Received: 14 December 2021 | Revised: 7 February 2022 | Accepted: 8 February 2022

DOI: 10.1002/emp2.12813

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
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ORIGINAL RESEARCH

Toxicology

# 4-Fluoroamphetamine (4-FA) intoxication results in exaggerated blood pressure effects compared to MDMA and amphetamine: A retrospective analysis

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**Funding and Support**: By *JACEP* Open policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.castoredc.com). The authors have stated that no such relationships exist.

## Abstract

**Objective:** 4-Fluoroamphetamine (4-FA) is an amphetamine-type stimulant, with effects comparable to amphetamine and 3,4-methylenedioxymethamphetamine (MDMA). Severe 4-FA-related complications, such as cardiomyopathy, myocardial infarction, and cerebral hemorrhage, have been described. The aim of this study was to explore the cardiovascular symptoms and complications in 4-FA and compare them to MDMA and amphetamine in intoxicated patients who presented to the emergency department (ED).

**Methods:** Between November 2015 and March 2020, all self-reported 4-FA, MDMA, and amphetamine-intoxicated adult patients that presented at the ED of an inner-city hospital in Amsterdam, were retrospectively analyzed for cardiovascular symptoms, vital parameters, cardiovascular complications, interventions, admission rate, and Poisoning Severity Score (PSS).

**Results:** A total of 582 patients were included, of which 31 (5.3%) with 4-FA intoxication (10/31 mono-intoxications, 32.3%), 406 (69.8%) with MDMA (59/406 mono-intoxications, 14.5%), 100 (17.2%) with amphetamine (10/100 mono-intoxications, 10.0%), and 45 (7.7%) with a cross intoxication of these drugs. 4-FA mono-intoxicated patients experienced more headache (n = 8; 80.0%) compared to MDMA (n = 2; 3.3%; $P < 0.001$) and amphetamine mono-intoxicated patients (n = 0; 0.0%; $P < 0.001$) and their systolic blood pressure was higher (164 mm Hg ± 31 vs 139 mm Hg ± 19; $P = 0.031$ vs 135 mm Hg ± 22; $P = 0.033$, respectively). Severe 4-FA-related cardiovascular complications included Takotsubo cardiomyopathy (n = 1; 3.2%), subarachnoid hemorrhage (n = 1; 3.2%), and hypertensive urgency (n = 2; 6.5%).

Supervising Editor: Karl Sporer, MD.

**Conclusions:** 4-FA intoxication-related ED symptoms resemble MDMA and amphetamine complications, although patients presented more often with headache and hypertension. Severe 4-FA-related cardiovascular complications occurred in 40% of mono-intoxications.

**KEYWORDS**
amphetamine, cardiovascular complications, emergency department, 4-fluoramphetamine, 4-FA, 3,4-methylenedioxymethamphetamine, MDMA

## 1 | INTRODUCTION

### 1.1 | Background

4-Fluoroamphetamine (4-FA), also called 4-FMP, PAL-303, Flux, 4-Fluor, 4-Flava, or 4-F, is an amphetamine type stimulant that inhibits norepinephrine, dopamine, and serotonin reuptake in the synaptic cleft of neurons.[1] Street 4-FA is available as a racemic mixture. Synthetic routes resemble those of the preparation of amphetamine.[2] The classic approach includes the reduction of 4-fluorobenzyl methyl ketone. Chemical analyses of street 4-FA powders and tablets have revealed the presence of impurities that point to the use of 4-fluorobenzyl methyl ketone as the starting material.

Although only limited research of the pharmacodynamics and pharmacokinetics of 4-FA is available, it seems that 4-FA exhibits features similar to 3,4-methyleendioxymethamfetamine (MDMA) and amphetamine.[3–5] The effects are described as intermediate between MDMA and amphetamine, most likely due to the more potent effect on norepinephrine and dopamine reuptake compared to MDMA and a more potent effect on serotonin reuptake compared to amphetamine.[6] Initially, 4-FA was used as an adulterant, but it became a drug of choice over the last decade.[7,8] Its prevalence of use among Dutch party-goers (15–35 years) increased rapidly from 9% in 2013 to 25% in 2016[9,10] and it showed a global presence on the drug market.[8,11–18] Although 4-FA is an illicit drug in the Netherlands since 2017, 4-FA continued to be the most prominent novel psychoactive substance in the Netherlands in 2018, with 0.9% of all Dutch adults having used 4-FA in that year, compared to 2.8% MDMA and 1.1% amphetamine use.[19]

### 1.2 | Importance

The popularity of 4-FA might be due to the described effect as intermediate between MDMA and amphetamine.[20,21] In case reports and small case studies, serious complications, such as heart failure, cardiomyopathy, myocardial infarction, cerebral hemorrhage, seizures, hyperpyrexia, and fatalities, have been described,[6,14–16,22–25] which are comparable to previously described MDMA- and amphetamine-related complications.[5] Due to these similarities, emergency department (ED) management of 4-FA intoxications is mostly similar to MDMA and amphetamine, although specific management may be indicated based on specific clinical effects of 4-FA.[1]

### 1.3 | Goals of this investigation

This study aimed to explore the prevalence and type of symptoms and cardiovascular complications in 4-FA and compare them to MDMA and amphetamine in intoxicated ED patients.

