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Characteristics and circumstances of death related to new psychoactive stimulants and hallucinogens in Australia

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ABSTRACT

Background: New psychoactive stimulants and hallucinogens comprise a range of "designer drugs" that have risen to prominence in the 21st century. The study aimed to: 1. Determine the characteristics, and circumstances of death, of all recorded cases of new psychoactive stimulant and hallucinogen-related death in Australia; 2. Determine the toxicology of such deaths; and 3. Determine the major organ pathology of cases.

Methods: All cases in which new psychoactive stimulants were a mechanism contributory to death were retrieved from the National Coronial Information System (2000–2017). Information was collected on cause of death, demographics, drug use history, circumstances of death, toxicology and major organ pathology.

Results: 82 cases were identified. The mean age was 30.7yrs and 86.6% were male. Circumstances of death were: accidental drug toxicity (59.8%), traumatic accident (15.9%), suicide (12.2%) and natural disease (2.4%). The most common clinical presentation observed proximal to death was delirium (26.8%). Delirium was mostly frequently observed after phenethylamine consumption (72.2%). The most common cardiovascular diagnosis at autopsy was replacement fibrosis, indicative of previous ischemia (10.5%). New psychoactive stimulants and hallucinogens detected in toxicology were: cathinones (75.7%), phenethylamines (22.0%) and piperazines (6.1%). Other substances were present in 83.5% of cases, most commonly established controlled psychostimulants (58.2%).

Conclusions: Acute toxicity was the most common cause of death, but more than a third of deaths were due to trauma. Cathinones were the most commonly detected of the new psychoactive stimulants and hallucinogens. Delirium was the most frequently reported clinical sign proximal to death and was strongly associated with the phenethylamines.

1. Introduction

New psychoactive substances (NPS) refer to a wide range of "designer drugs" that have risen to prominence in the 21st century and become a source of clinical concern (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2016; United Nations Office on Drugs and Crime (UNODC, 2017). New psychoactive stimulants and hallucinogen are sub-classes of NPS, These drugs include synthetic cathinones (e.g. MDPV), phenethylamines (e.g. NBOMe), piperazines (e.g. BZP) and tryptamines (e.g. 5-MeO-DMT). Some, notably phenethylamines such as NBOMe, have hallucinogenic effects (Darke et al., 2019; European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2016; Iversen et al., 2013; Tracy et al., 2017). They may be swallowed as pills, ingested sublingually in blotter form, and may be smoked, insufflated or injected. Males comprise the majority of people who use these drugs, use being highest among those aged 18–25 years (Home Office, 2017; Palamar et al., 2015; Sutherland et al., 2016; United Nations Office on Drugs and Crime (UNODC, 2017).

Toxic responses to these drugs include hypertension, tachycardia, vasoconstriction, hyperthermia, renal failure, seizures, stroke, myocardial infarction and serotonin syndrome (Darke et al., 2019; Gee et al., 2016; German et al., 2014; Karch, 2015; Logan et al., 2017). Behaviorally, toxic responses may manifest in delirium, hallucinations, paranoia, aggressive behavior and suicidality (Darke et al., 2019; Gee et al., 2016; German et al., 2014; Karch, 2015; Logan et al., 2017). Deaths have been reported, predominantly in case reports, related to the consumption of cathinones (Barrios et al., 2016; Kesha et al., 2013; Liveri et al., 2016; Loi et al., 2015; Murray et al., 2012; Nagai et al.,

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2014a, 2014b; Pearson et al., 2012; Wikstrom et al., 2010), phenethylamines (Kristofic et al., 2016; Kueppers and Cooke, 2015; Kronstrand et al., 2013; Lowe et al., 2015; Morini et al., 2017), piperazines (Chatterton et al., 2012; Elliott and Smith, 2008) and tryptamines (Dakic et al., 2017). The emerging clinical presentation includes delirium, hyperthermia, with possible progression to seizures, kidney failure and sudden cardiac arrest.

