. criminal activity

Secondary outcomes

1. use of other drugs
2. physical health
3. psychological health

Search methods for identification of studies

Electronic searches

1.Cochrane Central Register of Controlled Trials, which includes the Cochrane Drugs and Alcohol Group Register of Trials (CENTRAL - The Cochrane Library issue 4, 2008)
2.PubMed (January 2001 - December 2008)
3.Embase (January 2001- December 2008)
4.CINAHL (January 2001 - December 2008)
For details on searches see Appendix 1; Appendix 2; Appendix 3; Appendix 4
The search strategy was developed in consultation with a drug and alcohol research information specialist.

Searching other resources

1. Some of the main electronic sources of ongoing trials (National Research Register, meta-Register of Controlled Trials; Clinical Trials.gov, Agenzia Italiana del Farmaco)
2. Conference proceedings likely to contain trials relevant to the review (College on Problems of Drug Dependence - CPDD)
3. Library of Congress databases were also searched for studies and book chapters with the key terms: methadone, clinical trial, and randomised control trial.
4. National focal points for drug research (e.g., National Institute of Drug Abuse (NIDA), National Drug & Alcohol Research Centre (NDARC))
5. Reference lists of all relevant papers to identify further studies.
6. Authors of identified RCT's were consulted to find out if there were any other published or unpublished RCT's comparing the efficacy of methadone maintenance vs against another treatment which does not use opioid replacement therapy.
7. As several drug and alcohol journals are not indexed on the main electronic databases, the following databases were searched up until December 2008:

- "Current Contents
- "Psychlit
- "CORK [www. state.vt.su/adap/cork]
- "Alcohol and Drug Council of Australia (ADCA) [www.adca.org.au]
- "Australian Drug Foundation (ADF -VIC) [www.adf.org.au]
- "Centre for Education and Information on Drugs and Alcohol (CEIDA) [www.ceida.net.au]
- "Australian Bibliographic Network (ABN).

All searches included non-English language literature and studies with English abstracts were assessed for inclusion. When considered likely to meet inclusion criteria, studies were translated.

Data collection and analysis

Selection of studies

Each potentially relevant study located in the search was obtained and independently assessed for inclusion by two of three reviewers. Data extraction for each study was undertaken by the same two reviewers, again independently.

Data extraction and management

Each potentially relevant study located in the search was obtained and independently assessed for inclusion by two of three reviewers. Data extraction for each study was undertaken by the same two reviewers, again independently. A standardised checklist was used for data extraction. Disagreement was dealt with by the third reviewer, acting as a mediator. If unresolved disagreements on inclusion, study quality or extraction occurred they were referred to the editor.

Assessment of risk of bias in included studies

Due the type of comparisons analysed (MMT versus methadone detoxification or waiting list), blinding is often difficult to apply. As such, methodological quality was assessed by assessment of the randomisation procedure and the likelihood that randomisation was not biased:
A. Low risk of bias (allocation clearly independent of clinical staff);
B. Moderate risk of bias (some doubt about the independence of the allocation procedure); and

C. High risk of bias (inadequate separation of randomisation from clinical staff).

Measures of treatment effect

A standardised effect size was calculated for each study, based on the main outcome measure reported. Where possible (relative risks and 95% confidence intervals for dichotomous outcomes (retention) using a random effects model and standardised mean differences for continuous outcomes were presented. To assess for statistical heterogeneity a test of homogeneity was undertaken. A pooled effect size estimate was derived for each domain of measurement (retention in treatment, urine analysis results for heroin/morphine), self-reported heroin use, and criminal activity. The retention in treatment and urine results were reported as the number of patients retained or the number with a morphine-positive urine result at follow-up, a form of reporting that allowed for dichotomous analysis of those data.

Data synthesis

The results were integrated from the meta-analytic review into a discussion taking into consideration other publications including large-scale observational studies, studies of the pharmacology of methadone, and studies of the effect of MMT on HIV seroconversion. Convergence of the evidence from the meta-analysis and the narrative review was taken to indicate a robust conclusion.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We considered fourteen studies for inclusion, three were excluded because they did not satisfy the inclusion criteria (*see* Characteristics of excluded studies table) and eleven were included (Characteristics of included studies Charachteristics table) with a total of 1969 participants.

Included studies

Eleven studies were included in this review. Refer to Characteristics of included studies Table for more detailed information.

Treatment regimes and settings

The first study by Dole (Dole 1969) was a two group randomised trial where patients either received methadone or placed on a wait-list. The study by Gunne (Gunne 1981) randomly allocated patients to receive methadone maintenance or to be allocated to a drug-free rehabilitation. None of the patients allocated to drug-free rehabilitation took up the offer, refusing treatment after they had learnt that they would not receive methadone. There were two placebo controlled trials (Newman 1979, Strain 1993a). Finally, there have been six randomised clinical trials, three assessing methadone maintenance against methadone detoxification (Vanichseni 1991, Sees 2000, Gruber 2008) and the others assessing methadone maintenance against a wait-list control (Yancovitz 1991, Dolan 2003, Schwartz 2006).

Three studies were conducted in a prison setting (Dole 1969, Dolan 2003, Kinlock 2007). The remainder were conducted in medical or research facilities.

The sample sizes in these studies were sometimes small, in that two studies having sample sizes of 32 and 34 (Dole 1969, Gunne 1981), respectively. The remaining seven studies had sample sizes ranging from 100 to 240 (Newman 1979, Vanichseni 1991, Sees 2000, Gruber 2008) patients up to 247 to 382 patients (Strain 1993a, Yancovitz 1991, Dolan 2003, Schwartz 2006).

The dosages of methadone used in these studies appears to have been adequate. In the first study, (Dole 1969) the dose at release from prison was 35 milligrams but patients were entered into a community program where blockade doses of approximately 100 milligrams were standard. In the study by Gunne (Gunne 1981) the doses are not clearly stated. The placebo-controlled study by Newman (Newman 1979) have an average dose on 97 milligrams per day. An average of 74 milligrams per day was reported in the study from Thailand (Vanichseni 1991). Strain (Strain 1993a) used doses of methadone of 50 and 20 milligrams per day. The study by Dolan (Dolan 2003) had a mean methadone dose of 61mg. The study by Schwartz (Schwartz 2006) had a mean dose of 78.4mg and Sees (Sees 2000) had a mean methadone dose of 86.3mg. The study by Gruber (Gruber 2008) used a methadone dose range of 60-90mg and Kinlock (Kinlock 2007) set a target dose of 60mg. Finally, the study by Yancovitz (Yancovitz 1991) used a maintenance dose of approximately 80 milligrams per day. As such, the results from the studies appear to use moderate to high doses on average.

Duration of the trials

As shown in the table of included studies, the interventions generally lasted for significant time of several weeks up to two years, although one study only ran 45 days (Vanichseni 1991).

Countries in which the studies were conducted

The studies were conducted in a range of countries including; USA (Dole 1969, Yancovitz 1991, Strain 1993a, Sees 2000, Schwartz 2006, Gruber 2008), Sweden Gunne 1981), Australia (Dolan 2003), Hong Kong (Newman 1979) and Thailand (Vanichseni 1991).

Participants

The participants (N=1969) were largely typical of heroin dependant individuals, in terms of age and gender characteristics. In some studies, only males were included but where females were included the gender distribution was as one would expect, with majority of the participants being male. They tended to be approximately 30 to 40 years of age, often unemployed and unmarried, with previous treatment histories and prevalence of use of other drugs, consistent with what is known about heroin users presenting for treatment.

Types of comparisons

The review compared methadone maintenance treatment with no methadone maintenance treatment. All studies were assessed to determine whether they provided data on retention in treatment, codeable results from urine/hair analysis, self-reported drug use (particularly heroin use), criminal activity and mortality. After reviewing the studies, it was realised that it was not possible to include urine/hair results for cocaine and benzodiazepines as these were not reported in an analysable form for most studies. It was not possible to analyse data on either cocaine or benzodiazepine positive urines from these studies. However, it was possible to code data on retention in treatment, morphine positive urine or hair analysis, self-reported heroin use, criminal activity and mortality.

Excluded studies

Three studies were not included. Refer to the Characteristics of excluded studies for the reason for exclusion.

Risk of bias in included studies

Allocation

The study conducted by Dole (Dole 1969) had inadequate sequence generation for randomisation and was unclear on the concealment of allocation. The studies conducted by Sees 2000, Dolan 2003, Schwartz 2006, Gruber 2008 and Kinlock 2007 had adequate sequence generation for randomisation. The study by Dolan 2003 also had adequate concealment of allocation, as did the studies by Yancovitz 1991 and Newman 1979. It was unclear if the remaining studies had adequate sequence generation and concealment of allocation.

Blinding

Of the eleven studies included in this review, two were placebo-controlled trials (Newman 1979, Strain 1993a). Both of these studies were double-blind but Strain 1993a did not provide sufficient data to be confident about the concealment of allocation. The remaining studies were not blinded.

Incomplete outcome data

All studies addressed the issue of incomplete outcome data adequately and were independently deemed by reviewers to be free of other major bias (Figure 1; Figure 2).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

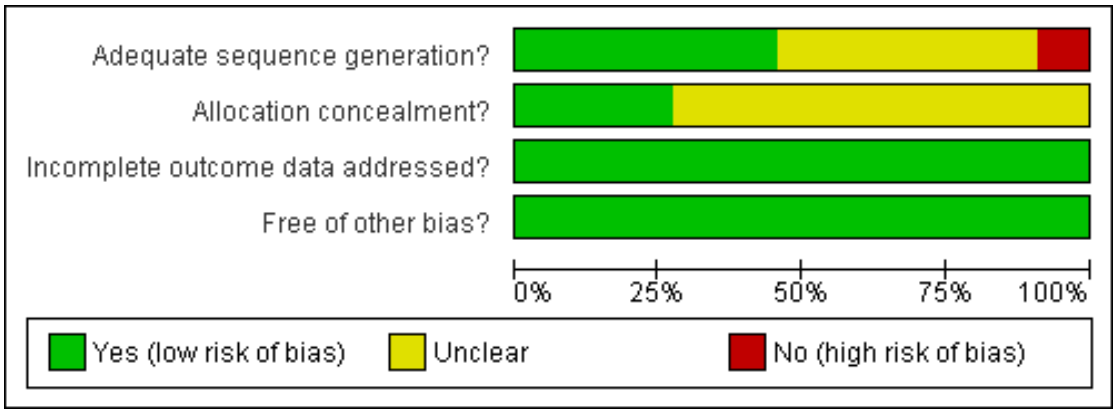
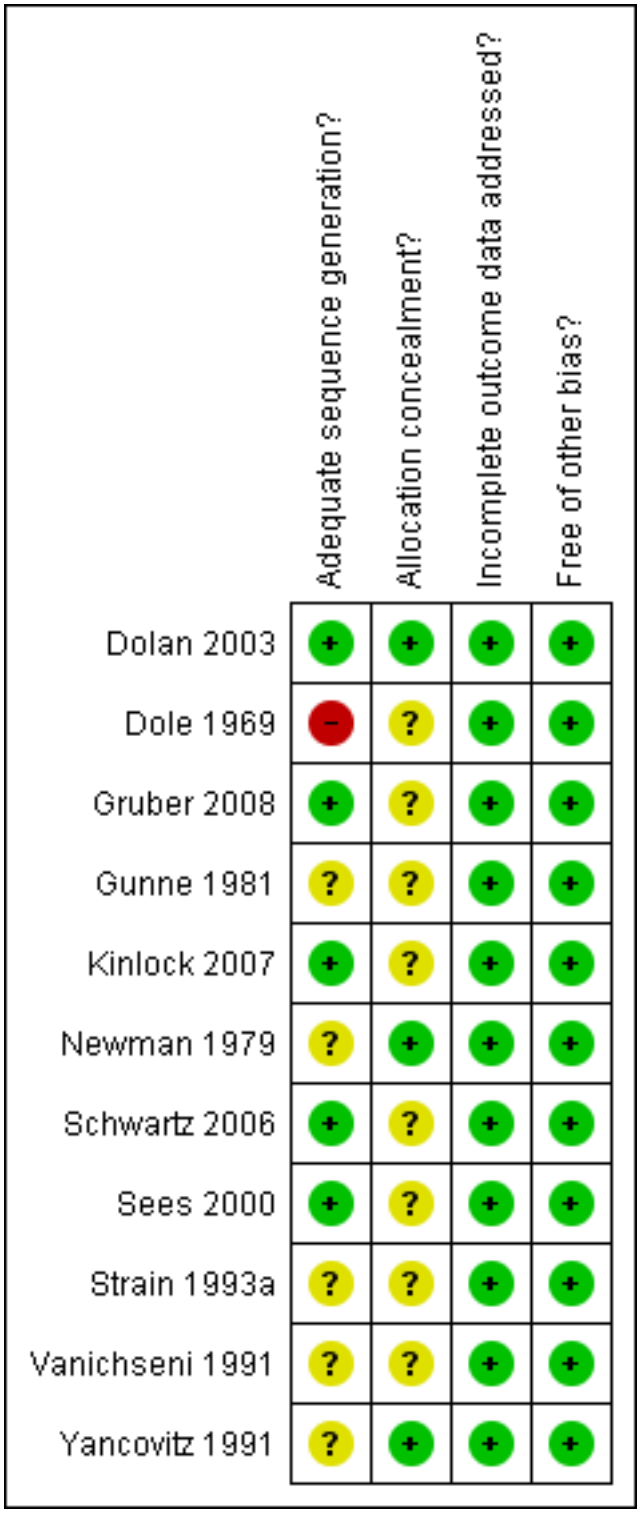


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison**

Results of meta-analyses

Comparison 01 Methadone maintenance treatment versus no methadone maintenance treatment

1.1 Retention in treatment:

7 studies; 1287 participants (Gruber 2008, Kinlock 2007, Newman 1979, Schwartz 2006, Sees 2000, Strain 1993a, Vanichseni 1991). The relative risk on a random effect model was applied. The chi-square test for heterogeneity was significant (p<0001) so a pooled estimate is not reported. However, the results from all studies showed that methadone has a superior retention rate compared with control conditions.Subgroup analysis was conducted examining the older studies (pre 2000) and the more recent studies, as differences in results can occur over time. The heterogeneity for the older studies (Newman 1979, Strain 1993a, Vanichseni 1991; 3 studies, 505 patients) was significant, as indicated in the previous published review. (Analysis 1.1.1). Data from the newer studies (Gruber 2008, Kinlock 2007, Schwartz 2006, Sees 2000) show the superiority of methadone over control in retaining patients in treatment (4 studies, 750 patients, RR=4.44, 95% CI:3.26-2.04). The test for heterogeneity was not significant (Analysis 1.1.2).

1.2 Morphine positive urine or hair analysis

6 studies, 1129 participants (Dolan 2003, Gruber 2008, Kinlock 2007, Schwartz 2006, Vanichseni 1991, Yancovitz 1991). Turning to the data from morphine positive urine/ hair analysis, five studies (Vanichseni 1991, Yancovitz 1991, Dolan 2003, Schwartz 2006, Gruber 2008) provided dichotomous data as to whether patients had morphine positive urine/hair at follow up. The results from these studies providing data on the presence/absence of morphine in urine at the follow-up showed an advantage of methadone above the control conditions (6 studies, 1129 patients RR = 0.66, 95% CI 0.56-0.78), in this case detoxification, wait-list or control, in reducing heroin use as shown by a lack of heroin metabolites in urine or hair. (Analysis 1.2)

1.3 Self-reported heroin use

6 studies, 682 participants (Dolan 2003, Dole 1969, Gruber 2008, Gunne 1981, Kinlock 2007, Vanichseni 1991). The results from the objective data on morphine positive urine/hair analysis were also supported by self-report data from five studies. In particular, studies from the USA, Sweden and Australia (Dole 1969, Gunne 1981, Yancovitz 1991, Dolan 2003, Kinlock 2007) all concurred to show an advantage for methadone above control in reduction of heroin use as reported by the patients. The study by Gruber 2008 showed no difference between groups. The test for heterogeneity was significant (p<0.000001) so a pooled estimate is not reported. (Analysis 1.3)

1.4 Criminal activity

3 studies, 363 participants (Dole 1969, Gunne 1981, Yancovitz 1991). The results for the criminal activity variable, available for three studies, were consistent with the reduction in heroin use, even though the advantage for methadone beyond control in reducing criminal activity was not statistically significant (3 studies, 363 patients RR=0.39, 95% CI:0.12-1.25). The test for heterogeneity was not significant. (Analysis 1.4)

1.5 Mortality

4 studies, 576 participants (Gunne 1981, Kinlock 2007, Newman 1979, Yancovitz 1991). Turning finally to the evidence concerning the ability of methadone to prevent deaths, available for four studies, the results showed a trend in favour of methadone that was not statistically significant (4 studies, 576 patients RR=0.48, 95% CI: 0.10-2.39). (Analysis 1.5)

Other measures (e.g., use of other drugs, physical health, and psychological health) are too infrequently and irregularly reported in the literature to be usefully integrated in the quantitative review. The results are also summarized in the Summary of findings table 1

DISCUSSION

Summary of main results

The results of the meta-analysis indicate that methadone is able to retain patients in treatment better than the drug-free alternatives (placebo medication, offer of drug-free treatment, detoxification, or wait-list control), to suppress heroin use based on morphine (the heroin metabolite) found in urine/hair samples, and patient self-report. There was a greater reduction in criminal activity and mortality among the MMT patients, but these differences were not statistically significant. There is evidence from other literature showing mortality (Gibson 2008, Clausen 2008) and criminal activity (Lind 2005) is decreased in patients who are in methadone treatment.