## 2 | METHODS

### 2.1 | Study design

A retrospective study.

### 2.2 | Setting

This study was performed at the ED of OLVG hospital, an inner city hospital in Amsterdam, the Netherlands.

### 2.3 | Patient selection

Patients ≥18 years old with self-reported and/or toxicology analysis confirmed 4-FA, amphetamine, and MDMA intoxication, presenting between November 2015 and March 2020, were identified from the OLVG toxicology registration and included for retrospective analysis. OLVG patients are prospectively included in a toxicology registry when they present to the ED with an intoxication-related complaint. Acceptable synonyms for these drugs were 4-FMP, XTC, ecstasy, speed, and pep. Patients were identified and selected for a specific study group via self-reported drug use (SRDU), and when available confirmed with a urine toxicology screening (UTS) or high-resolution mass spectrometry.[26] Toxicological analysis results were unavailable for most patients because serum analysis was not routinely performed. UTS was performed using a point-of-care immunoassay test (Triage TOX Drug Screen, Alere Inc.) able to detect methamphetamine/MDMA, amphetamine, cocaine, methadone,

**The Bottom Line**

4-Fluoroamphetamine (4-FA) is an amphetamine-like stimulant. This case series of over 500 cases of self-reported 4-FA, MDMA and amphetamine intoxication (alone or with other drugs) at one European hospital over 5 years demonstrated 4-FA symptoms are similar to MDMA and amphetamine intoxication. Although 4-FA patients were more likely to have hypertension and headaches.

tetrahydrocannabinol (THC), and benzodiazepine. UTS results were considered superior to SRDU, with the exception of benzodiazepines because they could have been administered by healthcare personnel and 4-FA because 4-FA is not detected by UTS. In a previous study, no false–positive results were found for amphetamine or methamphetamine with the Triage TOX Drug Screen.[27] A false–positive SRDU was deemed unlikely.

Patients with amphetamine type stimulant use other than 4-FA, MDMA, and/or amphetamine and non–intoxication-related primary ED presenting complaints were excluded. Included patients were divided into 3 study groups depending on the type of drug used, namely mono-drug intoxication (only 1 substance used), multi-drug intoxication (more than 1 substance used, but only 1 of the study substances 4-FA, MDMA, and/or amphetamine), or cross-drug intoxication (a combination of 4-FA, MDMA, and/or amphetamine, with or without other substances used). To determine mono- or multi-drug intoxication, SRDU, UTS results, and alcohol serum levels were used. A serum ethanol level above 0.1 g/L was considered an alcohol intoxication and, consequently, multi-drug intoxication.

## 2.4 | Measurements

Medical chart review was performed to obtain patient characteristics, past medical history, prescription medication, symptoms, vital parameters, investigations, complications, length of stay (LOS), and supplementary variables to calculate the Poison Severity Score (PSS), a standardized score for grading the severity of poisoning to evaluate morbidity.[28] Patients with a Dutch home address were considered Dutch residents. The medical history was specified in respiratory, cardiovascular, neurological, or psychiatric disease. Highest and lowest measurements of vital parameters were obtained. In case only 1 measurement was available, this was registered as highest, however, it was registered as lowest when it was below the lower reference value. The lowest Glasgow Coma Scale (GCS) score was registered, assuming patients were only discharged with a GCS of 15 (range, 3–15). An ECG reported abnormal was reassessed by an experienced cardiologist. Radiologist results were obtained, or when missing, the physicians report of the radiology investigation was included. Cut-off values and definitions are shown in Appendix A.

## 2.5 | Outcomes

The main outcome of the study was the prevalence of cardiovascular complications, like hypertensive urgency and hypertensive emergency, acute coronary syndrome, cardiomyopathy, and cardiogenic shock, all defined by the European Society of Cardiologist,[29–32] and intracranial hemorrhage as defined by the American Heart Society.[33] Secondary outcome measures were the differences between 4-FA, MDMA, and amphetamine mono–intoxication-related cardiovascular symptoms and complications and intoxication severity. We hypothesized that 4-FA mono-intoxication would result in significantly higher blood pressure and more frequent complications compared to MDMA and amphetamine mono-intoxication.