The current study aimed to provide a comprehensive clinical profile of a national case series of new psychoactive stimulant and hallucinogen-related death. Both stimulants and hallucinogens were examined as these drugs stand in contrast to the other two major classes of NPS: synthetic cannabinoids and depressants (e.g. GHB). Moreover, many of these drugs have both stimulant and psychedelic properties (Darke et al., 2017). Cases were retrieved from the The National Coronial Information System (NCIS). Specifically, the study aimed to:

1 Determine the characteristics, and circumstances of death, of all recorded cases of new psychoactive stimulant and hallucinogen-related death in Australia;
2 Determine the toxicology of such deaths; and
3 Determine the major organ pathology of cases.

2. Methods

2.1. National coronial information system

The NCIS is a database of medicolegal death investigation records provided by the coroners' courts in each Australian jurisdiction, commencing in 2000. A complete NCIS case file includes demographic information, a police narrative of circumstances, autopsy reports (including a narrative of circumstances), toxicology reports and the coronial finding. 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, 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 anesthesia 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. Ethical approval for the study was received from the NCIS and University of New South Wales Human Research Ethics Committees.

2.2. Case identification

All closed cases that occurred between 1/1/2000-31/12/2017 in which new psychoactive stimulant use (cathinones, phenethylamines, piperazines, tryptamines) was coded in NCIS after the completion of the coronial process as a mechanism contributory to death were identified and inspected by the authors. In 79 cases there was toxicological evidence of new psychoactive stimulant use consumption proximal to death. In three cases where the toxicology report was not available for inspection, the new psychoactive stimulant involved was specifically noted in the cause of death.

2.3. Measures

The following available reports in NCIS files were inspected: toxicology (79), police (73), coroner's (71) and autopsy (57). Information was collected on demographics, drug use history, suicidal intent, location and medical intervention. Documentation of signs and symptoms of acute stimulant toxicity were recorded, including sudden collapse, vomiting, delirium, seizure, chest pain, hyperthermia and labored breathing. For the purposes of analysis, manner of death was classified as: i. Accidental drug toxicity, ii. Combined Accidental drug toxicity and natural disease, iii. Natural disease, iv. Suicide, v. Traumatic accident, and vi. Homicide. Suicide was determined by the NCIS intent designation code "Deliberate self-harm".

The majority of cases undergo a standardized forensic autopsy, with examination of all major organs and quantitative toxicological analysis. In such cases data on major organ pathology were recorded. Cardiomegaly was diagnosed by heart weight exceeding the 95th percentile of normal weight ranges (Kitzman et al., 1998; Scholz et al., 1998), and severe coronary artery atherosclerosis as ≥ 75% cross-sectional area stenosis.

Toxicological data were reported for the major new psychoactive stimulants (cathinones, phenethylamines, piperazines, tryptamines), established psychostimulants, opioids, cannabis (Δ-9-THC), synthetic cannabinoids, alcohol, benzodiazepines, antidepressants and antipsychotics. All blood samples for toxicological analysis were taken from peripheral sites. In 10 cases of hospitalization prior to death, antemortem blood samples taken on or near admission to hospital were reported. Drugs administered by medical staff were excluded. All samples were screened by immunoassay and either by gas chromatography, high-performance liquid chromatography (HPLC) or liquid chromatography-quadrupole time of flight mass spectrometry (LC-QTOF-MS) for common drugs of abuse and select therapeutic substances. All specimens were stored at 4 °C prior to testing.

2.4. Statistical analyses

For normally distributed variables, means, standard deviations (SD) and ranges were presented, otherwise medians and ranges were reported. Differences between means were analyzed using t-tests, and chi square was used to analyze categorical variables. All analyses were conducted using IBM SPSS Statistics v. 25.0 (IBM, 2017).