Overall completeness and applicability of evidence

Interestingly, the results from these eleven randomised trials all showed statistically significant positive benefits from methadone treatment, despite their small sample sizes. Additional support for the efficacy of methadone maintenance treatment comes from the results of many observational studies wherein some statistical form

of control has addressed alternative explanations of apparent effectiveness. These large scale observational studies have generally supported the results from the randomised clinical trials in showing that methadone maintenance treatment reduces the use of heroin and decreases criminal activity (Ward 1998). As noted earlier there is a broader international literature showing advantages for methadone beyond other treatments in terms of reduction of death (Ward 1998), even though the randomised trial data do not show this result.

Another relevant outcome to be considered would be seroconversion for HIV, which is the object of a separate Cochrane review (Gowing 2004). Methadone maintenance treatment has been shown to reduce HIV risk taking behaviour (specifically reduction in needle sharing) and thereby has achieved a reduction in the transmission of HIV. Consistent with this it has been shown that methadone maintenance treatment is protective of patients, reducing HIV infection in geographic locations where HIV had spread rapidly among injecting drug users who had not entered treatment. We have commented elsewhere on two large prospective cohort studies in the USA which found methadone maintenance treatment protected against HIV infection (Ward 1998). This outcome could not be addressed here as there are no randomised trials of methadone that have included HIV status as a measure, the evidence coming from observational studies.

Quality of the evidence

It is notable that the doses of methadone used in the randomised clinical trials are probably slightly higher than are being used currently in routine clinical practice in some parts of the world. This relative underdosing in clinical practice may lead to a reduction in the effectiveness of methadone, as the response to methadone treatment is dose-dependent. In addition, it is important to recognise that methadone treatment in these trials was often provided with substantial ancillary services. These ancillary services have included counselling, psycho-social services, medical services and often psychiatric care. The quality of the therapeutic relationship with staff in methadone clinics plus the intensity of these ancillary services, combined with the dose of methadone prescribed will all act to enhance the outcome for methadone treatment. The extent that clinical programs move away from such an approach might be expected to impact on the effectiveness of methadone.

This does not imply that methadone maintenance treatment will become ineffective. Even allowing for some reduction in effectiveness when methadone is not provided in the fashion that it has been in the clinical trials, it is still likely to be effective. The effects of methadone may be modest, if they are judged by unrealistic expectations of patients can easily achieve enduring abstinence from opioid drugs. Methadone nonetheless attracts and retains more patients than alternative treatments, and it does produce better outcomes amongst those who complete treatment. Methadone maintenance appears to provide better outcomes than simple detoxification programs, where the evidence suggests that short-term detoxification has no enduring effect on drug use (Mattick 1996).

AUTHORS' CONCLUSIONS

Implications for practice

The implications of the results of the meta-analytic review conducted and reported herein for clinical practice are that methadone maintenance treatment is an effective intervention for the management of heroin dependence. Methadone retains patients in treatment and reduces heroin use. Methadone should be supported as a maintenance treatment for heroin dependence.

Implications for research

Overall there are a relatively limited number of randomised clinical trials on the efficacy of methadone treatment compared to placebo. It does not seem feasible at this stage to conduct further randomised trials of methadone treatment. However, evidence on reduction of criminal activity and mortality from clinical trials is lacking calling for an additional systematic review of observational studies. Moreover, monitoring of the outcome of standard methadone treatment in clinical practice may be important as a research activity to demonstrate its ongoing effectiveness, or to determine whether its effectiveness is being compromised through the reduction of ancillary services or reduction in adequate dose levels.

A number of measures (e.g., of other drug use, physical health, and psychological health) were too infrequently and irregularly reported in the literature to be usefully integrated in the quantitative review, but future research might address these important areas.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dolan 2003

Methods	Two group, open, randomised controlled trial. Randomisation: in blocks of ten by randomly drawing cards from an envelope. List of case numbers and group allocation not known to researcher or trial nurse. Follow up for four months.
Participants	Geographic region: Australia Study setting: Prison. Participants were inmates on a waiting list for MMT. n = 382 males mean age = 27 years Eligibility criteria: heroin problem confirmed by medical interview, serving sentences of more than four months, and able to provide informed consent.
Interventions	Treatment: methadone maintenance treatment - flexible dose (mean 61mg, range 1-180mg). Control: wait-list.
Outcomes	Heroin use - Hair analysis and self report. Syringe sharing. HIV and HCV seroprevalence.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Drawing lots.
Allocation concealment?	Yes	A-Adequate. Central allocation.
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome information balanced between groups. 191 randomised to each group, 124 and 129 followed up in each group.
Free of other bias?	Yes	Baseline characteristics similar.

Dole 1969

Methods	Two group, open, randomised controlled trial. Randomisation: release dates of treatment applicants were selected by lottery. Applicants who were not selected and demonstrated motivation for treatment became untreated controls. Follow-up for 50 weeks.
Participants	Geographic region: USA Study setting: Prison. Participants were inmates eligible for release over a four month period from New York City Correctional Institute for Men. n = 32 males

Dole 1969 (*Continued*)

	mean age = 30 years 15% European descent, 10% African American, 7% Hispanic Eligibility criteria: heroin dependence for 5 or more years, record of 5 or more previous convictions, not committed to custody of Addiction Services Agency.
Interventions	Control: wait-list Treatment: 10 day methadone maintenance pre-release. Initial dose 10 mg, increasing to 35 mg at release. Continued methadone maintenance in outpatient clinic after release.
Outcomes	Urinalysis (weekly for heroin, amphetamines, cocaine, barbituates and alcohol) Employment / education Reincarceration
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Used release dates in a lottery.
Allocation concealment?	Unclear	B- Unclear. Concealment of allocation not specified.
Incomplete outcome data addressed? All outcomes	Yes	No missing data.
Free of other bias?	Yes	

Gruber 2008

Methods	Three group randomised controlled trial. Randomisation: generated by statistician who placed assignments in sealed envelopes not revelaed to project staff. Allocation to group (21 day methadone detoxification, 6 months methadone with minimal counselling or 6 months methadone with standard couselling)revealed at conclusion of baseline interview.
Participants	Geographic region: USA Study setting Outpatient hospital detoxification program. n=111, 68% male mean age=41.9 years 54% White, 30% African American, 20% Hispanic, 4% Native American, 5% Asian/ Pacific Islander 85% unmarried Eligibility criteria; latent TB infection, DSM III R opioid dependence, aged 21-59, and willingness to receive isonaid preventive therapy and MMT. Excluded if pregnant or HIV positive or active liver disease.

Gruber 2008 (*Continued*)

Interventions	Treatment: 6 months methadone maintenance with minimal or standard counselling, followed by 6 week taper. Control: 21 day methadone detoxification.
Outcomes	Retention Illicit drug use - self report and urinalysis (monthly)
Notes	Results from the standard counseling and minimal counseling groups have been combined and compared to the detoxification group. Unpublished data - the author provided additional data to enable the coding of retention and heroin use. All participants have active TB infection - study part of a larger study examining TB.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"generated by a statistician".
Allocation concealment?	Unclear	B - Unclear. Individual sealed envelope not revealed to project staff. Does not state opaque.
Incomplete outcome data addressed? All outcomes	Yes	4 in detox group in MMT elsewhere
Free of other bias?	Yes	At baseline standard MMT group younger and detox group had more depressive symptoms.

Gunne 1981

Methods	Two group randomised clinical trial. Randomisation: after eligibility established subjects were randomly allocated to methadone maintenance or to drug-free treatment. Foow up for two years.
Participants	Geographic region: Sweden Study setting: psychiatric research centre n = 34, 76% male Eligibility criteria: 20-24 years, history of at least 4 years IV heroin use, withdrawal signs and positive urine on admission, a minimum of three completed detoxifications, not arrested or serving a sentence and no dominate abuse of non-opiate drugs. Exclusion: active infectious disease.
Interventions	Control: no treatment, could not apply for the methadone program for two years. Treatment: methadone maintenance treatment, no dosage information reported.

Gunne 1981 (*Continued*)

Outcomes	Illicit drug use / Urinalysis (3 x week) Criminality Vocational adjustment Health Mortality
Notes	2 controls obtained methadone from private practitioners and were excluded.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Randomly allocated"
Allocation concealment?	Unclear	B - Unclear
Incomplete outcome data addressed? All outcomes	Yes	No missing data. All controls refused drug free treatment and asked for discharge.
Free of other bias?	Yes	Only indiv 20-24. Baseline groups similar except gender - more women in MMT.

Kinlock 2007

Methods	Three group randomised controlled trial. Randomisation: after eligibility established subjects were randomly allocated to one of three groups. Randomisation process not described. Follow up for one month.
Participants	Geographic region: USA Study setting: Prison. Participants were inmates due for release in 3-6 months. n = 211 males mean age =40.3 years 70% African American, 24% Caucasian Eligibility criteria: DSM IV heroin dependence at time of incarceration, suitability for MMT as determined by medical assessment, willingness to enrol in prison MMT and residing in Baltimore on release. Individuals that did not meet dependence criteria were eligible if they had been enrolled in an opiate treatment program the year prior to incarceration.
Interventions	Treatment: Counseling and methadone maintenance in prison with transfer into treatment on release. Target methadone dose 60mg. Control: Counseling in prison with passive referal to treatment upon release
Outcomes	Entry into community MMT Illicit drug use - self report and urinalysis

Kinlock 2007 (*Continued*)

Notes	A third group received counseling in prison and active referal to MMT on release group. These results have not been included in the analysis.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Block randomisation procedure.
Allocation concealment?	Unclear	B- Unclear. Not specified.
Incomplete outcome data addressed? All outcomes	Yes	No missing data. Report ITT
Free of other bias?	Yes	No differences between group at baseline.

Newman 1979

Methods	Double blind randomised clinical trial Randomisation: subjects randomly allocated on discharge from hospital after 2 week stabilisation on 60mg methadone to detoxification or continued maintenance.	
Participants	Geographic region: Hong Kong Study setting: Hospital and outpatient clinic n = 100 males mean age = 38 years Eligibility criteria: male, 22-58 years, history of heroin dependence for at least 4 years and at least one previous treatment, current heroin dependence by three consecutive positive urine samples, voluntary application for admission (criminal justice referrals excluded), resident with fixed address, absence of past or present major psychiatric or medical illness.	
Interventions	Treatment: methadone maintenance - flexible dose (average 97 mg / day). Control: detoxification from 60mg methadone at 1mg/day for 60 days, placebo thereafter.	
Outcomes	Illicit drug use / Urinalysis (daily collection, analysed 2 x week for morphine only) Retention Criminal activity Mortality	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**

Newman 1979 (*Continued*)

Adequate sequence generation?	Unclear	'Randomly assigned'
Allocation concealment?	Yes	A - Adequate 'neither patients nor clinic staff knew which group' 'pharmacist only staff aware'.
Incomplete outcome data addressed? All outcomes	Yes	No missing data. Report ITT.
Free of other bias?	Yes	No difference between group at baseline

Schwartz 2006

Methods	Two group randomised controlled trial with participants randomised to interim methadone maintenance treatment or a wait list control. Random assignment generated by random number table and sealed in an envelope.
Participants	Geographic region: USA Study setting: community methadone treatment facility. n=319, 59% male mean age =41.4 years 93% African American 62% unemployed Eligibility criteria; DSM IV heroin dependence and informed consent. Exclusions; pregnant or acute medical or psychiatric illness.
Interventions	Treatment: interim methadone maintenance treatment for 120 days after which entry into a comprehensive methadone treatment program if unable to gain entry before 120 days. Control: wait-list
Outcomes	Entry into comprehensive methadone maintenance treatment at 4 months. Illicit drug use /self report and urinalysis. Criminal activity.
Notes	Mobile program that at time of study administered methadone from specially equipped recreational vehicle

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	'table of random numbers'
Allocation concealment?	Unclear	B - Unclear. Sealed envelope but unclear if opaque and sequentially numbered.

Schwartz 2006 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Missing outcome information balanced between groups. 95% MMT and 89% wait list located for follow up.
Free of other bias?	Yes	No difference between group at baseline

Sees 2000

Methods	Two group randomised controlled trial. Randomisation: participants randomly allocated from stratified blocks to methadone maintenance treatment or 180-day methadone assisted detoxification.
Participants	Geographic region: USA Study setting: Medical Center n=179, 59% male mean age = 39.4 years 52% Caucasian, 30% African American, 13% Hispanic 53% unemployed, 79% unmarried Eligibility criteria: opioid depeendent and urine screen positive for opioid and negative for methadone.
Interventions	Treatment: methadone maintenance for 14 months followed by a 2 month detoxification. Participants required to attend 1hr/wk group therapy and 1hr/wk individual theray for first 6 months. Flexible dose (max dose of 100mg/d) Control: 14 months of substance abuse treatment. 120 days induction and methadone maintenance followed by 60 days of dose reductions. Participants were required to attend 2hr/wk group therapy, 1hr /week education classes and weekly individal therapy sessions. During month 7-14 participants offered nonmethadone aftercare treatment - group and individual therapy and liaison services with criminal justice, medical clinics and social services.
Outcomes	Retention Illicit drug use - self report and monthly urinalysis. HIV risk behaviours
Notes	Retention data was taken at 180 days from Fig 3 in the published paper.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	'generated via computer software by statistician using various block sizes'
Allocation concealment?	Unclear	B - Unclear 'kept in sealed envelope'. Unclear if opaque and sequentially numbered.

Sees 2000 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Missing outcome information balanced between group.
Free of other bias?	Yes	No differences between group at baseline.

Strain 1993a

Methods	Three group, double-blind, placebo controlled randomised controlled trial. Patients were stratified by race and sex and randomly assigned to a fixed dose schedule at admission. Treatment group assignment, stabilisation dose and dosing schedules were blind to patient and clinic staff with patient contact.
Participants	Geographic region: USA Study setting: methadone treatment research clinic n = 247, 70% male mean age = 34 years 50% African American 62% unemployed, 84% unmarried Eligibility criteria: 18-50 years, history of IV opioid dependence, no chronic medical illness, absence of major mental illness, negative pregnancy test and at least three months since last treatment at the clinic.
Interventions	Initial treatment of active methadone for at least 5 weeks. 15 weeks of stable dosing at 50, 20 or 0 mg per day Gradual tapering for those receiveing active methadone from weeks 21-26 Individual counselling and group therapy (weekly).
Outcomes	Retention Treatment compliance Illicit drug use / Urinalysis (collected 3 x weekly, one sample selected at random for analysis for opioids, cocaine and benzodiazepines)
Notes	A subsample of 0mg patients (n=44) received an 8 week induction, reaching 0mg at 9 weeks. Data for patients in alternate 0mg treatment groups are collapsed

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	'randomly assigned' stratified by race and sex. Unclear not enough information.
Allocation concealment?	Unclear	B - Unclear
Incomplete outcome data addressed? All outcomes	Yes	

Strain 1993a (*Continued*)

Free of other bias?	Yes	Baseline groups similar.

Vanichseni 1991

Methods	Two group, open label, randomised clinical trial, with participants who applied for 45 day methadone detoxification and had at least six prior treatment episodes were randomly assigned to methadone maintenance or detoxification
Participants	Geographic region: Thailand Study setting: narcotics clinic n = 240 males 30% unemployed, 52% unmarried Eligibility criteria: heroin injectors applying for 45-day detoxification, at least 6 prior treatment episodes at the clinic.
Interventions	Treatment: methadone maintenance (flexible dose, average 74mg) Control: standard 45 day methadone detoxification
Outcomes	Retention Illicit drug use Urinalysis (2 x week for opiates)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear. Not enough information provided.
Allocation concealment?	Unclear	B - Unclear
Incomplete outcome data addressed? All outcomes	Yes	Urine provided for drop outs.
Free of other bias?	Yes	

Yancovitz 1991

Methods	Two group randomised clinical trial, with opioid dependent participants on waiting-lists for comprehensive methadone maintenance programs who were randomised to either the interim methadone program or wait list with frequent contact.
Participants	Geographic region: USA Study setting: interim methadone clinic n = 301, 79.4% male

Yancovitz 1991 (*Continued*)

	55% Hispanic, 35% African American, 10% White 86% unemployed Eligibilty criteria: wait list for comprehensive methadone maintenance program.
Interventions	Control: wait-list with frequent contact Treatment: "interim" methadone maintenance; standard physical exam on admission, flexible dosing 5 days a week, pick up on weekends from another site, minimal counselling, referral to community agencies
Outcomes	Urinalysis (2 x weekly for heroin and cocaine) Entry into conventional treatment
Notes	For the first 3 months of the study there were three experimental groups; interim methadone, wait-list with frequent contact and bi-weekly urinalysis, and the wait-list with no contact. Recruitment slowed which resulted in the protocol being changed two experimental groups; interim methadone and wait-list with frequent contact. The wait-list then only lasted one month at which time the participants were switched to a methadone program. Data from the initial discontinued minimal contact group is not include in the analysis.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	'randomly assigned'. Not enough information
Allocation concealment?	Yes	A - Adequate. 'assigned by administrative staff at another location'
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome information balanced between group. Follow up 50% in MMT and 36% for control.
Free of other bias?	Yes	No baseline differences.

Characteristics of excluded studies *[ordered by study ID]*

Bale 1980	The authors planned to conduct a randomised controlled trial comparing methadone maintenance, therapeutic communities and detoxification programs. Ethical and practical problems prevented random assignment and the study therefore does not meet inclusion criteria for this review.
Dolan 2005	This paper presents follow up results from the study reported in Dolan 2003.
Schwartz 2007	This paper presents follow up results from the study reported in Schwartz 2006.

DATA AND ANALYSES

Comparison 1. Methadone maintenance treatment vs No methadone maintenance treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Retention in treatment	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Old studies (pre 2000)	3	505	Risk Ratio (M-H, Random, 95% CI)	3.05 [1.75, 5.35]
1.2 New studies	4	750	Risk Ratio (M-H, Random, 95% CI)	4.44 [3.26, 6.04]
2 Morphine positive urine or hair analysis	6	1129	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.56, 0.78]
3 Self reported heroin use	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Criminal activity	3	363	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.12, 1.25]
5 Mortality	4	576	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.10, 2.39]

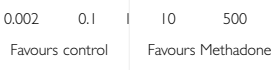
Analysis 1.1. Comparison 1 Methadone maintenance treatment vs No methadone maintenance treatment, Outcome 1 Retention in treatment.