## 2.6 | Analysis

Castor (https://www.castoredc.com) was used to store patient data anonymously. Data were analyzed with IBM SPSS statistics version 22. Descriptive statistics were presented in frequencies (%) for categorical variables, and median (interquartile range [IQR]) or mean SD for continuous variables. To determine the normality of distribution of continuous data, Shapiro-Wilk's tests, Skewness and Kurtosis values, visual histogram inspection, normal Q-Q plots, and boxplots were used. Independent sample *t* tests were used to compare normally distributed data, Mann-Whitney *U* tests were used for non-normally distributed data, and $\chi^2$ tests and Fisher's exact tests were used for categorical data. Statistical significance was defined as a *P*-value ($P < 0.05$). Approval was granted by the OLVG local ethics committee.

# 3 | RESULTS

## 3.1 | Characteristics of study subjects

A total of 4409 ED patients were recorded in the toxicology registry of whom 582 patients met the inclusion criteria (Figure 1). Baseline patient characteristics are shown in Table 1 (multi-intoxications) and Table 2 (mono-intoxications). Combined use of 2 or all 3 studied drugs was present in 45 patients (7.7%) included in the cross-intoxicated group, of whom 13 (28.9%) used 4-FA, 43 (95.6%) used MDMA, and 37 (82.2%) used amphetamine. There were more women among the patients presenting with a 4-FA intoxication (54.8%) then in the other groups, including MDMA 27.6% ($P = 0.001$), amphetamine 32% ($P = 0.022$), and cross intoxication 31.1% ($P = 0.039$). The patients in the MDMA group were more often tourists (44.8%; $P = 0.006$), and amphetamine patients most frequently reported a medical history (50%), mainly psychiatric disease ($P < 0.001$). For 148 (25.4%) patients, a UTS was performed. A UTS was performed for 8 of 31 patients with 4-FA intoxication, of whom 3 patients tested positive for amphetamine (1 self-reported 4-FA mono-intoxication), all of whom denied amphetamine use. In April 2017, the Dutch government banned 4-FA, making it an illegal substance. Of all 4-FA mono- and cross-intoxicated patients (n = 44), 23 presented before the ban on 4-FA

