Methylphenidate and (lis)dexamfetamine toxicity-related deaths of adults, Australia, 2000–24: analysis of NCIS data

Shane Darke[1], Amy Peacock[1], Johan A Duflou[2], Michael Farrell[1], Julia Lappin[3]

The stimulants methylphenidate, dextroamfetamine, and lisdexamfetamine are prescribed for the treatment of attention deficit hyperactivity disorder (ADHD) in adults.[1-4] The prescribing of ADHD medications has increased notably since 2000,[2] and, while they are considered to have good safety profiles, the number of poisonings in Australia has also increased.[3,4] Few reports on fatal poisonings with these drugs in adults have been published.[5-8]

We therefore conducted a retrospective observational study of deaths in Australia of people aged 15 years or older in which methylphenidate or (lis)dexamfetamine toxicity was implicated. We searched records in the National Coronial Information System (NCIS), a database of medico-legal death investigation records provided by the coroners' courts of each Australian jurisdiction; all suspected drug overdose deaths in Australia must be reported to coroners for investigation. We included all closed cases (deaths in which the coronial process had been completed) of deaths during 1 January 2000 – 30 July 2024 in which methylphenidate was listed in the NCIS drug coding fields set as contributing to death. These fields code for external factors that contributed to death according to the coronial investigation. We also searched records for "ADHD", "dexamphetamine", "lisdexamphetamine", and "dextroamphetamine", as well as for their registered brand names. The Justice Human Research Ethics Committee (M0063) and the University of New South Wales Human Research Ethics Committee (HC220754) approved the study. Our report conforms with STROBE (Supporting Information) guidelines for observational study reports.[9]

We identified 64 deaths in which ADHD medications were implicated: 41 methylphenidate-related, 23 (lis)dexamfetamine-related. The mean age at death was 38.2 years (standard deviation, 10.7 years); 45 were men. Substance use problems were documented in 45 cases. Evidence from witnesses or the death scene indicated probable injection of the drug as the terminal event in 18 cases. ADHD diagnoses were documented for 37 people, other mental health problems for 44 people. Fifty-one deaths were deemed unintentional. In 49 cases, death was attributed to polysubstance toxicity; the most frequent clinical presentation form was sudden collapse (20 cases) (Box 1).

Blood toxicology results that covered all major drug classes were available for 63 of 64 deaths. In no case was there evidence for use of both methylphenidate and (lis)dexamfetamine by an individual. In the cases in which they were detected, the median methylphenidate concentration was 0.06 mg/L (interquartile range [IQR], 0.03–0.20 mg/L; range, 0.01–2.50 mg/L); the median amfetamine concentration was 0.11 mg/L (IQR, 0.03–0.40 mg/L; range 0.01–1.20 mg/L). Other drugs were detected in 57 cases, most frequently sedative–hypnotics (35 cases: 33 benzodiazepines, two Z-class hypnotics) and antidepressants (32 cases) (Box 2).

Autopsy reports were available for 47 cases. Cardiomegaly (heart weight exceeding the 95th percentile of normal weight range)

1 Characteristics and circumstances of 64 deaths of adults (15 years or older) in which ADHD medication-related toxicity was implicated, Australia, 1 January 2000 – 30 July 2024

Characteristic	Implicated medication	
	Methylphenidate	(Lis)dexamfetamine
Number of deaths	41	23
Age (years), mean (SD)	38.5 (10.7)	37.8 (13.9)
Age (years), range	22–63	20–65
Sex (men)	28	17
Documented history		
Substance use problems	34	11
Injecting drug use	23	3
ADHD diagnosis	17	20
Other mental health problem	27	17
Affective disorders	23	15
Psychotic disorders	12	6
Circumstances of death		
Unintentional toxicity	30	21
ADHD medication only detected	5	10
Polysubstance use detected	36	13
Probable injection of ADHD medication	17	1
Clinical characteristics of death		
Sudden collapse	14	6
Seizure	2	4
Breathing difficulties	3	2
Hyperthermia	0	0

ADHD = attention deficit hyperactivity disorder; SD = standard deviation. ◆

[1] National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW. [2] Sydney Medical School, the University of Sydney, Sydney, NSW. [3] The University of New South Wales, Sydney, NSW. ✉ s.darke@unsw.edu.au • doi: 10.5694/mja2.52604

2 Blood toxicology findings for 63 deaths of adults (15 years or older) in which ADHD medication-related toxicity was implicated, Australia, 1 January 2000 – 30 July 2024

Characteristic	Implicated medication	
	Methylphenidate	(Lis)dexamfetamine
Number of deaths	40	23
Methylphenidate (mg/L)		
Median (IQR)	0.06 (0.03–0.20)	—
Range	0.01–2.50	—
0.01–0.10	26	—
0.11–0.20	5	—
0.21–0.30	2	—
0.31–0.40	2	—
0.41–0.50	2	—
More than 0.50	3	—
Amfetamine (mg/L)		
Median (IQR)	—	0.11 (0.03–0.40)
Range	—	0.01–1.20
0.01–0.10	—	11
0.11–0.20	—	4
0.21–0.30	—	0
0.31–0.40	—	2
0.41–0.50	—	2
More than 0.50	—	4
Other drugs	39	18
Sedative-hypnotics	22	13
Antidepressants	22	10
Opioids	15	10
Antipsychotics	16	8
Psychostimulants	12	1
Alcohol	8	3
Cannabis	8	2
Other*	6	4

IQR = interquartile range. * 5F-CUMYL-P7AICA, doxylamine, gabapentinoids, mitragynine. ◆

was evident in twelve people (eight of 28 methylphenidate-related deaths, four of 19 (lis)dexamfetamine-related deaths) and severe coronary artery disease in 17 (eleven methylphenidate-related deaths, six (lis)dexamfetamine-related deaths).