Review: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

Comparison: 1 Methadone maintenance treatment vs No methadone maintenance treatment

Outcome: 1 Retention in treatment

Study or subgroup	Methadone MT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Old studies (pre 2000)					
Newman 1979	38/50	5/50		22.2 %	7.60 [3.26, 17.71]
Strain 1993a	44/84	17/81		35.2 %	2.50 [1.56, 3.99]
Vanichseni 1991	91/120	41/120		42.6 %	2.22 [1.70, 2.90]
Subtotal (95% CI)	**254**	**251**		**100.0 %**	**3.05 [1.75, 5.35]**
Total events: 173 (Methadone MT), 63 (Control)					
Heterogeneity: Tau^2 = 0.17; Chi^2 = 8.01, df = 2 (P = 0.02); I^2 =75%					
Test for overall effect: Z = 3.91 (P = 0.000092)					
2 New studies					
Gruber 2008	46/72	4/39		16.7 %	6.23 [2.42, 16.02]
Kinlock 2007	43/71	5/70		18.4 %	8.48 [3.57, 20.14]
Schwartz 2006	151/199	25/120		33.5 %	3.64 [2.55, 5.21]
Sees 2000	78/91	18/88		31.5 %	4.19 [2.75, 6.38]



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Study or subgroup	Methadone MT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**433**	**317**	◆	**100.0 %**	**4.44 [3.26, 6.04]**
Total events: 318 (Methadone MT), 52 (Control)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.90$, df = 3 (P = 0.27); $I^2 = 23\%$					
Test for overall effect: Z = 9.48 (P < 0.00001)					

Analysis 1.2. Comparison 1 Methadone maintenance treatment vs No methadone maintenance treatment, Outcome 2 Morphine positive urine or hair analysis.

Review: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

Comparison: 1 Methadone maintenance treatment vs No methadone maintenance treatment

Outcome: 2 Morphine positive urine or hair analysis

Study or subgroup	MMT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Dolan 2003	39/125	43/117		13.0 %	0.85 [0.60, 1.21]
Gruber 2008	32/50	14/18		14.5 %	0.82 [0.60, 1.14]
Kinlock 2007	19/70	40/64		10.1 %	0.43 [0.28, 0.67]
Schwartz 2006	99/175	80/101		25.4 %	0.71 [0.61, 0.84]
Vanichseni 1991	70/120	109/120		25.5 %	0.64 [0.55, 0.75]
Yancovitz 1991	22/75	56/94		11.5 %	0.49 [0.33, 0.73]
Total (95% CI)	**615**	**514**	◆	**100.0 %**	**0.66 [0.56, 0.78]**
Total events: 281 (MMT), 342 (Control)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 10.79$, df = 5 (P = 0.06); $I^2 = 54\%$					
Test for overall effect: Z = 5.01 (P < 0.00001)					

Analysis 1.3. Comparison 1 Methadone maintenance treatment vs No methadone maintenance treatment, Outcome 3 Self reported heroin use.

Review: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

Comparison: 1 Methadone maintenance treatment vs No methadone maintenance treatment

Outcome: 3 Self reported heroin use

Study or subgroup	Methadone MT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Dolan 2003	41/129	92/124		0.43 [0.33, 0.56]
Dole 1969	2/12	15/15		0.20 [0.06, 0.61]
Gruber 2008	30/41	15/24		1.17 [0.82, 1.68]
Gunne 1981	5/17	12/17		0.42 [0.19, 0.93]
Kinlock 2007	28/70	39/64		0.66 [0.46, 0.93]
Yancovitz 1991	21/75	83/94		0.32 [0.22, 0.46]

Analysis 1.4. Comparison 1 Methadone maintenance treatment vs No methadone maintenance treatment, Outcome 4 Criminal activity.

Review: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

Comparison: 1 Methadone maintenance treatment vs No methadone maintenance treatment

Outcome: 4 Criminal activity

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Dole 1969	3/12	15/16		65.9 %	0.27 [0.10, 0.72]
Gunne 1981	0/17	2/17		13.9 %	0.20 [0.01, 3.88]
Yancovitz 1991	2/149	1/152		20.2 %	2.04 [0.19, 22.26]
Total (95% CI)	**178**	**185**		**100.0 %**	**0.39 [0.12, 1.25]**
Total events: 5 (Treatment), 18 (Control)					
Heterogeneity: Tau² = 0.29; Chi² = 2.54, df = 2 (P = 0.28); I² =21%					
Test for overall effect: Z = 1.59 (P = 0.11)					

Analysis 1.5. Comparison 1 Methadone maintenance treatment vs No methadone maintenance treatment, Outcome 5 Mortality.

Review: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

Comparison: 1 Methadone maintenance treatment vs No methadone maintenance treatment

Outcome: 5 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Gunne 1981	0/17	4/17		24.0 %	0.11 [0.01, 1.92]
Kinlock 2007	0/71	1/70		20.1 %	0.33 [0.01, 7.93]
Newman 1979	3/50	1/50		34.0 %	3.00 [0.32, 27.87]
Yancovitz 1991	0/149	2/152		21.8 %	0.20 [0.01, 4.21]
Total (95% CI)	**287**	**289**		**100.0 %**	**0.48 [0.10, 2.39]**
Total events: 3 (Treatment), 8 (Control)					
Heterogeneity: $Tau^2 = 0.66$; $Chi^2 = 3.98$, df = 3 (P = 0.26); $I^2 = 25\%$					
Test for overall effect: Z = 0.89 (P = 0.37)					

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials search strategy

1. OPIOID-RELATED DISORDERS*:ME
2. ((*opioid or opiate) and (*abuse or dependen* or disorder*or addict*))
3. 1 or 2
4. Heroin
5. Opioid* or Opiate*
6. #3 or #4 or #5
7. METHADONE:ME or methadone
8. (placebo or withdraw* or detox* or untreated or "no treatment" or "drug free" or "wait list" or waiting)
9. #6 and #7
10. #9 and #8

Appendix 2. PubMed search strategy

1. "substance-related disorders" [MH]
2. "opioid related disorders" [MH]
3. ((*opioid OR opiate) AND (*abuse OR dependen* OR disorder* OR addict*))
4. 1 OR 2
5. Heroin [MH] OR heroin
6. Narcotics [MH]
7. opioid* OR opiate*
8. 5 OR 6 OR 7
9. 4 OR 8

10. methadone [MH] OR methadone
11. 9 AND 10
12. (placebo OR withdraw* OR detox* OR untreated OR ”no treatment“ OR ”drug free“ OR ”wait list“ OR waiting)
13. 11 AND 12

combined with the phases 1 & 2 of the Cochrane Sensitive Search Strategy for the identification of RCTs as published in Appendix 5b2, Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006)
14. randomized controlled trial [PT]
15. randomized controlled trials [MH]
16. controlled clinical trial [PT]
17. random allocation [MH]
18. double blind method [MH]
19. single blind method [MH]
20. 14 OR 15 OR 16 OR 17 OR 18 OR 19
21. clinical trial [PT]
22. clinical trials [MH]
23. ((singl* OR doubl* OR trebl* OR tripl*) AND (blind* OR mask*))
24. PLACEBOS [MH] OR placebo*
25. random*
26. Research Design:ME
27. 14/26 OR
28. 13 AND 27
29. limit 28 to human

Appendix 3. EMBASE search strategy

1. drug abuse.me
2. Substance abuse.me
3. ((opioid or opiate) and (abuse$ or dependen$ or disorder$ or addict$))
4. 1 or 2 or 3
5. heroin.mp
6. Opiate.me or opiate$
7. opioid$
8. 5 or 6 or 7
9. 4 and 8
10. methadone.me or methadone
11. methadone treatment.me
12. 10 or 11
13. 9 and 12
14. (placebo or withdraw$ or untreated or ”drug free“ or detox$ or ”wait list“ or waiting)
15. 13 and 14
16. random$
17. placebo$
18. (singl$ or doubl$ or trebl$ or tripl$) and (blind$ or mask$))
19. crossover$
20. randomized controlled trial.me
21. phase-2-clinical-trial.me
22. phase-3-clinical-trial.me
23. double blind procedure.me
24. single blind procedure.me
25. crossover procedure.me
26. Latin square design.me
27. PLACEBOS.me

28. multicenter study.me
29. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 15 and 29
31. limit 30 to human

Appendix 4. CINAHL search strategy

1. exp "Substance Use Disorders"/
2. ((drug or substance) and (addict* or dependen* or abuse* or disorder*))
3. 1 or 2
4. exp heroin/ or heroin
5. (opioid* or opiate*)
6. exp methadone/or methadone
7. 3 or 4 or 5 or 6
8. (placebo or withdraw* or untreated or "drug free" or detox* or "wait list" or waiting)
9. 7 and 8
10. random*
11. (singl* or doubl* or tripl* or trebl*) and (mask* or blind*)
12. crossover*
13. allocate*
14. assign*
15. ((random*) and (allocate* or assign*))
16. exp Random Assignment/
17. exp Clinical Trials/
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 9 and 18

WHAT'S NEW

Last assessed as up-to-date: 18 February 2009.

5 March 2009	New citation required but conclusions have not changed	new trials included, analysis changed in respect to the previous version, quality assessment changed following the new rules of the Collaboration
19 February 2009	New search has been performed	new search, new studies found

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 4, 2002

23 February 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Contributions: Richard P Mattick, Jo Klimber and Courtney Breen reviewed the papers, with Courtney Breen and Richard P. Mattick coding data from the papers for meta-analysis.

Richard P. Mattick conceptualised the review and Courtney Breen conducted the initial literature searches.

Richard P. Mattick wrote the analysis sections and discussion. Marina Davoli was the contact editor of the review and contributed to the writing of the final version of the review.

The review was updated by Richard P. Mattick and Courtney Breen.

DECLARATIONS OF INTEREST

The first reviewer, Richard P. Mattick, is the fourth author on the Australian trial of methadone maintenance versus wait-list control in a prison setting (Dolan 2003).

SOURCES OF SUPPORT

Internal sources

- National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia.

External sources

- Commonwealth Department of Health and Aged Care, Canberra, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Metabolic Detoxication, Drug; Methadone [*therapeutic use]; Narcotics [*therapeutic use]; Opioid-Related Disorders [*rehabilitation]; Randomized Controlled Trials as Topic

MeSH check words

Humans

3

Sterile Needle and Syringe Access, and Outreach and Education

For those who are unable to stop using or injecting drugs, sterile needle and syringe access aims to reduce HIV transmission by increasing access to sterile injecting equipment, removing contaminated needles from circulation, and preventing needles and syringes from being discarded in the community, where others might reuse them or suffer needle sticks. Access can be ensured through needle and syringe exchange, pharmacy and prescription-based sales, vending machines, supervised injecting facilities, and disinfection programs. Many sterile needle and syringe access programs also encourage the cessation of drug abuse through referrals to drug treatment, and the reduction of sex-related risk through the provision of condoms. All these interventions can be combined with outreach and education.

This chapter starts with a discussion of needle and syringe exchange (NSE).[1] In many regions of the world where it has been implemented and evaluated, needle and syringe exchange is usually part of a multi-component HIV prevention effort. To properly reflect this, the Committee refers to such programs as multi-component HIV prevention programs

[1]Needle and syringe exchange refers broadly to supplying clean needles and syringes to IDUs and collecting used injecting equipment. While some programs require exchange of used needles for clean ones, need-based programs allow unlimited distribution of needles and syringes.

that include needle and syringe exchange. These are defined as interventions that combine needle and syringe exchange with any one or more of the following services: outreach, health education in risk reduction, condom distribution, bleach distribution coupled with education on needle disinfection, and referrals to substance abuse treatment and other health and social services. In this report, the term multi-component HIV prevention programs does not include drug dependence treatment and other medical or social services (discussed in Chapter 2), but does include referrals to these services. While this separation may seem somewhat artificial, the Committee felt it was necessary to accurately describe the evidence related to needle and syringe exchange.

The following two sections then examine alternatives to NSE for providing access to clean injecting equipment. One of these two sections focuses on pharmacy and prescription sales, vending machines, and supervised injecting facilities, while the other section focuses on disinfection distribution and education programs.

The chapter then evaluates empirical evidence on the effectiveness of outreach and education in preventing HIV transmission among IDUs. Outreach and education are sometimes part of multi-component HIV prevention programs, as they are often used to direct drug users to services such as needle and syringe exchange. They can also stand alone as a means of educating IDUs on HIV prevention, and can also be used to refer drug users to drug treatment and other health and social services. The final section of the chapter discusses specific areas in need of further research in high-risk countries.

NEEDLE AND SYRINGE EXCHANGE

To evaluate the effectiveness of NSE, the Committee reviewed studies identified by a literature review (see Appendix B). As discussed in Chapter 2, the Committee then used a structured qualitative method based on an approach developed by the GRADE Working Group to evaluate the strength of the evidence (GRADE Working Group, 2004) (see Chapter 2 for further detail).

The majority of evidence on the effectiveness of NSEs comes from observational studies, including numerous prospective cohort studies, supplemented by results from ecological and cross-sectional studies. (Appendix D provides a summary of these studies, grouped by study design.) The Committee did not identify any randomized controlled trials of NSE. This is not completely unexpected for such a public health intervention, particularly one with such immediacy and assumed efficacy and face validity. The Committee identified three case-control studies. Such studies enroll participants based on the presence or absence of a disease, and then com-

pare the characteristics of a previous exposure to NSE. The Committee identified 26 prospective cohort studies, which enroll participants based on their risk characteristics, and follow them to compare related outcomes. The committee felt that 14 of these studies were especially strong in terms of study design and relevance (and noted those studies with an asterisk in a table in Appendix D). Case-control and prospective cohort studies were ranked as having the strongest available study design.

The Committee also identified six ecological studies, which examine populations rather than individuals and cannot establish causal links. Finally, the Committee identified many cross-sectional and serial cross-sectional studies. Cross-sectional studies describe the associations between a disease and risk factors in a population at a specific point in time. The Committee considered such studies as having the weakest design because causal inferences cannot be drawn from them. Serial cross-sectional studies examine groups of people at multiple time points, and offer stronger evidence of shifts in associations over time. As opposed to prospective cohort studies which examine individual-level changes in risk behavior, well-designed serial cross-sectional studies can indicate patterns of behavior change at the community level. As supporting evidence, the Committee included six cross-sectional and four serial cross-sectional studies in Appendix D, based on their strong study design and relevance to the Committee's statement of task.

The Committee used caution in interpreting the results of studies reviewed in this chapter because of their generally weak designs and serious limitations. One limitation is that the studies identified do not randomly assign subjects to treatment and control groups—rather, participants deliberately choose whether to use NSEs and other services. This creates an unavoidable risk of selection bias, and means that differences in rates of risk behaviors and HIV infection may not be due to use of the service itself. Another limitation is that the study designs generally do not allow separate examination of program elements, so the independent contribution of improving access to sterile needles and syringes cannot be assessed. For example, NSE is often one component of a multi-component HIV prevention program, making it difficult to isolate the exact effects of NSE alone.

Another concern is that studies of drug abuse, like most behavioral research, depend heavily on self-reported data on drug use, risk behavior, and precautions taken to reduce risk. Studies evaluating the effectiveness of NSEs are no exception. Self-reported data can introduce bias, as drug abuse is illegal in most settings, and drug users may underestimate risk behavior and overestimate protective behavior. Still, the self-reports of drug users on the incidence of drug abuse and drug-related risks have generally been shown to be valid (Darke, 1998) and remain the major type of outcome measures used in studies of NSE.

Studies comparing audio computer-assisted self-interviews with interviewer-administered surveys show that IDUs tend to under-report risk behavior such as needle sharing (Metzger et al., 2000; Des Jarlais et al., 1999) and over-report protective behaviors such as condom use and syringe disinfection (Macalino, 2002) in face-to-face interviews. However, Safaeian et al. (2002) compared self-reports to NSE records and found that the majority of self-reports of NSE attendance in Baltimore were valid. This study also found that persons who over-reported NSE attendance were more likely to have injected frequently (adjusted odds ratio [AOR]=1.29; 95% confidence interval [CI]: 1.04–1.61), denied needle sharing (AOR=0.69; 95% CI: 0.52–0.89), and seroconverted to HIV (AOR=1.83; 95% CI: 1.11–.01). In the Baltimore study, model predictors of HIV infection based on self-reports compared with actual program data underestimated the protective effect of NSE participation by 18 percent (Safaeian et al., 2002).

Evaluations of NSE often include a range of outcome measures (see Box 3.1). Desirable outcomes may include a reduction in high-risk behavior, more referrals to drug treatment, and declines in rates of HIV infection. Negative outcomes may include more frequent injection among participants, new initiates to injecting drug use, greater drug use in the community, and more needles discarded in public places. In the following sections,

BOX 3-1 Potential Outcomes from Needle and Syringe Exchange

Drug-related risk behavior
- Frequency of drug use
- Frequency of injection
- Frequency of equipment sharing
- Use of disinfectant
- Number of injecting partners

Sex-related risk behavior
- Number of sexual partners
- Frequency of unprotected sex
- Sale of sex for drugs or money

Unintended consequences
- Recruitment of new IDUs
- Increase in unsafe disposal of needles
- Increase in prevalence or frequency of drug use

Links to health and social services
- Referral to services
- Extent of use of services
- Referral to drug treatment

Incidence/prevalence
- HIV
- Hepatitis C
- Hepatitis B

the Committee presents evidence categorized by outcome measure, including the impact of NSEs on drug-related and sex-related risk behavior, the impact of NSEs on HIV incidence and prevalence, any unintended consequences, and the impact of NSEs on links to health and social services.