3. Results

3.1. Case characteristics

A total of 82 cases were identified (Table 1). The first death occurred in 2007, and the most recent in 2017. The mean age was in the early thirties, with the largest proportion aged in their twenties (Table 1). Males comprised 86.6% of cases. Fewer than half were employed at the time of death, and a fifth were in a married/defacto relationship. A third had a documented history of injecting drug use. Few were enrolled in a drug treatment program, all of whom were enrolled in opiate substitution treatment. Two thirds of fatal incidents occurred in a private home, with only a single case having occurred at a music festival. Resuscitation was attempted in fewer than half, and a quarter survived to hospital admission. In more than half of cases the route of NPS administration proximal to death was not able to be determined. The most common route amongst cases where it was able to be determined was by injection.

3.2. Clinical characteristics

The most common circumstance of death was accidental drug toxicity (Table 1). In two cases death was attributed to combined drug toxicity/cardiovascular disease. Death due to various forms of trauma was common, comprising 35.4% of cases. One in six cases were due to traumatic accident. Accidents other than motor vehicle accident comprised drowning (3), fall from height (2), restraint asphyxia after an agitated delirium (1) and fire (1). There ten cases of death due to suicide, predominantly by violent means, and one in ten cases were homicides. Of the cases of suicide, 8 were positive for cathinones and two for phenethylamines. There were two cases where death was due to natural disease following new psychoactive stimulant use, namely

Table 1
Case characteristics and circumstances of death of new psychoactive stimulant-related fatalities.

	Males (n = 71)	Females (n = 11)	All (n = 82)
Characteristics			
Age (mean yrs.)	31.1 (SD 10.8, 15–59)	28.1 (SD 7.2, 20–41)	30.7 (SD 10.4, 15–59)
Age range % (n)			
< 20 yrs.	12.7 (9)	0.0 (0)	11.0 (9)
20–29 yrs.	36.6 (26)	72.7 (8)	41.5 (34)
30–39 yrs.	25.4 (18)	18.2 (2)	24.4 (20)
40–49 yrs.	19.7 (14)	9.1 (1)	18.3 (15)
≥50 yrs.	5.6 (4)	0.0 (0)	4.9 (4)
Employed % (n)	40.8 (29)	45.5 (5)	41.5 (34)
Married/Defacto relationship % (n)	19.7 (14)	27.3 (3)	20.7 (17)
Documented history of injecting drug use % (n)	35.2 (25)	18.2 (2)	32.9 (27)
Enrolled in drug treatment	7.0 (5)	9.1 (1)	7.3 (6)
Location of fatal incident % (n)			
Private	66.2 (47)	63.6 (7)	65.9 (54)
Public	33.8 (24)	36.4 (4)	34.1 (28)
Resuscitation attempted % (n)	42.3 (30)	27.3 (3)	40.2 (33)
Hospitalized prior to death % (n)	26.8 (19)	18.2 (2)	25.6 (21)
Route of final NPS Administration % (n)			
Unknown	52.1 (37)	63.6 (7)	53.7 (44)
Injection	22.5 (16)	0.0 (0)	19.5 (16)
Swallowed	16.9 (12)	9.1 (1)	15.9 (13)
Insufflated	6.1 (2)	27.3 (3)	6.1 (5)
Smoked	4.9 (4)	0.0 (0)	4.9 (4)
Circumstance of death % (n)			
Accidental drug toxicity	59.2 (42)	63.6 (7)	59.8 (49)
Toxicity	56.3 (40)	63.6 (7)	57.3 (47)
Toxicity + cardiovascular disease	2.8 (2)	0.0 (0)	2.4 (2)
Traumatic accident	18.3 (13)	0.0 (0)	15.9 (13)
Motor vehicle accident	8.5 (6)	0.0 (0)	7.3 (6)
Other	9.9 (7)	0.0 (0)	8.5 (7)
Suicide	12.7 (8)	18.2 (2)	12.2 (10)
Violent means	8.5 (6)	18.2 (2)	9.8 (8)
Deliberate drug toxicity	2.8 (2)	0.0 (0)	2.4 (2)
Homicide	9.9 (7)	9.1 (1)	9.8 (8)
Natural disease	1.4 (1)	9.1 (1)	2.4 (2)

Note: There were no statistically significant differences by sex. Due to small cell sizes, circumstance of death was dichotomized as drug toxicity versus other. As in more than half of cases the final route of administration was not able to be determined, this variable was not analyzed.

status asthmaticus and sepsis due to intramuscular cathinone injection.