We identified 64 AHDH medication-related deaths in Australia during 2000–24. As methylphenidate was dispensed 1 270 397 times and (lis)dexamfetamine 2 001 934 times during 2023 alone,[10] recorded ADHD medication toxicity-related deaths were rare. About 20% of the deaths were intentional, a proportion similar to those in other reports on stimulant poisoning in Australia,[3,4] and mental health or substance use problems were each recorded for about 70% of the people who died.

Blood methylphenidate and amfetamine concentrations each ranged across two orders of magnitude. Reported blood concentrations in stimulant-related deaths in other studies ranged between 0.05 and 3 mg/L for methylphenidate and 0.5 to more than 40 mg/L for amfetamine.[1,5,8] Drugs other than ADHD medications were detected in 49 cases; the concomitant use of other drugs can increase the toxicity risk of ADHD medications.[3,4,11]

The small number of deaths we identified provides reassurance that ADHD medications have a relatively good safety profile. There are, however, people for whom greater caution is warranted, including those with histories of substance misuse or of mental health problems. People who use these medications need to be warned about the risk of polypharmacy. Given that psychostimulants may exacerbate cardiovascular disease, and that evidence of such disease was frequently recorded at autopsy in the cases we reviewed, people with cardiovascular disease may require closer monitoring.

Our series did not include deaths for which the coronial process was not yet complete. While all suspected fatal drug overdoses must be reported to coroners for investigation and will be recorded in the NCIS, some deaths may not have been reported. Clinical histories were restricted to details documented in NCIS case files. Blood drug concentrations at the time of death or hospital admission may not be the peak concentrations. Toxicological analysis may not have detected new psychoactive substances. Finally, assessment of intent is difficult in all studies of mortality; classification as self-harm was based upon the NCIS code for "intentional self-harm".

In summary, we identified 64 deaths of adults in which the ingestion of methylphenidate, dextroamfetamine, or lisdexamfetamine was deemed to be a contributory factor; in 20% of cases, the death was judged to be intentional. In 78% of cases, people had ingested more than one drug, and 70% of people had known substance use problems.

Acknowledgements: This study was funded by the National Drug and Alcohol Research Centre at the University of New South Wales. The Centre is funded by the Australian Department of Health and Aged Care. We acknowledge the Victorian Department of Justice and Community Safety as the source organisation for the data we analysed and the National Coronial Information System as the data source. We thank the staff at the National Coronial Information System. Amy Peacock is funded by a National Health and Medical Research Council Investigator Fellowship (1174630).

Open access: Open access publishing facilitated by the University of New South Wales, as part of the Wiley – University of New South Wales agreement via the Council of Australian University Librarians.

Competing interests: Amy Peacock has received untied educational grants from Seqirus and Mundipharma for post-marketing surveillance of pharmaceutical opioids; the organisations had no role in study design, analysis, or reporting, and their funding was for work unrelated to this project. Michael Farrell has received untied educational grants from Seqirus, Mundipharma, and Indivior for post-marketing surveillance of pharmaceutical opioids; the organisations had no role in study design, analysis, or reporting, and their funding was for work unrelated to this project.

Data sharing: The data upon which the study is based comprise confidential medico-legal documents. Ethics agreements and legal obligations prevent making these data available for sharing. ■

1 Baselt RC. Disposition of toxic drugs and chemicals in man; 12th edition. Seal Beach (USA): Biomedical Publications, 2020.

2 Raman SR, Man KK, Bahmanyar S, et al. Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases. *Lancet Psychiatry* 2018; 5: 824-835.

3 Cairns R, Daniels B, Wood DA, Brett J. ADHD medication overdose and misuse: the NSW Poisons Information Centre experience, 2004–2014. *Med J Aust* 2016; 204: 154. https://www.mja.com.au/journal/2016/204/4/adhd-medication-overdose-and-misuse-nsw-poisons-information-centre-experience

4 Martin C, Harris K, Wylie C, Isoardi K. Rising prescription stimulant poisoning in Australia: a retrospective case series. *Toxicol Commun* 2023; 7: 2174689.

5 Levine, B, Caplan, YH, Kauffman, G. Fatality resulting from methylphenidate overdose. *J Anal Toxicol* 1986; 10: 209-210.

6 Massello W, Carpenter DA. A fatality due to the intranasal abuse of methylphenidate (Ritalin). *J Forensic Sci* 1999; 44: 220-221.

7 Farquhar S, Fawcett P, Fountain J. Illicit intravenous use of methylphenidate (Ritalin) tablets: a review of four cases. *Aust Emerg Nurs J* 2002; 5: 25-29.

8 Cantrell FL, Ogera P, Mallett P, McIntyre IM. Fatal oral methylphenidate intoxication with postmortem concentrations. *J Forensic Sci* 2014; 59: 847-849.

9 von Elm E, Altman DG, Egger M, et al; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370: 1453-1457.

10 Services Australia. Pharmaceutical Benefits Scheme Schedule item reports. http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp (viewed Aug 2024).

11 Nevels RM, Weiss NH, Killebrew AE, Gontkovsky ST. Methylphenidate and its under-recognized, under-explained, and serious drug interactions: a review of the literature with heightened concerns. *German Journal of Psychiatry* 2013; 16: 29-42.

Supporting Information

Additional Supporting Information is included with the online version of this article.