Drug-Related Risk Behavior

The Committee did not identify any case-control studies that examined the impact of multi-component programs that include needle and syringe exchange on drug-related risk behavior. As noted, the Committee considered prospective cohort studies the strongest study design along with case-control studies. Of 26 prospective cohort studies identified, 18 examined the impact of these programs on drug-related risks. Thirteen found that participation in multi-component programs that include needle and syringe exchange reduced self-reported needle sharing. (Sharing is defined as lending or borrowing used needles or syringes.) Four studies found no increase in injection frequency among NSE participants, and one of these found a decrease (see Appendix D and Table 3.1). The sections below discuss studies selected by the Committee for their strong study design and relevance.

Sharing drug preparation equipment such as cookers used to melt drugs, cotton used to filter out particles when drawing the drug into the syringe, and water used to rinse syringes, has been associated with hepatitis C (HCV) infection (Diaz et al., 2001; Hagan et al., 1999, 2001; Hahn et al., 2002; Thorpe et al., 2002). Few studies have examined whether NSEs reduce the sharing of other injection equipment such as cookers, cotton, or water—possibly because NSEs do not always provide such equipment. One prospective cohort study by Ouellet et al. (2004) shows that when NSEs do provide such drug paraphernalia, sharing declines. A cross-sectional study in Providence, Rhode Island, where an NSE provides alcohol swabs and cookers, supports this finding (Longshore et al., 2001). Two prospective cohort studies found no association between NSE use and the sharing of other injecting equipment (Hagan et al., 2000; Huo et al., 2005).

In 2004 in Chicago, Ouellet et al. compared NSE users (n=558)—defined as those who obtained at least half their needles from an NSE—to non-users (n=175). Non-users were recruited from a neighborhood that did not have an NSE. Using multivariate analysis, the researchers found that regular NSE users were less likely to share needles (AOR=0.30; 95% CI: 0.19-0.46), lend used needles (AOR=0.47; 95% CI: 0.31–0.71), or use a needle for more than one injection (AOR=0.15; 95% CI: 0.08–0.27).

Similarly, Bluthenthal and colleagues (2000) interviewed 340 street-recruited IDUs semi-annually to determine whether NSE use was associated with a decrease in syringe sharing. IDUs participating in the study also received HIV testing and counseling at the time of interview. The study

found that 60 percent reported cessation of syringe sharing. Compared with non-NSE users, IDUs who began using an NSE were more likely to stop sharing syringes (AOR=2.68; 95% CI: 1.35–5.33), as were those who continued using the NSE (AOR=1.98; 95% CI: 1.05–3.75).

Schoenbaum and colleagues (1996) studied the injection behavior of NSE users and non-users in the Bronx, New York City. The study found that male gender, HIV-seropositive status, and younger age were independently associated with NSE attendance, and that NSE users shared needles less often than non-users ($p<0.05$).

A study by Gibson et al. (2002) examined whether NSE use is protective against high-risk behavior such as more frequent injection and syringe borrowing. The study sample included 338 untreated opiate-addicted IDUs, 77 percent of whom were included in follow-up (n=212). The study found that NSE users did not differ from non-users in injection frequency, but were less likely to report borrowing a used syringe. In univariate analysis, NSE use was protective against HIV risk (OR=0.45; 95% CI: 0.21–0.92). Multivariate analyses were used to correct for potential differences between IDUs who use NSE versus those who choose not to. These analyses found that NSE use had a more than six-fold protective effect against HIV risk behavior among IDUs using NSE as their sole source of syringes.

In Baltimore, Vlahov et al. (1997) examined the drug-related behavior of 221 NSE participants at entry into the NSE, 2 weeks after entry, and 6 months after entry. At 6-month follow-up, reductions were reported in using a previously used syringe, lending syringes, backloading (drawing drug into a syringe and then transferring a portion into a second syringe by removing the plunger), and sharing cookers and cotton.

A few studies have found that NSEs have no effect on drug-related risk behavior. For example, in a prospective cohort study in Amsterdam, Hartgers et al. (1992) found that NSE users did not borrow needles and syringes more or less often than non-NSE users. A cross-sectional study by Hagan et al. (1993) interviewed NSE users and asked about injection behavior during the month before first use of the NSE and the most recent month since starting to use the NSE. The study found no change in self-reported frequency of injection, but did find a decline in self-reported frequency of unsafe injection.

Based on this evidence, the Committee concludes:

Conclusion 3-1: Nearly all programs included in our literature search combine needle and syringe exchange with other components such as outreach, risk reduction education, condom distribution, bleach distribution and education on needle disinfection, and referrals to substance abuse treatment and other health and social services.

TABLE 3-1 Studies with Drug-Related Risk Outcomes

Study	Result
Bluthenthal et al., 2000, California (prospective cohort)+	NSE users decreased syringe sharing.
Bruneau et al., 2004, Montreal (prospective cohort)+	NSE and pharmacy users less likely to stop injecting.
Cox et al., 2000, Ireland (prospective cohort)	NSE users decreased needle and syringe sharing and frequency of drug use.
Des Jarlais et al., 2000, New York City (ecological)	Injection risk behaviors declined significantly in presence of NSE.
Gibson et al., 2002, California (prospective cohort)+	NSE users decreased syringe sharing; no change in injecting frequency.
Hagan et al., 2000, Seattle, Washington (prospective cohort)+	NSE users less likely to inject with a used syringe; no association with sharing of other injection equipment.
Hagan et al., 1993, Tacoma, Washington (cross-sectional)	NSE users report no change in frequency of injection; the frequency of unsafe injection declined.
Hammett et al., 2006, Vietnam and China (serial cross sectional)	Drug-related risk behavior declined in frequency.
Hart et al., 1989, London (prospective cohort)	NSE users decreased syringe sharing; no increase in frequency of injection.
Hartgers et al., 1992, Amsterdam (prospective cohort)	No difference in sharing between NSE users and non-users.
Huo et al., 2005, Chicago (prospective cohort +	NSE users less likely to share syringes; no association with sharing of other injection equipment.
Keene et al., 1993, Wales (cross-sectional)+	NSE users less likely to share syringes.
Klee et al., 1991, UK (cross-sectional)	NSE users more likely to lend syringes.
Longshore et al., 2001, Providence, Rhode Island (cross-sectional)	NSE users less likely to report syringe sharing; more likely to report cleaning their skin; less likely to report sharing cookers.
Marmor et al., 2000, New York City (prospective cohort)	NSE users decreased rates of drug injecting.
Monterroso et al., 2000, multiple U.S. cities (prospective cohort)	NSE users less likely to share needles and syringes.
Ouellet et al., 2004, Chicago (prospective cohort)+	NSE users decreased sharing of needles, syringes, and other equipment.
Schoenbaum et al., 1996, New York City (prospective cohort)+	NSE users shared less than non-NSE users.
Van Ameijden and Coutinho, 1998, Amsterdam (prospective cohort)	NSE users showed large initial reduction in sharing needles and frequency of injection.
Van Ameijden et al., 1994, Amsterdam (serial cross sectional)	NSE users are less likely to reuse needles/ syringes.

continued

TABLE 3-1 Continued

Study	Result
Van den Hoek et al., 1989, Amsterdam (prospective cohort)	NSE users decreased needle and syringe sharing; no increase in frequency of drug use.
Vazirian et al., 2005, Iran (cross-sectional)	NSE users decreased needle/syringe sharing.
Vertefeuille et al. 2000, Baltimore (prospective cohort)	NSE users decreased syringe sharing; increased participation in drug treatment.
Vlahov et al., 1997, Baltimore (prospective cohort)	NSE users decreased syringe sharing.
Watters et al., 1994, San Francisco (serial cross-sectional)	NSE users reported decrease in frequency of injection; less likely to share needles/syringes.
Wood et al., 2002, Vancouver (prospective cohort)+	NSE users less likely to share needles and syringes.
Wood et al., 2003, Vancouver (prospective cohort)	NSE users more likely to frequently inject cocaine; more likely to safely dispose of syringes.

+ Indicates that the study compared NSE users with non-users.

Conclusion 3-2: Moderate evidence from a large number of studies and review papers—most from developed countries—shows that participation in multi-component HIV prevention programs that include needle and syringe exchange is associated with a reduction in drug-related HIV risk behavior. Such behavior includes self-reported sharing of needles and syringes, safer injecting and disposal practices, and frequency of injection.

Sex-Related Risk Behavior

Few studies have evaluated the effect of NSEs on sex-related HIV risk behavior (see Table 3-2). This is not surprising, because reduction in sexual risk (often evaluated by reports of condom use) is often not a primary goal of NSEs. However, two early prospective cohort studies associated use of an NSE with a decline in the number of sexual partners (Donoghoe et al., 1989; Hart et al., 1989). Donoghoe and colleagues measured the sexual behavior of 142 NSE clients in England and Scotland at baseline and 2 to 4 months later. Seventy-seven percent of clients reported having one or more sexual partner in the 3 months prior to the first interview. Forty-six percent of these sexually active clients had non-IDU partners. At follow-up, the number of NSE clients having no sexual partners increased from 23 to 31

TABLE 3-2 Studies with Sex-Related Risk Outcomes

Study	Result
Donoghoe et al., 1989, UK (prospective cohort)	Number of NSE participants having no sexual partners increased; number having multiple sexual partners decreased.
Hart et al., 1989, London (prospective cohort)	Significant correlation between multiple sexual partners and condom use; and a reduction in the proportion of clients with multiple partners.
Cox et al., 2000, Ireland (prospective cohort)	NSE users reported no significant change in levels of condom use.

percent, and the number having multiple partners decreased slightly from 26 to 21 percent.

Hart et al. (1989) monitored an NSE in London and followed 121 NSE clients from November 1987 to October 1988. Clients were interviewed 1 month after entry into the NSE and again three months later. The study found a highly significant correlation between multiple sexual partners and condom use, and a reduction in the proportion of NSE clients with multiple partners.

Based on this evidence, the Committee concludes:

Conclusion 3-3: Needle and syringe exchange is not primarily designed to address sex-related risk behavior. In two early prospective cohort studies, NSE participants reported decreases in sex-related risk behavior. However, this issue has not been well studied, and the existing modest evidence is insufficient to determine the effectiveness of needle and syringe exchange in reducing sex-related risk.

Effects of NSE on HIV Incidence/Prevalence

Few site-specific studies have explored the relationship between NSE participation and HIV incidence, although several ecological studies have found positive associations between the introduction or presence of NSEs and reduced HIV prevalence and incidence (see Table 3-3). As mentioned, whether NSE alone is responsible for the impacts is unclear, given myriad design and methodological issues noted in the majority of studies.

Two prospective cohort studies from Montreal and Vancouver in the 1990s associated NSE participation with higher risk of HIV seroconversion (Strathdee et al., 1997; Bruneau et al., 1997). In Montreal, Bruneau et al.

TABLE 3-3 Studies with HIV Incidence or Prevalence Outcomes

Study	Result
Bruneau et al., 1997, Montreal (prospective cohort)	Increased HIV seroconversion among NSE users.
Des Jarlais et al., 2005a, New York City (ecological)	From 1990–2001, HIV prevalence declined.
Des Jarlais et al., 2005b, New York City (serial cross-sectional)	Strong negative relationship between the number of syringes exchanged and estimated HIV incidence.
Hammett et al., 2006, Vietnam and China (serial cross-ectional)	HIV prevalence among IDUs declined in Vietnam and remained stable in China.
Hurley et al., 1997, worldwide (ecological)	Increased HIV prevalence in cities without NSE.
MacDonald et al., 2003, worldwide (ecological)	Increased HIV prevalence in cities without NSE.
Mansson et al., 2000, Sweden (prospective cohort)	No new HIV cases during a median of 31 months among NSE participants.
Patrick et al., 1997, Vancouver (case control)	No association with frequency of NSE use and HIV seroconversion.
Schechter et al., 1999, Vancouver (prospective cohort)	Cumulative HIV incidence was significantly elevated in frequent NSE attenders.
Strathdee et al., 1997, Vancouver (prospective cohort)	Increased HIV and HCV prevalence in the presence of NSE.
Van Ameijden et al., 1992, Amsterdam (case control)	No association between NSE participation and HIV seroconversion.

(1997) used three risk-assessment approaches to examine the association between NSE use and HIV infection. All three analytical approaches associated NSE attendance with a substantial and consistently higher risk of HIV infection. For example, in the cohort approach, in which there were 89 incident cases of HIV infection, the researchers found a 33 percent cumulative probability of HIV seroconversion for NSE users, compared with a 13 percent probability for non-users. In the nested case-control study, consistent NSE use was associated with HIV seroconversion during follow-up (OR=10.5; 95% CI: 2.7–41.0). The analyses employed methodologies to control for a range of confounders, including drug of choice and frequency of injecting drug use in the previous month. These findings persisted after controlling for confounders.

The authors and commentators on this research pointed out that the Montreal NSE appeared to have attracted high-risk cocaine injectors, who injected much more often than heroin users. Also, as shown by the seroprevalence data at baseline, Montreal NSE users had high baseline rates of HIV and hepatitis B infection (Bruneau et al., 1997). The NSE also originally strictly limited the number of needles and syringes users could

receive during any one visit. The authors further noted that the ready availability of clean injecting equipment through pharmacies might have meant that the NSE attracted marginalized, high-risk individuals (Bruneau et al., 1997).

These early research results prompted the Montreal NSE to remove limits on the number of needles and syringes users could obtain, to provide access to other injection equipment, and to expand the number of distribution points to 25 (Personal communication, Carole Morissette and Pascale Leclerc, Health Protection Sector, Public Health Department, Agence de Santé et Des Services Sociaux de Montréal, June 6, 2006). In addition to syringes, NSEs began to provide alcohol swabs, individual disposal containers, sterile water vials, and "stericups" (kits containing a filter, cooker, and post-injection swab). Of 429 pharmacies in Montreal, injection equipment is available at roughly 40 percent, and some (n=70) sell kits containing four syringes, condoms, alcohol swabs, sterile water vials, stericups, and education material for $1.

Following these changes, HIV incidence among participants in the Montreal SurvUDI study dropped from 6.1 per 100 person-years in 1995 to 4.7 per 100 person-years in 2004. The SurvUDI study is a surveillance network that began in 1995 and targets hard-to-reach, mostly out-of-treatment IDUs in Eastern Central Canada (Hankins et al., 2002). HCV incidence—reported retrospectively among Montreal SurvUDI participants between 1997 and 2003—remains high, at about 26 per 100 person-years. (Personal communication, Carole Morissette and Pascale Leclerc, Health Protection Sector, Public Health Department, Agence de santé et des services sociaux de Montréal, June 6, 2006). The SurvUDI network also provides data on trends in syringe sharing in Montreal, including the proportion of participants injecting with a syringe used by someone else (at first study participation). That proportion fell from 45 percent in 1995 to 28 percent in 2004.

In Vancouver, Strathdee et al. (1997) also found that frequent NSE attendance was an independent predictor of HIV seroconversion. After adjusting for confounders, the authors found that the adjusted odds ratio for HIV infection status among NSE users compared with non-NSE users was 1.68. The authors noted that cocaine was the drug of choice among 72 percent of HIV-seropositive IDUs, and that cocaine puts IDUs at elevated risk because it is associated with more frequent injection (Anthony et al., 1991; Chaisson et al., 1989). A follow-up study by Schechter et al. (1999) in the same setting found no relationship between NSE use and HIV incidence, and a case-control study found borrowing of syringes to be the most significant behavior associated with seroconversion among IDUs (Patrick et al., 1997). After multivariate analysis controlling for confounders, the au-

thors found no association between frequency of NSE use and seroconversion.

As in Montreal, the Vancouver NSE originally operated with strict limits on the number of needles and syringes that users could exchange at any one time, and the program operated in only one location. The Vancouver program also made dramatic changes in response to early results. Specifically, the NSE switched from a limited exchange approach to a need-based approach—allowing unlimited distribution of needles/syringes—and greatly increased the number of access points. The program also began offering a variety of distribution methods, including fixed, mobile, and home delivery. HIV incidence among IDUs has since fallen by 30 percent (Personal communication, Chris Buchner, Vancouver Coastal Health Authority, May 5, 2006).

Several studies in Amsterdam found no significant relationship in either direction between NSE participation and HIV incidence (van Ameijden et al., 1992; Coutinho, 2005). Several other papers by these authors (van Ameijden and Coutinho, 1998, 2001) found initial reductions in risk behavior after NSE and other interventions began, but no further reductions over time. These studies also found that NSE was not associated with an increase in injecting drug use, and attributed declines in injecting to cultural and ecological factors. Krol (2006) reached the same conclusion.

Several ecological studies from the developed world found that early, comprehensive programs of outreach, prevention, education, and access to sterile injecting equipment may prevent the expansion of IDU-driven epidemics. Ecological studies, as well as serial cross-sectional studies, reflect community-level patterns of prevalence and risk behaviors rather than patterns or changes at the individual level. For example, Des Jarlais et al. (1995) examined five cities (Glasgow, Scotland; Lund, Sweden; Sydney, Australia; Tacoma, U.S.; and Toronto, Canada) where HIV was introduced into the IDU population but infection rates remained below 5 percent for at least 5 years. The authors found that all five cities had pursued early prevention activities, such as offering sterile injection equipment and community-based outreach. Such interventions may also help reduce HIV prevalence and incidence among IDUs in more mature HIV epidemics, such as in New York City (Des Jarlais et al., 2005a).