The most commonly observed clinical presentation prior to death was delirium, documented in a quarter of cases (Table 2). Delirium was more frequently reported in cases involving phenethylamines: phenethylamine (73.3%, 11/15) phenethylamine + cathinone (66.7%, 2/3), cathinones (15.3%, 9/59), piperazines (0.0%, 0/5) ($\chi^2_3 = 24.8$, $p < .001$). Hyperthermia was documented in a tenth, as was seizure. Signs and symptoms of stimulant toxicity were overwhelmingly reported amongst accidental toxicity cases, including all cases of seizure, sudden collapse and chest pain.

Autopsy reports were available for inspection in 57 cases. In nine cases no autopsy was conducted and in 16 the report was not available. There were low levels of organ pathology. The most common cardiovascular diagnosis was replacement fibrosis, indicative of previous ischemia, all but one of whom died due to accidental drug toxicity. Pneumonia was noted in a seventh, all but one of whom died due to accidental toxicity.

3.3. Toxicology

By far the most commonly observed new psychoactive stimulants were cathinones, with methcathinone, MDPV and α-PVP comprising the vast majority (Table 3). Phenethylamines were present in a fifth, NBOMe being the most common. Piperazines were present in five cases, and no case involved tryptamines. Quantitation was available for 33 cases. Median blood concentrations were: cathinones (n = 20, 0.105 mg/L, range 0.002–2.000 mg/L), phenethylamines (n = 13, 0.250 mg/L, range 0.003–9.200 mg/L), piperazines (n = 1, 0.020 mg/L).

Complete toxicology reports were available for inspection in 79 cases, among whom other substances were present in the majority. The most commonly co-occurring drugs were psychostimulants, most frequently methamphetamine. Opioids were present in a third, most frequently morphine. Pharmaceuticals were present in substantial minorities. Alcohol was present in over a quarter (median blood alcohol concentration = 0.054 g/100 ml, range 0.010-0.378 g/100 ml). Cannabis was present in a fifth, and synthetic cannabinoids in two cases.

4. Discussion

Cases were mostly young, overwhelmingly male, and the fatal incident most likely to have occurred in a home environment. While predominately young, it is notable that close to a quarter were aged in their forties or fifties. Attempts to resuscitate were documented in a sizable minority, but the majority did not survive to hospital. The most frequent cause of death was accidental drug toxicity. The level of traumatic death was, however, substantial, representing more than a third of cases, a pattern observed amongst both males and females. Such a high level of traumatic death is similar to that reported in a recent case series of mephedrone deaths (Loi et al., 2015), and for established psychostimulants such as methamphetamine (Darke et al., 2017). In terms of social profile, more than half were unemployed and a third known to be injecting drug users.

The 82 cases in this series should be put in the context of deaths due to other drugs in Australia. Between 2007 and 2016 (broadly the period in which these cases occurred) there were 8531 opioid-induced, and 473 methamphetamine-induced, deaths (Roxburgh et al., 2018). These figures reflect the low population prevalence of NPS use, being in the order of 0.5–1% (Australian Institute of Health and Welfare, 2017). In terms of future trends, the use of these drugs has become more prevalent, as is the toxicological capacity to detect these drugs.

The new psychoactive stimulants most commonly implicated in these deaths were cathinones, with methcathinone, MDPV and α-PVP present in the vast majority of such cases. It is not clear whether this reflects the epidemiology of their use, or differences in toxicity. A recent national wastewater study, however, reported cathinones as the most frequently detected new psychoactive stimulant in Australia (Bade et al., 2019). Wastewater analysis cannot, however, provide estimates on the relative numbers of people who use substances, only the relative concentrations of drugs. Similarly, it is not clear whether the predominance of cathinones amongst cases of suicide reflected epidemiology or a propensity to induce suicidal behaviors.