In a study of 81 cities, Hurley and colleagues (1997) found that annual HIV seroprevalence between 1988 and 1993 rose by 5.9 percent in 52 cities without NSEs, and fell by 5.8 percent in 29 cities with NSEs. In a similar analysis of 99 cities, MacDonald and colleagues (2003) found that annual HIV prevalence fell by 18.6 percent in cities that introduced NSEs, and rose by 8.1 percent in cities without NSEs. Critics objected that this study did not account for the stage of the epidemic in these cities, and that the researchers used different protocols to collect data on seroprevalence in

different populations (Käll, 2005). To address the possibility that the effect of NSEs can vary with the stage of epidemic, both Hurley et al. and MacDonald et al. analyzed cities where the initial measured seroprevalence among IDUs was less than 10 percent. In the Hurley et al. study, the authors did not find a significant association between NSE presence and the trajectory of the epidemic. However, MacDonald and colleagues did find a significant relationship: the mean annual weighted increase in HIV prevalence was 32.1 percent in cities that did not introduce NSEs, compared with a mean annual decrease of 7.8 percent in cities with NSEs (p=0.03).

Multiple studies show that NSEs do not reduce transmission of HCV, which has been attributed to the apparent failure of NSEs to provide enough ancillary injecting equipment such as sterile cotton, water, and alcohol wipes. While NSEs do reduce the frequency of reported needle and syringe sharing, they do not appear to reduce the sharing of other injecting equipment, such as cookers, cotton, rinse water, and drug solution (Hagan and Thiede, 2000; Sarkar et al., 2003; Taylor et al., 2000; Mansson et al., 2000). In contrast, a case-control study by Hagan et al. (1995) in Seattle found that NSE attendance was associated with a six-fold decrease in acquisition of hepatitis B virus (HBV), and a seven-fold decline in HCV acquisition. Given the high prevalence of HCV among IDUs, this represents an important area for future research.

Based on this evidence, the Committee concludes:

Conclusion 3-4: Four ecological studies have associated implementation or expansion of HIV prevention programs that include needle and syringe exchange with reduced prevalence of HIV in cities over time and after considering the local prevalence of HIV at the time of program implementation or expansion—although a causal link cannot be made based on these studies. The evidence of the effectiveness of NSE in reducing HIV prevalence is considered modest, based on the weakness of these study designs.

Conclusion 3-5: Moderate evidence indicates that multicomponent HIV prevention programs that include needle and syringe exchange reduce intermediate HIV risk behavior. However, evidence regarding the effect of needle and syringe exchange on HIV incidence is limited and inconclusive.

Conclusion 3-6: Five studies provide moderate evidence that HIV prevention programs that include needle and syringe exchange have significantly less impact on transmission and acquisition of hepatitis C virus than on HIV, although one case-control study shows a dramatic decrease in HCV and HBV acquisition.

Mathematical Models

A previous National Research Council and Institute of Medicine (IOM) report (NRC and IOM, 1995) and a University of California review (Lurie et al., 1993) reviewed mathematical models and their conclusions regarding the impact of NSE on HIV incidence. Thus this section will examine such models only briefly, and the evidence presented is considered supplementary to the empirical studies described above.

Mathematical models used by Kaplan and colleagues (Kaplan and Heimer, 1992; Kaplan and O'Keefe, 1993) used a set of two dynamic equations and their associated steady states to link the size of NSE programs to HIV incidence in injecting equipment and IDUs (Kaplan and O'Keefe, 1993). A syringe tracking system developed for this purpose allowed the researchers to assess infection rates in injecting equipment directly from an existing NSE in New Haven, Connecticut. The researchers used those rates to infer the impact of New Haven's needle and syringe exchange on HIV incidence among IDUs. A key finding was that the NSE reduced steady state prevalence in injecting needles by one-third. From this, the researchers deduced that HIV incidence also fell by one-third in steady state. A separate modeling exercise showed that annual HIV incidence fell by 1–3 per 100 participant-years.

More recently, a variant of this mathematical framework has been used to assess the impact of extending coverage of needle distribution programs on HIV transmission among injecting drug user populations of Belarus and the United Kingdom when injectors share needles in the confines of small sub-groups of the population (Vickerman et al., 2006). Its main finding, based on simulations, is that the biggest reductions in steady-state HIV prevalence usually occur only after certain threshold levels of service coverage have been achieved.

Questions have been raised about the underlying technical assumptions of mathematical models in general and specifically the New Haven studies. One concern is whether the law of conservation of needles—a key element of the Kaplan model—is valid in practice. This law requires that the number of new needles handed out and the number handed in be roughly the same. This was the case with the New Haven NSE, and the weight of evidence for other NSE programs supports this assumption (Guydish et al., 1991; Ksobiech, 2004).

A second issue is whether the composition of program participants changed over time—for instance, whether persons more likely to be HIV-seropositive dropped out of the program and were replaced by persons less likely to be HIV-seropositive. Under this scenario, the model would tend to overestimate the effectiveness of NSE. Kaplan et al. (1994) argue that little evidence suggests that such a shift occurred in the New Haven NSE.

A third area of concern is the model's relative lack of attention to behavioral aspects of HIV transmission. For instance, Bloom et al. (2006) argue that needles turned in to the needle exchange program are likely to be older and to have been used more frequently—not a random selection of circulating needles. Thus infection rates among these old needles are likely to be "terminal" rather than "average." These two rates can sometimes move in opposite directions, so the data for New Haven may not offer ready insight into the impact of NSE on HIV incidence among humans. Additionally, in the case of the model used for the Belarus and United Kingdom study (Vickerman et al., 2006), we do not know how the size and composition of injecting drug user sharing groups respond to needle distribution programs and hence their efficacy in reducing HIV transmission.

After evaluating these concerns, the IOM review (NRC and IOM, 1995) concluded: "The model-based evaluation of the New Haven needle exchange program provides important insights into the dynamics of such programs and useful preliminary estimates of their efficacy. We cannot attach the same level of confidence to these model-based estimates as we could to evaluation programs that included a suitable control group in which individuals were tested (directly) for HIV infection" (p. 231).

While there are questions about specific numerical estimates of the efficacy of needle exchange programs derived from mathematical models of HIV transmission among IDU, such models do have the advantage of illustrating the relationships among the major parameters such as the probability of transmission, the size of needle sharing groups and the frequency of shared needle use that influence the transmission of HIV among IDU. Moreover, models can highlight some common areas of concern such as how the relatively high probability of transmission of HCV from a single unsafe injection means that even if needle exchanges achieved high coverage rates, they would be much less efficacious in preventing HCV than HIV.

Unintended Consequences of Needle and Syringe Exchange

This section reviews evidence regarding the effect of NSE on the frequency of drug use, the recruitment of new injecting drug users, unsafe disposal of needles, and trends in crime. The Committee did not identify any studies that focus on these outcomes as their main objective, but some studies report them as secondary outcomes.

Of the prospective cohort studies (see Appendix D), five found no increase in frequency of injecting among NSE attenders (Hart et al., 1989; van Den Hoek et al., 1989; Cox et al., 2000; Gibson et al., 2002; Marmor et al., 2000). Hart et al. (1989) found that the frequency of injecting did not increase among NSE clients in London, and that the incidence of drug use-related abscesses fell among this group. van Den Hoek et al. (1989) found

no increase in the proportion of participants injecting drugs or the frequency of drug use among 263 IDUs in Amsterdam. A serial cross-sectional study in San Francisco found that NSE users reported a drop in injections from 1.9 to 0.7 per day (Watters et al., 1994).

Other studies suggest that programs that include NSE do not increase the number of new IDUs. During a 5.5-year study period, Watters et al. (1994) found that the proportion of persons who reported first injecting drugs in the previous year decreased from 3 to 1 percent. In Tacoma, Washington, Hagan et al. (1993) found no increase in drug use. The study measured initiation into drug use by collecting injection histories of NSE users. Only 1 of 204 users began using drugs after the NSE opened, and only 13 users had started injecting in the previous 2 years. In Vancouver, when NSE users were asked where they had met their new sharing partners, only 1 of 498 cited the NSE (Schechter et al., 1999).

Studies have not linked NSEs to a higher number of discarded used needles (Oliver et al., 1992; Broadhead et al., 1999; Doherty et al., 2000). A prospective study in Ireland by Cox et al. (2000) found that at 6-month follow-up, the proportion of NSE users discarding needles in the street, alley, sewer, or gutter declined from 28.2 percent to 15.6 percent ($p < 0.001$), and the proportion discarding needles in the garbage or a dumpster fell from 42.4 percent to 29.1 percent ($p<0.001$). Similarly, a prospective study in Vancouver by Wood et al. (2003) found that NSE use was independently associated with safer syringe disposal (AOR=2.69; 95% CI: 1.38–5.21).

A study in Baltimore examined whether the introduction of a needle and syringe exchange was associated with increased crime rates (Marx et al., 2000). Using arrest records, the study compared trends in arrests in NSE areas and non-NSE areas of the city before and after introduction of the NSE. Arrest trends were modeled and NSE areas were compared to non-NSE areas. No significant differences were found (Marx et al., 2000). A cross-sectional study in an inner-city neighborhood of New York City assessed the association between proximity to an NSE and violence (Galea et al., 2001). Results showed no significant association between distance from the nearest NSE and reporting a fight (OR=1.05; p=0.89); robbery in the neighborhood in the previous 6 months (OR=1.13; p=0.71); having ever experienced violence (OR=0.72; p=0.52); or having ever been robbed by drug users (OR=1.05; p=0.91) (Galea et al., 2001).

Based on this evidence, the Committee concludes:

Conclusion 3-7: Few studies have specifically evaluated whether HIV prevention programs that include needle and syringe exchange lead to unintended consequences, such as increases in new drug users, more frequent injection among established users, ex-

panded networks of high-risk users, more discarded needles in the community, and changes in crime trends. Modest evidence shows that NSE does not increase the number of discarded needles in the community, and that injection frequency does not increase among NSE participants. Weak evidence and limited data suggest that programs that include NSEs do not lead to new users, expanded drug networks, or increases in crime.

Links to Health and Social Services

NSEs can serve as important links to health and social services for drug users who otherwise might not have access to treatment and care. Examples of such services include referrals to drug treatment, voluntary HIV counseling and testing, and medical care such as vaccinations and diagnosis of infections.

To assess the role of NSEs as a bridge to treatment, Strathdee et al. (1999) conducted a prospective cohort study in Baltimore. The study found that NSE attendance and health care use were each independently associated with entry into detoxification. HIV-seropositive NSE attenders were more than three times as likely to enter a detoxification program in the first year after the NSE began, but this result diminished over time. One explanation is that IDUs seeking treatment visited the NSE in large numbers when it first opened. A study at a New Haven NSE found that known syringe exchangers accounted for only 27 percent of requests for drug treatment (Heimer, 1998). Among the requesters, there was a strong association between heroin use and use of the NSE, and between alcohol use and non-users. This reveals that many people seeking drug treatment are not NSE clients, and that a treatment referral program could reach a larger target audience.

IDUs are likely to use services offered through an NSE beyond referrals for drug treatment. Porter et al. (2002) conducted a cross-sectional study at a needle and syringe exchange in Philadelphia offering four types of services: HIV voluntary counseling and testing, medical care, drug treatment referrals, and referrals to other services. The sample (n=43) included needle and syringe exchange users and non-users. Thirty-nine percent of the sample used at least one service besides needle exchange, with most of these participants using services that did not require outside follow-up. Twenty-eight percent had heard of at least one service beyond needle and syringe exchange, but had not used the additional service. Reasons for not using available services included access to these services through other means, and unwillingness to spend time waiting for them. The remaining study participants were either not aware that additional services existed or were aware that other services were available but had no knowledge of the

specifics types. All the respondents who used the needle exchange fell into the first two categories, while non-users fell into the latter two.

Examining the characteristics of NSE participants associated with health care and drug treatment (n=269) in Baltimore, Riley et al. (2002) found that 58 percent reported using primary health care in the previous 3 years. Being age 40 years or older, having health insurance, and exchanging more than seven syringes per visit were positively associated with use of primary health care.

Some studies have illustrated the range of unique health services provided with NSEs. For example, a study by Grau et al. (2002) described a wound and abscess clinic incorporated into an NSE in Oakland, California. In New York City, an NSE administered influenza and pneumococcal vaccines to IDUs (Stancliff et al., 2000); while in Baltimore an NSE provided tuberculosis services (Riley et al., 2002).

Pollack et al. (2002) examined whether a mobile NSE-based health care delivery system reduced the use of hospital emergency rooms by out-of-treatment IDUs in New Haven. Of 373 IDUs, 117 were NSE clients and 256 were not. After the system was implemented, use of the emergency room fell among clients and rose among non-clients.

Based on this evidence, the Committee concludes:

Conclusion 3-8: Few empirical studies have evaluated whether HIV prevention programs that include needle and syringe exchange effectively link IDUs to ancillary health and social services. The few studies examining this issue show moderate uptake of these services among NSE attendees. However, none of the studies had comparison or control groups, so the overall use of such services among drug users who do not use NSE is unknown.

Summary Conclusion and Finding on Multi-Component HIV Prevention Programs that Include NSE

Summary Conclusion: Moderate evidence from developed countries points to a beneficial effect of multi-component HIV prevention programs that include needle and syringe exchange on injection-related HIV risk behavior, such as self-reported needle sharing and frequency of injection. Modest evidence also points to decreasing trends in HIV prevalence in selected cities studied over time. Although many of the studies have design limitations, the consistency of these results across a large number of studies supports these conclusions.

Finding 3-1: The Committee finds that almost all published studies of multi-component HIV prevention programs that include needle and syringe exchange originate in North America, Western Europe, and Australia.

ALTERNATIVE ACCESS TO STERILE NEEDLES AND SYRINGES

Pharmacy Access

Pharmacists can play a key role in preventing HIV infection among IDUs. They can provide advice, including information on safe needle use and substance abuse treatment, and also sell condoms and sterile needles and syringes (Jones and Coffin, 2002). In the United States, many states have "deregulated" or removed laws to allow increased access to sterile needles and syringes through pharmacy sales or physician prescription (Burris et al., 2003). As noted in Chapter 1, syringe prescription laws prohibit the sale of needles and syringes without a prescription and pharmacy regulations may limit the number of syringes a person can purchase at one time (Burris et al., 2003). Relaxation of such laws and regulations governing pharmacy sales of syringes has improved attitudes toward selling to injecting drug users, and increased the number of IDUs who turn to pharmacies for clean injecting equipment (Coffin et al., 2002; Deren et al., 2006).

A well-studied example of the effects of deregulating the availability of syringes through pharmacies is the New York Expanded Syringe Access Demonstration Program (ESAP). This program began in 2001 by allowing pharmacies, health care facilities and practitioners to register and provide up to 10 syringes without a prescription to persons at least 18 years old (Klein et al., 2002). Studies show that IDUs began using pharmacies as a result of this legislation (Deren et al., 2003; Des Jarlais et al., 2002; Fuller et al., 2004).

A serial cross-sectional study by Pouget et al. (2005) found that self-reports of receptive sharing fell significantly—from 13.4 percent in 2001 to 3.6 percent in June 2003 following the legislative change. The number of IDUs obtaining syringes from an ESAP source, mostly pharmacies, rose from 7.5 percent to 25 percent. Deren et al. (2006) examined syringe sources pre- and post-ESAP (n=130). Most drug users who reported obtaining syringes at an NSE before ESAP began continued using that source, although 10 percent reported some use of ESAP. Of drug users who originally relied on unsafe sources, 19 percent reported some ESAP use. Overall, 14 percent of the sample reported some ESAP use.

Other regions of the United States have also experimented with this form of alternative access. Groseclose et al. (1995) examined syringe-

sharing practices before and after Connecticut partially repealed laws requiring prescriptions for needles and drug paraphernalia. Syringe sharing fell from 52 percent to 31 percent (p=0.02) after the change in laws, and 78 percent of IDUs purchased syringes from a pharmacy, compared with 19 percent before.

Singer et al. (1997) surveyed pharmacists in Hartford and its peripheral neighborhoods to study access to over-the-counter syringes. Results showed that 72.2 percent of inner-city pharmacies and 55.6 percent of periphery pharmacies sold syringes without prescription. Some pharmacists cited negative incidents as their reason for requiring a prescription for syringes. Examples of such incidents included improper disposal of used syringes in or near the pharmacy, drug use on pharmacy property, and increased shoplifting.

In a cross-border HIV prevention project for IDUs in China and Vietnam, peer educators distribute sterile needles and syringes directly, as well as vouchers for sterile needles and syringes and other prevention supplies that drug users may redeem at participating pharmacies (Hammett et al., 2005). In Vietnam, the voucher scheme has proved very popular among IDUs: about two-thirds of all needles and syringes provided by the project over 3 years occur through vouchers, with about 8,000 redeemed per month. In China, the vouchers were initially popular, but the novelty appears to have worn off quickly, and most IDUs now prefer to receive needles and syringes directly. This difference between the two countries may reflect differences in concerns about police, the convenience of pharmacy locations, and pharmacists' attitudes toward IDUs (Hammett et al., 2005).

Attitudes of Pharmacists Toward Selling or Providing Syringes

Individual pharmacists can often decide whether to sell syringes without a prescription in areas where it is legal to do so. Many studies have examined the willingness of pharmacists to sell or provide syringes to IDUs, and the factors surrounding their decision. A study in Atlanta found that the personal attitudes and beliefs of individual pharmacists are the most influential factor (Taussig et al., 2002). Some pharmacists fear that IDUs will discard syringes unsafely, and that the presence of IDUs in their pharmacy will be bad for business, while others view syringe access as an HIV prevention method, and see drug dependence as a disease. In Denver, pharmacists viewing syringe sales as a method for preventing disease were more likely to sell syringes to IDUs (Lewis et al., 2002). Concerns also arose in that city, with pharmacists worrying about the effect of IDUs on business and the possibility of discarded syringes near the store.

In Rhode Island, most pharmacists who work in stores that sell non-prescription syringes (n=101) were willing to sell syringes to IDUs (65 percent), were in favor of providing syringe disposal containers (68 percent), and supported providing pamphlets on safe injecting practices (88 percent) (Rich et al., 2002).

Characteristics of IDUs Using Pharmacies for Sterile Needle and Syringe Access

Studies show that IDUs who use pharmacies tend to have lower risk profiles. Miller et al. (2002) compared risk behavior in Vancouver among IDUs who cited pharmacies, fixed NSE, and mobile exchange vans as their primary source of needles and syringes. Pharmacy users had the lowest risk profiles, although they continued to report needle sharing. Studies in Marseille, France (Obadia et al., 1999), and Baltimore, Maryland (Riley et al., 2000), suggest that drug users who rely on pharmacies for equipment are more socially integrated than those who rely on NSEs. As Vlahov (2000) noted, the availability of clean injecting equipment through pharmacies might result in the NSE attracting higher-risk IDUs. Therefore access to pharmacy syringes may influence the findings of studies that compare NSE users with non-users (Ouellet et al., 2004; Gibson et al., 2002; Bruneau et al., 1997).

Physician Prescription Access

The Committee identified one program that offered access to needles and syringes though physician-provided prescriptions. In 1999, a pilot project in Rhode Island aimed to offer medical services, access to syringes, risk reduction counseling, and referrals to other services through syringe prescriptions from physicians (Rich et al., 2004). On the first visit, the physician encouraged an IDU to undergo HIV testing and assessed the need for drug treatment and other services. For IDUs who said they would continue to inject despite advice not to, physicians prescribed up to 100 syringes, providing instructions for proper use and disposal. Participants could then request refills over the phone, and the health clinic made other injecting supplies available. The study found that the syringe prescription program was feasible, and that it attracted a high-risk, underserved IDU population. This type of program served as a link to care, and a basis for substance abuse treatment and other medical and social services. However, the evidence from this pilot study must be considered in light of the limitations associated with a case study.

Overdose deaths and Vancouver's supervised injection facility

The report by Brandon Marshall and colleagues (April 23, p 1429),[1] in which it is claimed that the opening of a supervised injection facility on Sept 21, 2003, in Vancouver, BC, Canada, was associated with a 35% decrease in overdose deaths in its immediate surrounding, contains serious errors.

The claim that all overdose deaths in Vancouver declined between 2001 and 2005 is strongly affected by the highly questionable inclusion of the year 2001—a year of much higher heroin availability and overdose fatalities than all subsequent years. A study period starting from 2002 in fact shows an increasing trend of overdose deaths both for Vancouver and for the Downtown Eastside area in which the facility, Insite, is situated (figure),[2] the control areas compared in Marshall and colleagues' study.

Curiously, the higher availability of heroin up until 2001, which declined by 2002 and which has remained low since that year, was specifically tracked in two previous articles[3,4] by three of the current paper's researchers and therein treated as extraordinary. In their latter 2007 study,[4] the aforesaid three researchers noted that, in a large cohort of Vancouver drug users, 21% had reported non-fatal overdoses in the previous 12 months in 1997, dropping to 12% at the beginning of 2001 and to 5% by the end of 2001, rising to 6% in 2004. They clearly point to reduced heroin supply as the reason, and yet in the *Lancet* paper specifically state that "we have no evidence that significant changes in drug supply or purity occurred during the study period", which of course was 2001 to 2005.

Of even greater concern is the statement in the *Lancet* paper that "we know of no changes in policing policy that could have confounded our results". Again, three of the researchers were so well appraised of major policing changes in the area immediately around Insite during 2003, the same year it opened, that they wrote a 2004 article tracking the "displacement" of drug users out of the policed area around Insite and into other areas of Vancouver.[5] In that article they record counts of discarded needles reducing by 46% in the policed areas whereas needle counts in other areas of Vancouver increased by similar proportions. Most of the overdoses that were the subject of the questionable 35% reduction immediately around Insite lay specifically in the 12 city blocks patrolled by 48–66 police added in 2003 and operative to this day (personal communication). This major change in policing around Insite is clearly the most likely cause of any real reductions in overdoses that might be found in the immediate vicinity of the injection facility.

Finally, Marshall and colleagues do not declare that 41% of British Columbia's overdose mortality is non-injection-related.[6] This being the case, the researchers had the obligation of declaring the specific proportion of deaths that were non-injection-related in the vicinity of Insite, compared with the rest of Vancouver.

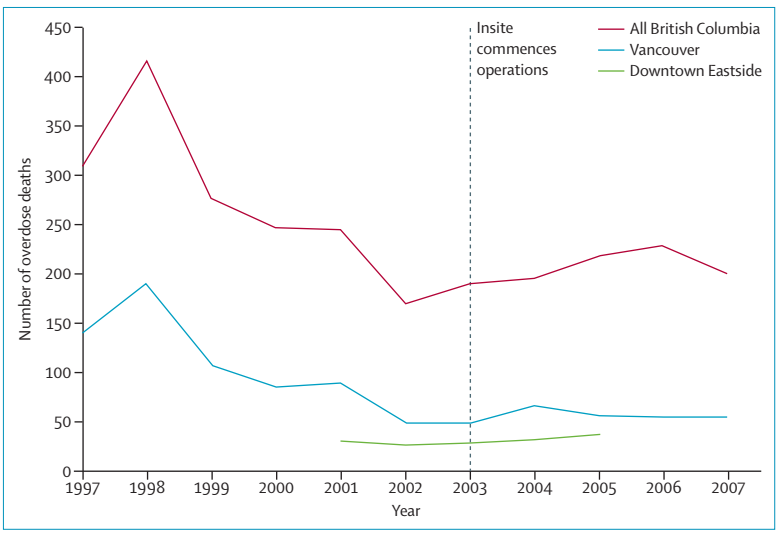

Figure: **Drug overdose deaths 2001–05**

An extended analysis is available online. We declare that we have no conflicts of interest.

For the **extended analysis** see http://www.drugfree.org.au/fileadmin/Media/Global/Lancet_2011_Insite_Analysis.pdf

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Authors' reply

Gary Christian and colleagues raise various concerns in reference to our paper that showed a 35% reduction in overdose mortality within the vicinity of Vancouver's supervised injecting facility. They refer to publicly available data from the British Columbia Vital Statistics Agency to argue that overdose deaths increased rather than decreased in the geographic area of interest between 2001 and 2005. This apparent discrepancy can be explained by several problematic assumptions that underlie Christian and colleagues' critique.

First, our study focused on an a-priori-defined area in close proximity to the supervised injecting facility that included 41 city blocks, the centroid of each being within 500 m of the facility. The data considered by Christian and colleagues refer to a much larger region (ie, the entire local health area) that includes about 400 city blocks (figure). As shown clearly in figure 3 of our paper,[1] the reduction in overdose mortality was only noted in close proximity to the supervised injecting facility, with the effect diminishing strikingly beyond this area.

Second, although we restricted our analysis to deaths deemed by the coroner to be caused by an accidental illicit drug overdose, the data referred to by Christian and colleagues include all drug-induced deaths (eg, suicides and adverse effects of drugs in therapeutic use).[2] Finally, we examined mortality rates as opposed to absolute death counts to account for changes in the population at risk.

Christian and colleagues further claim that the noted reduction in overdose mortality was due to increased heroin availability in 2001; however, we have previously published data to show that daily heroin use remained stable between 2001 and 2005.[3,4] These data were referenced in our original report. Additionally, publicly available assessments of the police crackdown to which Christian and colleagues refer show that this operation ended within weeks of the opening of the supervised injecting facility and was not ongoing as they claim;[5] therefore, any brief displacement of drug users would have probably resulted in a conservative bias by differentially reducing overdose mortality in the area of interest before the facility's opening.

Finally, regarding mode of drug use, we note that coroners' records do not indicate whether deaths were injection-related or not. However, if we restrict our analysis to records in which injection drug use was indirectly suggested, including for example discarded injection paraphernalia surrounding the decedent (ie, 85% of the original 89 deaths occurring within 500 m of the supervised injecting facility), our estimate for the reduction in overdose mortality is slightly greater at 36%.

The results of our study show that Vancouver's supervised injecting facility had a localised yet significant effect on overdose mortality. These facilities can and should be a central component of evidence-based responses to reducing drug-related harms in communities with a high burden of overdose related to injection drug use.

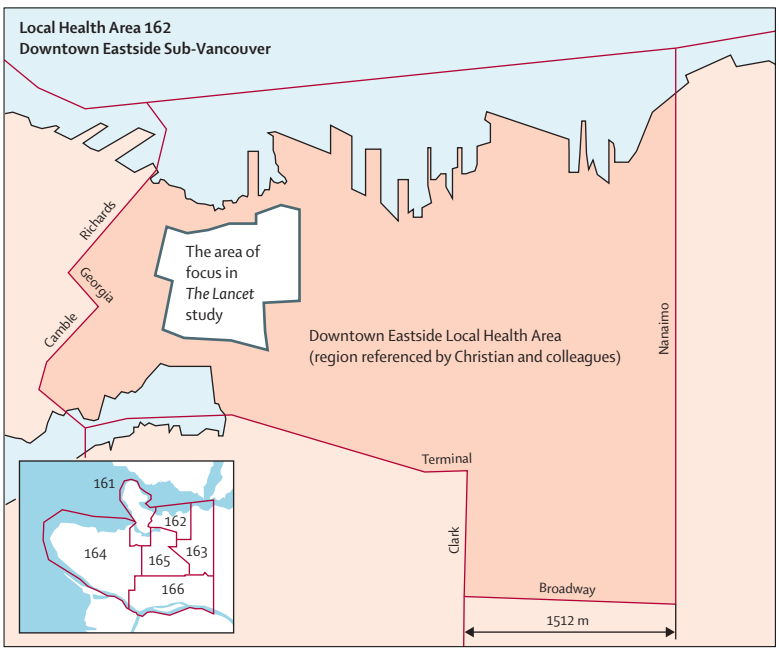

Figure: **Comparison of geographic regions defined as the area of interest in our paper versus that referred to by Christian and colleagues**
Figure modified and reproduced from publicly available documentation maintained by BC Stats. For this documentation see http://www.bcstats.gov.bc.ca/data/pop/maps/LHApdf/hamap162.pdf.

JSGM as received educational grants from and served as an ad-hoc adviser to or speaker at various events sponsored by Abbott Laboratories, Agouron Pharmaceuticals, Boehringer Ingelheim, Borean Pharma, Bristol-Myers Squibb, DuPont Pharma, Gilead Sciences, GlaxoSmithKline, Hoffmann-La Roche, Immune Response Corporation, Incyte, Janssen-Ortho, Kucera, Merck Frosst Laboratories, Pfizer Canada, Sanofi Pasteur, Shire Biochem, Tibotec, and Trimeris. All other authors declare that they have no conflicts of interest.

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Pelvic floor muscle training after prostate surgery

The conclusion of the scientifically robust study by Cathryn Glazener and colleagues (July 23, p 328),[1] that pelvic-floor muscle exercise taught by a continence health professional after prostate surgery is unlikely to be effective or cost effective, is misleading and possibly erroneous.

Glazener and colleagues should have considered that their *intervention* was not effective and provided a more critical appraisal of its failure. The intervention was weak on several counts but particularly lacked a plausible biological rationale, since it did not address the importance of control of the urethral sphincter, which did not rate a mention anywhere. Men were only—and repeatedly—instructed to "contract the pelvic floor as if holding on to wind" and assessed at each of four visits per anum. This not only provided inappropriate sensory feedback but also taught and reinforced inappropriate motor control.

Lacking was the action of flow-stopping, which produces an antero-cranial movement of the urethra at the bladder base, owing to activation of the puboperineales, and activation of the external *urethral* sphincter.[2] The ability to lift the urethra more than 2 mm with this action has been correlated with early recovery of urinary control.[2] Examination per anum might be a reproducible test of pelvic floor muscle function in men,[3] but that does not make it a valid test of urethral sphincter function. Information from the internet[4] might have reinforced such erroneous concepts for the 50% of men in the control group doing exercises, contributing to the lack of between-group difference and poor results overall.

We declare that we have no conflicts of interest.

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1 Glazener C, Boachie C, Buckley B, et al. Urinary incontinence in men after formal one-to-one pelvic-floor muscle training following radical prostatectomy or transurethral resection of the prostate (MAPS): two parallel randomised controlled trials. *Lancet* 2011; **378:** 328–37.
2 Nishida S, Utsunomiya N, Nishiyama H, Kamoto T, Ogawa O, Kinoshita H. Urethral mobility at catheter removal predicts early recovery of urinary continence after radical prostatectomy. *Int J Urol* 2009; **16:** 375–78.
3 Wyndaele JJ, van Eetvelde B. Reproducibility of digital testing of the pelvic floor muscles in men. *Arch Phys Med Rehabil* 1996; **77:** 1179–81.
4 Australian Government Department of Health and Ageing. Pelvic floor muscle training for men. http://www.bladderbowel.gov.au/assets/doc/Factsheets/English/05PelvicFloorMenEnglish.pdf (accessed Nov 29, 2011).

In the MAPS trial, Cathryn Glazener and colleagues[1] noted similar high rates of incontinence at 12 months after radical prostatectomy or trans-urethral resection of the prostate in patients randomised to therapist-guided pelvic-floor muscle training or to standard care. We did a similar trial after radical prostatectomy,[2] which Glazener and colleagues state had unexplained differential dropout from the control group. We wish to add some comments on this matter as well as on other aspects of Glazener and colleagues' Article.

First, the relatively high dropout rate (13 of 53) in the control group of our trial[2] did not jeopardise the randomisation efficacy of the two groups. Additionally, the heterogeneity of a Cochrane meta-analysis, to which Glazener and colleagues suggest that our trial added, is due to variability in several features, such as patient selection, surgeon technique and volume, definition of urinary incontinence, duration and frequency of training, and choice of control.

Second, in our trial, long-term physician-guided pelvic-floor muscle training until urinary continence was achieved or for up to 12 months proved to be more effective than no training. This effect is supported by the results of a randomised trial by Overgård and colleagues,[3] which showed that patients who received long-term physiotherapist-guided pelvic-floor muscle training compared with those training on their own had a significantly lower incontinence rate at 12 months (3 of 36 *vs* 11 of 39), despite a similar continence rate at 3 months.

Third, although in the MAPS trial[1] a pad test was not used because of practical difficulties and the apparently more important role of subjective incontinence measures, we consider it important to discriminate the degree of incontinence, since in our[2] and others'[4] experience pelvic-floor muscle training seems to be more effective for mild and moderate incontinence.

We declare that we have no conflicts of interest.

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1 Glazener C, Boachie C, Buckley B, et al. Urinary incontinence in men after formal one-to-one pelvic-floor muscle training following radical prostatectomy or transurethral resection of the prostate (MAPS): two parallel randomised controlled trials. *Lancet* 2011; **378:** 328–37.
2 Manassero F, Traversi C, Ales V, et al. Contribution of early intensive prolonged pelvic floor exercises on urinary continence recovery after bladder neck-sparing radical prostatectomy: results of a prospective controlled randomized trial. *Neurourol Urodyn* 2007; **26:** 985–89.

A second letter was sent to Lancet on 6 April 2012, a letter which Lancet chose not to publish. We note that the Chief Editor of Lancet is a co-Board member of a drug law reform organisation of which two of the authors of the erroneous Lancet study which we have here addressed are also members as per http://www.icsdp.org/network/scientific_board.aspx.

Gary Christian
DFA Research Coordinator

The Lancet Editor

We have read the authors' response and respectfully repeat our request for retraction of the study on the grounds that the authors' conclusions are based on demonstrable fallacies.

The central fallacy which invalidates the study is the claim that the authors knew of no changes in policing that could otherwise explain their findings. We have previously demonstrated that there was a police crackdown commencing at the mid-point of the study period so effective that drug use indicators were reduced by 46%. This occurred precisely in the Vancouver city blocks where the highest concentrations of overdose mortality studied by the authors had previously occurred. These policing changes readily explain the 35% decrease in overdose mortality around Insite claimed by the authors.

The authors' response also incorrectly claims that the April 2003 crackdown ceased after 6 months, when Insite opened in September 2003. To support that claim the authors cite a City of Vancouver evaluation of the crackdown. However, if read in its entirety, this document clearly states, "as of August 2004, the initiative is still ongoing, albeit in a slightly modified form."[i][i] At best, the authors' response lacks the appropriate rigour.

Furthermore, we have forwarded a written statement by the Vancouver Police commander directing the ongoing crackdown throughout the second half of the Lancet article's study period ending 2005. This statement unambiguously contradicts the authors' response that the crackdown ceased in September 2003. There was, in fact, only a change of operational name for the policing crackdown (CET became BET) with no significant change in operational approach, personnel or strategy. The continuation of the crackdown to this day is beyond conjecture. On these grounds alone, the authors' central claim about the impact of Insite is rendered invalid. There are, however, other substantive errors in the authors' response.

Plummeting heroin use between 1998 and 2002, which the authors continue to deny in their response, is verified in another study of Vancouver's VIDUS cohort by the same authors. It states, "As indicated in Fig. 1, the proportion of participants reporting a non-fatal overdose has declined steadily since enrolment, with 21% of individuals reporting a non-fatal overdose in 1997 compared with just 6% in 2004. The most substantial decline occurred during 2001, with the proportion of participants reporting a non-fatal overdose declining from 12% to 5% during this year."[ii][ii]

Consistent with this, Vancouver experienced a 74% decrease in heroin mortality between 1998 and 2002, with non-fatal overdoses decreasing in the VIDUS cohort between 1997 and 2001 (as would be expected) by 76%, as per quote above. Yet the authors' response cites largely irrelevant VIDUS cohort *daily heroin use* figures rather than overdose percentages, in a study focusing on overdose mortality. Where Canadian heroin users were estimated to inject on average four times daily, daily use figures will remain relatively unchanged even

though the average number of daily injections declines along with a 75% reduction in heroin supply and a 75% reduction in overdoses.[iii][iii] Tracking non-fatal overdoses and overdose mortality is a more accurate measure of fluctuations in supply, as is done by these same researchers in two previously studies quoted in our analysis, and by Australian researchers correlating overdose mortality with a heroin drought.[iv][iv] Elevated heroin supply and elevated overdoses ended with 2001, making that year invalid for inclusion in the study period. Its inclusion creates the illusion of a subsequent decline in overdose mortality. In fact there is a trend towards an increase in overdose mortality from 2002 onwards, starting the year before Insite opened.