Other drugs were present in the vast majority of cases. The overall clinical presentation was of a psychostimulant-oriented group, with other psychostimulants (most notably methamphetamine) being present in over half of cases. A similar toxicological profile was reported in a recent case series of mephedrone deaths (Loi et al., 2015). What needs to be borne in mind is that the use of multiple psychostimulants is likely to increase the severity of acute hypertension and the risk of cardiac arrhythmia (Darke et al., 2019).

Witness descriptions of a state of delirium immediately preceding death were by far the most common presentation prior to death. Moreover, delirium was not restricted to toxicity deaths, being prominent in traumatic death. Indeed, all suicide cases who exhibited delirium used violent means. In these cases, behaviors during a delirium appear to have contributed to death. Delirium was strongly associated with the phenethylamines, and such drugs appear to carry particular risk for this serious clinical condition. It was notable that, with the

Table 2
Clinical characteristics of new psychoactive stimulant-related fatalities.

	Accidental drug toxicity % (n = 49)	Natural disease % (n = 2)	Traumatic accident % (n = 13)	Suicide % (n = 10)	Homicide % (n = 8)	All cases % (82)
Signs and symptoms at fatal incident						
Delirium	28.6 (14)	0.0 (0)	46.2 (6)	20.0 (2)	0.0 (0)	26.8 (22)
Hyperthermia	16.3 (8)	0.0 (0)	7.7 (1)	10.0 (1)	0.0 (0)	11.0 (9)
Seizure	14.3 (7)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	8.5 (7)
Labored breathing	10.2 (5)	50.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	7.3 (6)
Vomiting	8.2 (4)	0.0 (0)	0.0 (0)	10.0 (1)	0.0 (0)	6.1 (5)
Sudden collapse	8.2 (4)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	4.9 (4)
Chest pain	2.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.2 (1)
Organ pathology[*]	(n = 34)	(n = 2)	(n = 12)	(n = 2)	(n = 8)	(n = 57)
Cardiovascular						
Replacement fibrosis	14.7 (5)	0.0 (0)	0.0 (0)	0.0 (0)	12.5 (1)	10.5 (6)
Severe atherosclerosis	5.9 (2)	50.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	5.3 (3)
Cardiomegaly	2.9 (1)	0.0 (0)	0.0 (0)	0.0 (0)	12.5 (1)	3.5 (2)
Ventricular hypertrophy	2.9 (1)	0.0 (0)	8.3 (1)	0.0 (0)	0.0 (0)	3.5 (2)
Pulmonary						
Pneumonia	20.6 (7)	50.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	14.0 (8)
Emphysema	2.9 (1)	0.0 (0)	8.3 (1)	0.0 (0)	0.0 (0)	3.5 (2)
Hepatic						
Severe steatosis	2.9 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.8 (1)
Cirrhosis	2.9 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.8 (1)
Renal						
Fibrosis	2.9 (1)	0.0 (0)	0.0 (0)	0.0 (0)	12.5 (1)	3.5 (2)

[*] Autopsies conducted in and available for inspection in 57 cases.

Table 3
Toxicology of new psychoactive stimulant-related fatalities.

Drug class	% (n)
NPS stimulants	(n = 82)
Cathinones	75.7 (62)
(Methcathinone 27, MDPV 16, α-PVP 16, Mephedrone 2, Methylone 1, Ethypentylone 2, EBPD 1, Ethylone 1)	
Phenethylamines	22.0 (18)
(25C-NBOMe 4, 25I-NBOMe 4, 25H-NBOMe 3, 25B-NBOMe 1, PMMA 6, 5-APB, B-phenethylamine 1)	
Piperazines	6.1 (5)
(TFMPP 4, BZP 2)	
Other drugs[*]	(n = 79)
Other drugs present	83.5 (66)
Psychostimulants	58.2 (46)
Methamphetamine	49.4 (39)
MDMA	10.1 (8)
Cocaine	10.1 (8)
Dimethylamylamine	1.3 (1)
Opioids	30.4 (24)
Morphine	17.7 (14)
Methadone	7.6 (6)
Fentanyl	5.1 (4)
Buprenorphine	3.8 (3)
Tramadol	2.5 (2)
Oxycodone	2.5 (2)
Hydromorphone	1.3 (1)
Alcohol	27.8 (22)
Δ^9 THC	21.5 (17)
Synthetic cannabinoids	2.5 (2)
Hypnosedatives	17.7 (14)
Antidepressants	16.5 (13)
Antipsychotics	16.5 (13)