We also note that the authors' response claims there are flaws in our analysis. We refute these as follows.

1. Contrary to the authors' assertion, Vital Statistics coroner's data are never used in our analysis to infer any increases in overdose deaths in the 41 block area where the claimed 35% decline occurred. Rather, BC Coroner's data is used to show that there was an increasing trend in overdose deaths for the CONTROL AREA of the City of Vancouver, and the Vital Statistics coroner's dataset was used to show that the same increasing trend was true for the 400+ block area around Insite from 2002-2005.
2. Contrary to the authors' assertion, we did exclude the 5 of 155 Vital Statistics deaths, leaving the same 150 DTES non-intentional overdoses on which the authors deliberated. We thereby demonstrated increases in DTES area deaths for 400+ city blocks from 2002 to 2005 even after these 5 intentional/other deaths were excluded.
3. The authors are also incorrect in their statement that we failed to do an in-depth analysis of the 41 block area where the 35% decrease was alleged to have occurred. Rather, our analysis contains a map with the exact location of all 89 deaths within the 41 block area. We further demonstrated that two-thirds of these deaths fall within the 12 block area patrolled by the 48-66 extra police deployed since April 2003. This suggests that the majority of these deaths likely happened in the pre-Insite comparison period when these blocks were an 'open drug scene'.
4. We have noted elsewhere that, "When . . . increases in overdose deaths are compared against population growth in both Vancouver and the DTES the increases in deaths well overwhelm any changes in population. The Lancet study, at Table 2, calculates a 3% change in Vancouver's population between 2001 and 2005, yet drug deaths increased by a much greater 14% from 2002. The Lancet study calculated an 8% increase in population for the DTES, yet drug deaths increased by 37% from 2002. In the scenario where all 5 intentional/other deaths, as discussed previously, occurred in the DTES in 2005 alone, the increase in drug deaths would still be 18%, well beyond the 8% population increase for that area of Vancouver."[v][v]

In summary, in their response to our analysis, the authors have failed to satisfactorily address any of our criticisms. The Lancet Insite article therefore remains seriously flawed on multiple grounds. It should be retracted.

[i][i] Dandurand Y et al., Confident Policing in an Troubled Community – Evaluation of the Vancouver Police Department's City-wide Enforcement Team Initiative p 49 http://www.vancouveragreement.ca/wp-content/uploads/ConfidentPolicing2004sm.pdf
[ii][ii] Kerr T, Fairbairn N, Tyndall M, Marsh D, Li K, Montaner J, Wood E. Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. Drug and Alcohol Dependence 87 (2007) p 40 http://www.ncbi.nlm.nih.gov/pubmed/16959438
[iii][iii] Canadian Government's Final Report of the Expert Advisory Committee, Vancouver's INSITE service and Other Supervised Injection Sites: What has been learned from the Research? See par. 4 of Background section http://www.hc-sc.gc.ca/ahc-asc/pubs/_sites-lieux/insite/index-eng.php#insite
[iv][iv] WA DAO, Heroin trends tracking: relationships between indices of heroin and crime. DAO Monograph No. 3 pp 20-22 http://www.dao.health.wa.gov.au/DesktopModules/Bring2mind/DMX/Download.aspx?Command=Core_Download&EntryId=63&PortalId=0&TabId=211
[v][v] Pike G, Santamaria J, Reece AS, DuPont R, Mangham C, Christian G, Analysis of the 2011 Lancet study on deaths from overdose in the vicinity of Vancouver's Insite Supervised Injection Facility. Journal of Global Drug Policy & Practice Vol 5 Iss 3, Fall 2011 http://www.globaldrugpolicy.com/Issues/Vol%205%20Issue%203/Vol%205%20Issue%203%20sm.pdf

From: John McKay [mailto:john_mckay@shaw.ca]
Sent: Friday, 23 March 2012 8:28 AM
To: 'Gary Christian'
Subject: Fw: Statement to Lancet

STATEMENT TO LANCET

Beat Enforcement Team (BET) - Vancouver Police Department 2003 - 2006

John Mc-Kay - then Officer in Charge (BET)

Downtown East Side Vancouver - Policing Rationale

The inception of what eventually became known as the Beat Enforcement Team (BET) occurred in early 2003. At that time the Vancouver Police Department recognized that the Vancouver Agreement between 3 levels of government with the so called " 4 Pillars approach" was going to have a major effect on the VPD's ability to successfully police the Down Town East Side (DTES) of Vancouver. This was largely due to the harm reduction pillar which emphasized the value of the Supervised Injection Site which was going to be located in the heart of the DTES in the 100 block of East Hastings.

While the VPD could not at the time argue against the 4 Pillars approach – harm reductionists using statistics and opinion on European Model success – they believed that there had to be some control over the situation in the DTES because of the impact on the community once the dealers figured out that their clients were not being charged and indeed allowed to be in possession of the drugs. VPD feared that there would be a free for all and open warfare between dealers who wanted a greater share of the clientele. As well, the harm reduction philosophy might bring "drug tourists "into the area which would add to the policing problem.

Closely associated to the drug use in the DTES was the movement of stolen property into the local pawnshops of which there were 49 in the immediate area. Selling stolen property was a method of obtaining hard cash for the purpose of buying drugs.

In order to maintain some control over the potential outcomes of the new harm reduction philosophy the VPD began what was known at the Beat Enforcement Team. This unit was made up of 4 squads of police, administration staff, and a police Inspector totaling 65 personnel.

The unit consisting of 65 officers was originally named CET for Citywide Enforcement Team. The name was used because other parts of the city also wanted more beat cops so the effort in the DTES was disguised as a unit that could go anywhere to patrol, hence the name "Citywide Enforcement Team." The original concept under Inspector Doug Lepard, the OIC CET, and DCC, Bob Rich, was to have members stand on the corner and intercept drugs and stolen property. They had a high profile and there was some success with the mandate which was to disrupt the flow of stolen property etc.

The mission of BET was to interrupt the flow of stolen property and disrupt the trafficking of drugs in the area. As the officer in charge of the unit from September 2003 – September 2006 it was my role to achieve these goals.

In order to achieve these goals I spent as much time on the street as possible learning and from several good civilian contacts who had been working in the area for years I was able to glean a lot of background knowledge about the people and the issues around addiction. I implemented a combination of surveillance, undercover work, high presence uniform police and intelligence driven tactics. In a nutshell we shut down all but 7 pawnshops for failure to comply with the law on property and due to specifically targeted undercover operations we gained a lot of success in getting rid of the dealers. Many of these operations such as Operation Lucille, New Boy, became high profile media covered events.

It is my understanding that the effect of 65 police officers in the DTES is negated in the Lancet analysis produced by the harm reduction proponents. That attitude is much too convenient for them because the truth of the matter is that the police were integral to the lowered death rates by being on the street and in and out of the various Single Residence Occupancy hotels in which the addicts reside. The projects and contacts that police made in SROS and on the street with the mentally ill also helped to lower death rates because of the positive nature for the most part of the officers assigned to that beat.

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Research Paper

MDMA-related deaths in Australia 2000 to 2018

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ABSTRACT

Background: MDMA markets have undergone substantial changes internationally, with increasing manufacture of high purity MDMA recorded. This study examined trends in MDMA-related deaths in Australia, investigating characteristics, circumstances and toxicology of these deaths.

Methods: Analysis of MDMA-related deaths in Australia between 2001 and 2018, extracted from the National Coronial Information System (NCIS). Deaths were categorized into (1) drug toxicity deaths, where MDMA (with and without other drug) toxicity was considered by the coroner to be the underlying cause of death; and (2) other cause deaths, with MDMA (with and without other drug) intoxication/toxicity considered contributory to death.

Results: 392 deaths were identified, with a median age of 26 years. 81% were male. Females were significantly younger than males (24 vs. 27 years). Two-thirds (62%) of deaths were attributed to drug toxicity (48% multiple drug toxicity and 14% MDMA toxicity alone), and one third (38%) to other causes (predominantly motor vehicle accidents) with MDMA recorded as a contributory factor. Death rates increased significantly between 2001 and 2007, declined between 2008 and 2010, and increased again between 2011 and 2016. Median MDMA concentration was 0.45 mg/L, and was significantly higher amongst females than males (0.70 vs. 0.42 mg/L). Deaths attributable to MDMA toxicity alone had a significantly higher blood MDMA concentration than multiple drug toxicity deaths (1.20 vs. 0.43 mg/L).

Conclusions: Deaths occurred predominantly among males in their mid-twenties, with females likely to be significantly younger. Three marked periods of trends in death rates (increases and declines) were observed, consistent with international supply trends. While most deaths were due to multiple drug toxicity, a notable proportion were attributed solely to MDMA toxicity.

Introduction

There are an estimated 22 million users of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'), with an estimated 0.4% of the global population reporting recent use (United Nations Office on Drugs & Crime, 2018). Over the past decades MDMA markets across Europe, where the majority of MDMA is manufactured (European Monitoring Centre for Drugs & Drug Addiction, 2016), have undergone substantial changes with implications for use and harm. An international shortage in 2008 of the precursor safrole, used to manufacture MDMA, impacted on the availability and use of MDMA globally up until 2010 (European Monitoring Centre for Drugs & Drug Addiction, 2016; Mounteney et al., 2018). Since then, however, MDMA manufacture, use, seizures and purity have been increasing in Europe, the United States, the United Kingdom, central America and Australia (European Monitoring Centre for Drugs & Drug Addiction, 2018; Home Office Statistics, 2018; Mounteney et al., 2016; 2015; Substance Abuse & Mental Health Services Administration, 2015,2018; United Nations Office on Drugs & Crime, 2018). Moreover, during this period the purity of MDMA appears to have increased, with the use of high purity crystalline forms becoming more prevalent (Mounteney et al., 2016).

Increased manufacture, purity and prevalence of MDMA use is of concern as the drug is associated with a range of harms. MDMA is a psychostimulant and shares effects with methamphetamine and amphetamine such as increased arousal and alertness. This can result in adverse effects such as muscle tension, jaw clenching and tooth grinding (Kalant, 2001). Elevated heart rate and blood pressure are also common and can fluctuate for days after MDMA consumption (Kalant, 2001). As a result of the pharmacokinetic actions related to MDMA use, the more serious adverse effects include hypertension, hyperthermia, serotonin syndrome, seizures, stroke, hyponatremia and

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cardiac arrest, as well as an elevated risk for traumatic injury and suicide (Darke, Duflou, Kaye, Farrell & Lappin, 2019; Darke, Lappin & Farrell, 2019; Elliott, 2005; Kaye, Darke & Duflou, 2009; Schifano, 2004). The mechanisms of MDMA-related death are complex and some, including hyperthermia, involve multiple factors including not only the pharmacologic action of MDMA (which impedes the temperature-regulating center in the brain) (Green, O'Shea & Colado, 2004) but also other factors such as environment (dancing in high temperatures in crowded spaces) (Darke, Lappin et al., 2019) . Hyponatremia, (low sodium concentration in the blood) may lead to seizures and coma, and has been documented in the context of over-hydrating in a hot environment following MDMA consumption (Darke, Duflou et al., 2019). Serotonin syndrome, characterised by marked increases of the neurotransmitter serotonin being released following consumption (resulting in seizures and coma), cardiac arrest, and intracranial hemorrhage have also been documented in MDMA-related deaths (Schifano, 2004).

The relationship between MDMA consumption and the experience of adverse effects is also complex, with some research suggesting that the probability of these experiences increases rapidly with MDMA doses exceeding 120 mg (Brunt, Koeter, Niesink & van den Brink, 2012), while other research suggests that adverse effects may in part be driven by individual differences in the metabolic processing of MDMA (Kalant, 2001).

Previous work has examined the number of MDMA-related deaths in Australia between 2000 and 2005 (Kaye, Darke & Duflou, 2009), however, given the substantial changes over the past decade in MDMA markets internationally, more contemporary investigation of these deaths is crucial. This study extends previous work, reporting median concentrations of MDMA reported in postmortem toxicology. Analysis of coronial data provides a unique opportunity to differentiate MDMA-related deaths from amphetamine-related deaths (using objective toxicology data and coroner attributed medical cause of death fields), which is not possible using deaths data that are coded under the current ICD-10 coding system (World Health Organization, 2010).

Aims

1 Describe trends in MDMA-related death rates in Australia 2001 to 2016;
2 Describe the characteristics and circumstances of MDMA-related death; and
3 Describe the toxicology of MDMA-related deaths.

Methods

National coronial information system (NCIS)

The NCIS is an online database containing information relating to all deaths that are reportable to the coroner. Cause of death is ascertained by a forensic pathologist and documented on the autopsy and coroner's report. The forensic pathologist may report on: i. the direct cause of death, ii. the antecedent cause, and iii. other significant conditions associated with the death. Although it varies from one jurisdiction to another in Australia, a death is generally 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 anaesthesia and/or various medical and surgical procedures; 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; or the identity of the decedent is unknown.

Categorization of deaths

Only deaths where MDMA was considered by the coroner to be the underlying cause of death (with or without other drug toxicity) and deaths where MDMA toxicity or intoxication were considered contributory to the death were included. Deaths were selected if the medical cause of death (underlying and contributory) was noted as MDMA toxicity. In the case of multiple drug toxicity deaths, if MDMA was noted by the coroner as one of the drugs, these deaths were included. Deaths where MDMA was detected in toxicology but the coroner attributed the death to causes unrelated to MDMA and where MDMA toxicity was not noted as the medical cause of death, were excluded. MDMA related deaths were identified from the NCIS for the period July 2000 to November 2018. Trends over time are only shown for deaths occurring between 2001 and 2016, given that data for 2000 only represent a 6-month period, and that 2017 and 2018 data are likely to be incomplete.

Circumstances of death

Investigative reports, including police narratives, autopsy and coroners' findings, and toxicology reports are attached to most death cases in the NCIS. These reports were searched for the location of where the death occurred to determine the proportion of deaths that occurred in public locations such as music festivals or events, and in private locations. Coroners findings and toxicology reports were used to assess the presence and contribution of other drugs to MDMA-related deaths.

Toxicology

Toxicological data were reported for MDMA, other psychostimulants, hypnosedatives, alcohol, opioids, cannabis (Δ-9-THC), GHB, ketamine, antidepressants and antipsychotics. In cases of hospitalization prior to death, antemortem blood samples taken on or near admission to hospital were reported, and drugs administered by hospital and medical staff excluded.

Statistical analyses

MDMA death rates per 100,000 population aged 15–64 were calculated using estimates of the resident population of Australia at June of each year (Australian Bureau of Statistics, 2016). Rates were modelled using negative binomial regression where there was over-dispersion, and Poisson regression where there was not (Coxe, West & Aiken, 2009). Trends were analysed within three distinct time periods: Time period 1 (2001–2007) prior to the global shortage of the precursor safrole, Time period 2 (2008–2010) during which the shortage occurred and reduced MDMA use and availability was recorded, and Time period 3 (2011–2016), during which an increase in international MDMA availability and use was recorded, as well as increases in drug purity. For dichotomous categorical variables, odds ratios (OR) and 95% confidence intervals (95% CI) were reported. Where distributions were highly skewed, medians were reported, and differences assessed using the Mann–Whitney *U* test. Analyses for trends in rates of deaths were made using SAS 9.4 (Inc., 2013). All other analyses were conducted in SPSS 23.0 (IBM inc., 2016).

Ethics approval

Ethics approval to access the NCIS was granted by the Victorian Department of Justice and Community Safety and the University of New South Wales Human Research Ethics Committee.

Results

392 MDMA-related deaths were identified during the period 2000–2018, 62% of which were due to drug toxicity. MDMA-related death rates fluctuated between 2001 and 2016, with three distinct trends apparent (Fig. 1). MDMA-related death rates increased between

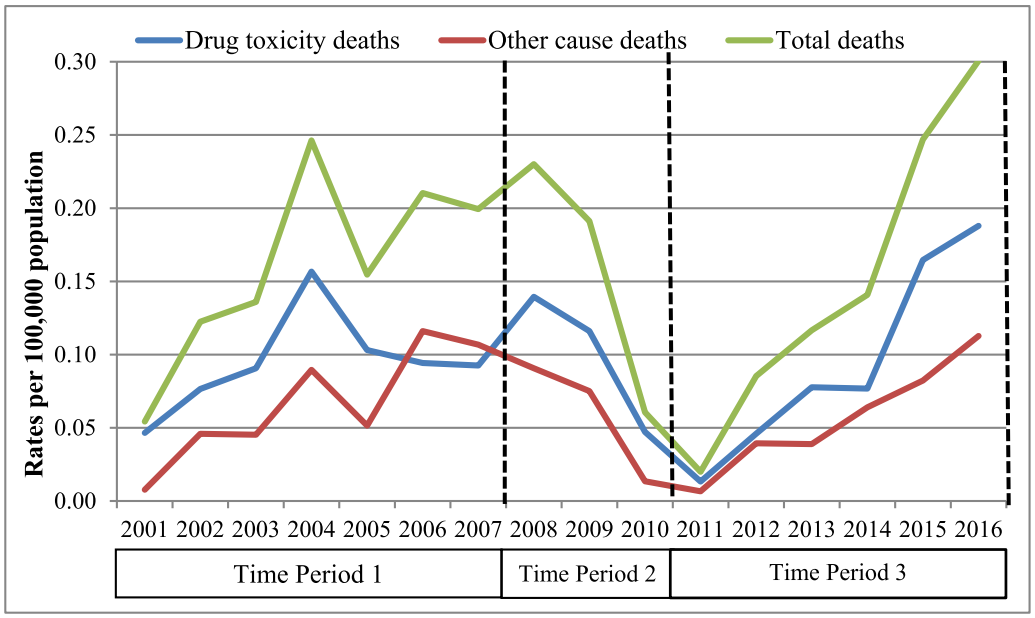

Fig. 1. Rates of MDMA-related deaths per 100,000 population, Australia 2001 to 2016
Time Period 1: 2001–2007, prior to the global shortage of the precursor safrole (used to manufacture MDMA)
Time Period 2: 2008–2010, during the precursor shortage and a period of reduced MDMA use and availability
Time Period 3: 2011–2016, after the precursor shortage, and a period of increased MDMA use and availability.

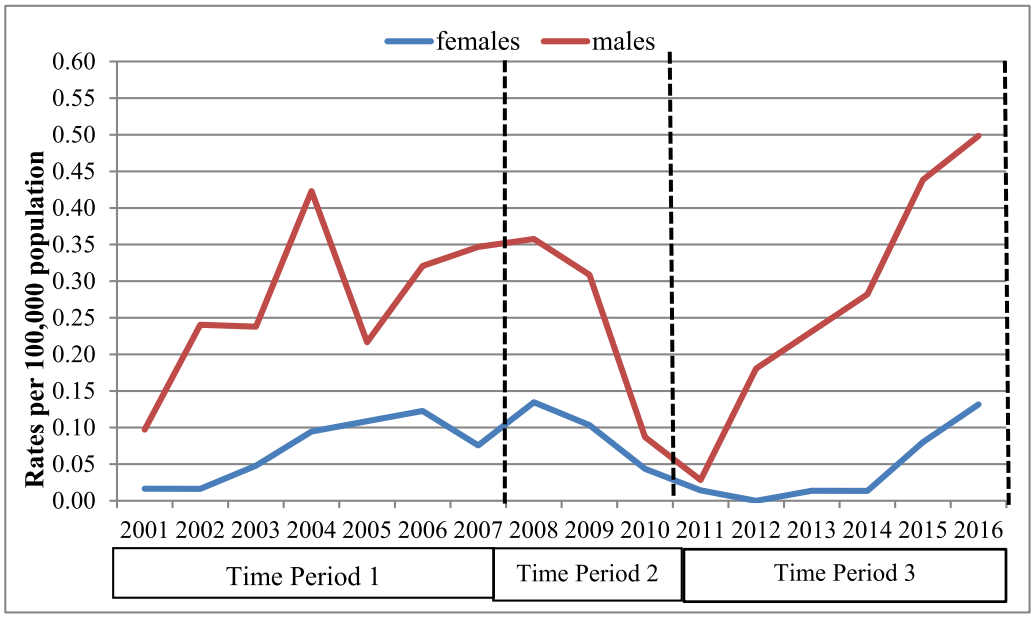

Fig. 2. Rates of MDMA-related deaths per 100,000 population by gender, Australia 2001 to 2016
Time Period 1: 2001–2007, prior to the global shortage of the precursor safrole (used to manufacture MDMA)
Time Period 2: 2008–2010, during the precursor shortage and a period of reduced MDMA use and availability
Time Period 3: 2011–2016, after the precursor shortage, and a period of increased MDMA use and availability.

2001 and 2007 ($p<0.01$), declined significantly between 2008 and 2010 ($p<0.0001$), and increased significantly from 2011 to 2016 ($p<0.0001$). Increases during this period were driven in part by multiple drug toxicity deaths ($p<0.0001$). The number of deaths increased from 7 in 2001 to 33 in 2008, declined to 9 in 2010, and increased to 48 in 2016. These trends were evident for both drug toxicity and other cause deaths (Fig. 1). Rates of MDMA-related deaths were higher among males than females, and increases in these deaths were largely driven by males (Fig. 2).

Characteristics

Deaths occurred predominantly among males (81%), with a median age of 26 (range 15–58) (Table 1). Females were significantly younger than males (24 v 27 years, $U = 9036.5$, $p<0.01$). Most decedents (62%) were employed, and a fifth were married or in a defacto relationship. More than half (56%) of all incidents occurred in a private location, as did three-quarters of the toxicity incidents. Significantly higher proportions of drug toxicity incidents occurred in private locations (73%) compared to other cause incidents (29%) (OR 2.6, 95% CI 2.3–4.4, $p<0.0001$) (Table 1).The most common public location was streets/roadways, followed by outdoor areas (parks, beaches and

Table 1
Characteristics of MDMA-related deaths by cause of death, Australia.

	Total deaths n = 392 % (n)	Drug toxicity n = 244 % (n)	Other cause n = 148 % (n)
Demographics			
Median age (range)	26 (15–58)	26 (15–56)	25 (16–58)
Male	81 (318)	77 (188)	88 (130)
Employed	62 (242)	59 (145)	66 (97)
Married/Defacto	20 (77)	20 (48)	20 (29)
Location			
Private location	56 (220)	73 (177)	29 (43)
Public location	44 (172)	27 (67)	71 (105)

Table 2
Cause and intent of MDMA-related deaths, Australia.

All deaths	Total *n* = 392 % (*n*)	Female *n* = 74 % (*n*)	Male *n* = 318 % (*n*)
Drug toxicity	62 (244)	76 (56)	59 (188)
Multiple drug toxicity	48 (189)	43 (32)	49 (157)
MDMA toxicity only	14 (55)	33 (24)	10 (31)
Other cause	38 (148)	24 (18)	41 (130)
Traumatic accident	29 (115)	19 (14)	32 (101)
Violent suicide	6 (23)	3 (<5)	7 (21)
Disease	3 (10)	3 (<5)	3 (8)

countryside). Only 7% ($n = 17$) of drug toxicity incidents occurred at music festivals or dance parties.

Cause and intent of death

Two thirds (62%) of deaths were attributed to drug toxicity (Table 2). Approximately half of all deaths were attributed to multiple drug toxicity, and one seventh to MDMA toxicity alone. The remaining deaths (38%) were due to other causes, with MDMA considered as contributing to death (Table 2).

The overwhelming majority (84%, $n = 206$) of drug toxicity deaths were accidental, with 13 (5%) attributed to deliberate self-poisoning (i.e. suicide), and intent undetermined among the remaining 25 (10%) drug toxicity deaths.

One third (29%) of other cause deaths were due to traumatic accidents (predominantly motor vehicle accidents), with MDMA considered as contributing to the death. Small proportions of other cause deaths were due to violent suicide (6%), and disease (3%).

Gender differences were apparent in relation to the cause of death, with deaths among females significantly more likely to be attributed to drug toxicity than among males (OR 1.3, 95% CI 1.1–1.5). Specifically, women were significantly more likely to die as a result of MDMA toxicity alone than men (OR 3.3, 95% CI 2.0–5.3). Investigating other causes of death, women were significantly less likely to die as a result of a traumatic accident than men (OR 0.5, 95% CI 0.2–0.9).

Among females, where death was attributed to drug toxicity, the median age was 5.5 years younger than among males (22 vs. 27.5 years, $U = 3496.5$, $p < 0.001$). There was no difference in the age of females and males where death was attributed to other causes (25.5 vs. 25 years) (Table 2).

Toxicology

Toxicology data were available in 342 of the deaths (87%) (50 cases did not have data available), with MDMA detected in all deaths. The median blood MDMA concentration was significantly higher amongst females than males among all deaths ($U = 7081.5$, $p < 0.05$) and drug toxicity deaths ($U = 3236.0$, $p < 0.05$) (Table 3). Deaths attributable to MDMA toxicity alone had a significantly higher blood MDMA concentration than multiple drug toxicity deaths ($U = 2189$, $p < 0.001$). There were no differences in median blood concentrations between intentional drug toxicity and accidental drug toxicity deaths. Overall, drug toxicity deaths had significantly higher blood MDMA concentrations than other cause deaths ($U = 10{,}611.5$, $p < 0.01$). Median MDMA concentrations over time varied widely and small numbers prevent confident interpretation of these trends (data not shown).

Table 4
Presence of other drugs in toxicology by cause of death, Australia.

Drug	Total *n* = 342* % (*n*)	Drug toxicity *n* = 215 % (*n*)	Other cause *n* = 127 % (*n*)
No other drug detected	15 (51)	21 (45)	5 (6)
Psychostimulants	54 (183)	55 (119)	50 (64)
Methamphetamine	44 (150)	44 (94)	44 (56)
Cocaine	15 (50)	19 (41)	7 (9)
PMA#	3 (9)	4 (9)	0 (0)
Other^	3 (9)	8 (18)	7 (9)
Alcohol	43 (148)	29 (62)	68 (86)
Opioids	30 (104)	46 (98)	5 (6)
Cannabis	25 (87)	18(39)	38 (48)
Benzodiazepines	23 (80)	33 (70)	8 (10)
Antidepressants	11 (39)	15 (32)	6 (7)
Ketamine	4 (13)	5 (10)	<5
GHB	3 (11)	5 (11)	0 (0)
Antipsychotics	3 (9)	4 (8)	<5

Paramethoxyamphetamine.
^ including methcathinone, 3,4-Methylenedioxy-N-ethylamphetamine - MDEA, methylenedioxypyrovalerone – MDPV, and 3′,4′-Methylenedioxy-α-pyrrolidinobutiophenone – MDPBP.
* 50 deaths did not have toxicology results available.

Other substances were commonly detected in addition to MDMA in post-mortem toxicology (Table 4). Psychostimulants (54%) (predominantly methamphetamine: 82% of psychostimulants; 44% of all toxicology cases) were the most common drug, followed by alcohol (43%), opioids (30%), cannabis (25%), benzodiazepines (23%) and antidepressants (11%). Other drugs such as ketamine, GHB, PMA, methcathinone, MDPV and MDEA were each detected in less than 10% of deaths.

Discussion

The current study provides novel data on long-term trends in MDMA deaths, their toxicology and the circumstances in which they occurred. Decedents were aged, on average, in their mid-twenties, were predominately male and likely to be employed. Females were on average three years younger than their male counterparts.

There appeared to be three distinct periods of MDMA deaths across

Table 3
Median blood concentrations of MDMA by cause of death and gender, Australia.

	All deaths *n* = 342* mg/L median (range)	Males *n* = 279 mg/L median (range)	Females *n* = 63 mg/L median (range)
Drug toxicity	0.59 (0.01–64.00)	0.50 (0.01–64.00)	0.85 (0.02–22.00)
Multiple drug toxicity	0.43 (0.01–22.00)	0.42 (0.01–9.40)	0.70 (0.02–22.00)
MDMA toxicity	1.20 (0.04–64.00)	1.30 (0.07–64.00)	1.10 (0.04–11.50)
Intentional toxicity	1.40 (0.01–64.00)	1.40 (0.01–64.00)	22 (22.00–22.00)
Accidental toxicity	0.60 (0.01–17.00)	0.50 (0.01–17.00)	0.90 (0.04–11.50)
Other cause	0.30 (0.01–8.40)	0.30 (0.01–8.40)	0.36 (0.17–5.10)
All Deaths	0.45 (0.01–64.00)	0.42 (0.01–64.00)	0.70 (0.02–22.00)

* 50 cases did not have toxicology results available.

the study: a marked increase between 2001 and 2007, a sharp decline between 2008 and 2010, and another marked increase between 2011 and 2016. During the latter period rates rose to exceed the peak of the first period. Notably, these patterns were observed for both toxicity and other cause deaths. These trends are consistent with changes in international MDMA market indicators, with the global shortage of the precursor safrole in 2008 having a major impact on MDMA manufacture and use globally, and the global increases in MDMA manufacture and use observed from 2011 onwards (European Monitoring Centre for Drugs & Drug Addiction, 2018; Mounteney et al., 2018; United Nations Office on Drugs & Crime, 2018). Global MDMA markets in the most recent period have also been characterised increasingly by higher purity MDMA being manufactured (Mounteney et al., 2018).

Despite much of the media attention on MDMA-related deaths focusing on deaths that occur at public events, more than half of all deaths (and three-quarters of drug toxicity deaths) in this study occurred in private locations, largely at home. Only 7% of drug toxicity deaths (and 4% of all deaths) occurred at music festivals or dance parties.

There were notable findings concerning MDMA blood concentrations. MDMA -related deaths attributed to drug toxicity had MDMA concentrations approximately twice that of MDMA-related deaths due to other causes. Moreover, deaths attributed solely to MDMA toxicity had concentrations three times that of those attributed to multiple drug toxicity. The higher concentration seen amongst female drug toxicity deaths (although not for other cause deaths) was marked, and puzzling, perhaps reflecting behavioural or, as has been suggested, physiological differences (Allott & Redman, 2007).

Concomitant drug use was prevalent among these deaths, with other psychostimulants most commonly detected in addition to MDMA. All psychostimulants place stress upon the cardiovascular system, and toxicity deaths are primarily due to these cardiovascular effects (Darke Lappin et al., 2019; Karch, 2015). The use of multiple psychostimulants is likely to increase the probability of psychostimulant toxicity. The high levels of alcohol detected among these MDMA-related deaths are also relevant. This finding is consistent with research among MDMA consumers showing that one-third of this group engages in high-risk drinking patterns in combination with their MDMA use (Kinner, George, Johnston, Dunn & Degenhardt, 2012). The use of alcohol with methamphetamine increases heart rate and blood pressure beyond that seen for methamphetamine use alone (Kirkpatrick, Gunderson, Levin, Foltin & Hart, 2012). The use of both these drugs in conjunction with MDMA is likely to increase the risk of a toxic reaction. Finally, there was frequent concomitant use of pharmaceutical drugs particularly benzodiazepines and antidepressants. Previous reports have noted the potentially fatal drug interactions between MDMA and a range of antidepressant drugs which may increase risk for a number of harms including serotonin toxicity (Pilgrim, Gerostamoulos & Drummer, 2011). Less is known about the interaction between MDMA and the use of central nervous system depressants such as benzodiazepines and opioids (Schifano, 2004). Of note, there were less than 10 deaths where known contaminants (e.g. paramethoxyamphetamine – PMA and dextromethorphan) were detected, and less than 10 deaths where other synthetic analogues (e.g. methylenedioxypyrovalerone – MDPV, methcathinone) were detected.

The findings of this study have clinical and public health implications. Importantly, the findings clearly show that fatal MDMA toxicity may occur in the absence of another substance. Harm reduction messages tend to focus on the risks associated with contaminants contained in MDMA (Kinner et al., 2012), however consumers need to be made aware of the dangers associated with MDMA toxicity alone. Given the age of decedents reported in this study, engagement of young consumers in the delivery of these messages is crucial. The preponderance of incidents occurring in private locations also suggests that dissemination of messages across a range of settings (e.g. secondary and tertiary education institutions, nightclubs and music festivals) is warranted. Research has shown that peer led interventions, delivering harm reduction messages about the risks of MDMA are effective in engaging young consumers attending nightclubs and festivals (Bleeker et al., 2009), and increased funding for peer education was amongst the key recommendations made by a recent government report into MDMA related harms (New South Wales Government, 2018). The role of other substances in increasing the likelihood of a toxic reaction also needs to be emphasised. Consistent with other research (Darke, Degenhardt & Mattick, 2007; Roxburgh et al., 2017), the majority of drug toxicity deaths in this study were due to MDMA in combination with other drug toxicity. This highlights the need for messages specifically targeting the dangers associated with concomitant MDMA and other substance use, and further research on these issues is required. Investigating the mechanism of death involved in MDMA fatalities is also an important focus for future research. Onsite medical support as well as spaces to rest have been successful harm reduction strategies employed at large scale events, and continued support for these services is important. Messages around the potential increased neurotoxicity of combining MDMA with other substances including alcohol, the potential for toxic reactions of overheating and overhydrating, and seeking medical assistance early, are critical to reduce MDMA-related harms in these environments. Finally, drug checking (both fixed-site and field-based) services have been in operation in Europe since the 1990s (Barratt, Kowalski, Maier & Ritter, 2018; Brunt, 2017), and more recently in the United Kingdom (UK), North America and Australasia (Barratt et al., 2018; Measham, 2019). Drug-checking services provide an opportunity to engage with young MDMA consumers, who may not be in contact with other services (Degenhardt et al., 2009; Measham, 2019), about the risks associated with MDMA use.

Strengths and limitations

A major strength of this study was the ability to differentiate deaths due to MDMA from amphetamine-related deaths, which is not possible using deaths data that are coded under the current ICD-10 coding system (World Health Organization, 2010). Another major strength was the use of investigative reports to report objective toxicology data on median MDMA blood concentrations and other drugs involved in these deaths. Finally, the availability of historical data from the NCIS over a period of 15 years provides a valuable opportunity to analyze longer-term trends in MDMA-related deaths at a national level.

As with all studies, however, limitations need to be considered. Firstly, the study may not have captured all the deaths that occurred within the study period, as not all deaths may have been reported to a coroner. Due to the complexities of coronial investigations, with some likely to be ongoing, some deaths may not yet be captured in the NCIS. Secondly, the study will not have captured deaths attributed to other drugs that were sold as MDMA to a decedent. Thirdly, it was not possible to account for the amount of MDMA consumed prior to death as in many cases this data was not reported. Finally, care must be taken in extrapolating these findings to other populations of MDMA users. The characteristics of these deaths were, however, comparable to those reported elsewhere.

Conclusions

MDMA-related deaths predominantly occurred among males aged in their mid-twenties, with females significantly younger than their male counterparts. Most incidents occurred in private locations. Three marked periods of increases and declines in death rates were observed, consistent with international MDMA supply trends. While most deaths were due to multiple drug toxicity, a notable proportion were attributed solely to MDMA toxicity. Also of note, almost one-third of deaths were due to accidents (predominantly motor vehicle accidents) that occurred during MDMA intoxication.

Engagement with young consumers about the risks associated with MDMA use alone, and in combination with other drugs, is critical, particularly in the context of rapidly changing drug markets globally, and the increasing purity of MDMA being manufactured (Mounteney et al., 2018). Implementation of harm reduction strategies across multiple settings is crucial.

Conflict of Interest Statement

Neither of the authors have any conflicts to declare.

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