[*] Toxicology for other drugs available for 79 cases.

exception of delirium, other signs and symptoms of stimulant toxicity such as seizure, hyperthermia and sudden collapse were heavily concentrated amongst cases of accidental drug toxicity. Major organ pathology was present in low proportions, a probable reflection of the young demographic profile. Again, these pathologies were concentrated amongst accidental drug toxicity cases.

The current study has clinical and public health implications. While attempts to revive the individual were made in close to half of cases, only a minority survived to hospital. Early recognition of the signs and symptoms of new psychoactive stimulant toxicity by witnesses to these events, such as delirium and seizure, might well improve survival times Recognition of the need to seek medical help for individuals experiencing delirium appears particularly important. The fact that new psychoactive stimulants are being created on a regular basis (EMCDDA, 2017; United Nations Office on Drugs and Crime (UNODC, 2017), creates problems for rapid testing in clinical settings to determine the particular drug involved. As it may not be possible to determine the specific drug, acute treatment must be in response to the clinical presentation, which appears to resemble those of the established psychostimulants and hallucinogens (Abdulrahim and Bowden-Jones, 2015). Few were in treatment, and none in a treatment for stimulant dependence. Indeed, there are no specific treatments for new psychoactive stimulant dependence, and no proven agonist (Darke et al., 2019). This is of particular relevance to the cathinones, for which there is emerging evidence of a dependence syndrome (German et al., 2014; Karila et al., 2018). While no specific treatment exists, there is good evidence for the effectiveness of residential rehabilitation for the established psychostimulants (Malivert et al., 2012). In addition, both cognitive behavioral therapy and contingency management have shown moderate efficacy in the treatment of psychostimulant dependence (Walters and Rotgers, 2012), and may be useful for the treatment of dependence on the new stimulants. Finally, people who use these drugs may not be aware of the risk of the concomitant use of other substances, and of psychostimulants in particular.

As in all studies caveats must be borne in mind. As new psychoactive stimulants are being created on a regular basis, no toxicology laboratory is able to identify every one of these drugs. It is thus likely that this series is conservative. Moreover, this series comprised closed cases, i.e. cases in which the Coronial investigation has been completed. Cases in which investigations were still being undertaken were not available for inspection. The study thus presents the clinical characteristics of deaths known to be related to new psychoactive stimulant use. Caution should also be exercised in relation to the description of signs and symptoms observed at fatal incidents. These were, by necessity, restricted to cases in which witnesses were present. The prevalence of these phenomena at unwitnessed incidents is not known.

In summary, acute toxicity was the most common cause of death, but more than a third of deaths were due to trauma. Cathinones were

the most commonly detected the new psychoactive stimulants and hallucinogens. Delirium was the most frequently reported sign of toxicity and was strongly associated with the phenethylamines.

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All authors confirm that there is no financial, or personal interest or belief that could affect their objectivity in the conduct of this study.

Contributors

Professor Darke designed the study, conducted data collection, conducted the statistical analyses and was the lead author in the write-up of the paper. Professor Duflou aided in study design, provided specialist forensic medical and toxicological comment, and reviewed the manuscript. Dr Amy Peacock aided in study design, conducted literature searches and reviewed the manuscript. Professor Michael Farrell provided specialist medical comment and reviewed the manuscript. Dr Julia Lappin provided specialist medical comment and reviewed the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

No conflict declared.

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