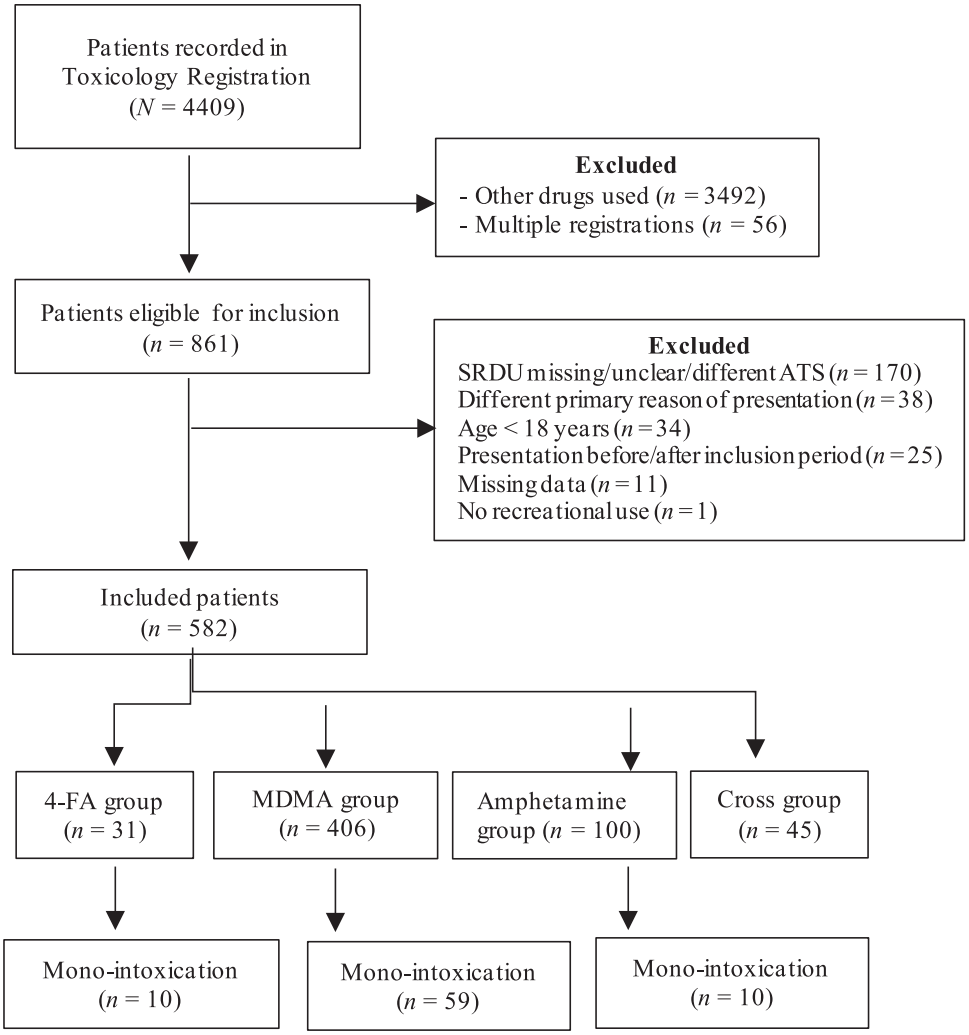


**FIGURE 1** Patient selection. Abbreviations: SRDU, self-reported drug use; ATS, amphetamine type stimulants; 4-FA, 4-fluoroamphetamine; MDMA, 3,4-methyleendioxymethamfetamine.

(over 571 days), and 21 patients presented after the ban (1012 days), resulting in a decrease of 51.5% when corrected for duration of inclusion.

## 3.2 | Main results

Vital parameters of mono-intoxicated patients are displayed in Table 2. Lowest measured parameters were unavailable for more than half of the 4-FA patients and were therefore not included in the statistical analysis. Headache was the most common complaint of 4-FA mono-intoxicated patients, (n = 8, 80%), This was significantly more prevalent as compared to MDMA (n = 2, 3.3%, $P < 0.001$) and amphetamine mono-intoxicated patients (n = 0, 0.0%, $P < 0.001$). No other differences in cardiovascular symptoms were found.

The complaints of headache were without exception accompanied by hypertension in 4-FA mono-intoxicated patients. The maximum systolic blood pressure (164 mm Hg ± 31) was significantly higher in the 4FA patients as compared to MDMA (139 mm Hg ± 19, $P = 0.031$) and amphetamine mono-intoxicated patients (135 mm Hg ± 22, $P = 0.033$). None of the 4-FA patients presented with a decreased GCS score. An ECG was obtained in 19 (61%) 4-FA intoxicated patients (5 mono-intoxications), of whom 2 mono-intoxicated patients showed ST-segment abnormalities. One of these patients (female, 31 years old) presented with severe headache and a hypertensive urgency (200/110 mm Hg) that responded well to administration of antihypertensives. Another patient (male, 20 years old) was diagnosed with reversed Takotsubo cardiomyopathy and this case was previously reported.[6] A third patient (male, 20 years old) showed a right bundle branch block after presenting with a headache and hypertensive urgency (169/124 mm Hg) and recovered without any interventions. Computed tomography (CT) scans of the head were obtained for 6 (19%) 4-FA intoxicated patients (3 mono-intoxications), for severe headache (n = 5), and suspected head injury (n = 1). One of these headache patients (female, 24 years old) that presented with a hypertensive emergency (178/112 mm Hg) was diagnosed with a subarachnoid hemorrhage.

Hypertension (blood pressure >140/100 mm Hg) was observed in 50% (n = 29) of MDMA mono-intoxicated patients. A decreased

**TABLE 1** Baseline characteristics

| | Study group | | | | | | |
|---|---|---|---|---|---|---|---|
| | 4-FA (N = 31) | MDMA (N = 406) | *P*-value | Amphetamine (N = 100) | *P*-value | Cross-intoxications (N = 45) | *P*-value |
| Age in years, mean ± SD[a] | 27 ± 8 | 28 ± 8 | 0.583 | 29 ± 9 | 0.251 | 27 ± 6 | 0.727 |
| Male, n (%)[b] | 14 (45.2) | 294 (72.4) | **0.001** | 68 (68.0) | **0.022** | 31 (68.9) | 0.039[d] |
| Dutch resident, n (%)[b] | 25 (80.6) | 224 (55.2) | **0.006** | 81 (81.0) | 0.965 | 34 (75.6) | 0.601 |
| Presentation before ban, n (%)[b] | 18 (58.1) | 138 (34.0) | **0.007** | 36 (36.0) | **0.029** | 22 (48.9) | 0.431 |
| Medical history, n (%)[b] | 6 (19.4) | 79 (19.5) | 0.989 | 50 (50.0) | **0.003** | 8 (17.8) | 0.862 |
| Cardiovascular[c] | 1 (3.2) | 8 (2.0) | 0.488 | 6 (6.0) | 1.000 | 0 | 0.408 |
| Respiratory[c] | 0 | 6 (1.5) | 1.000 | 8 (8.0) | 0.197 | 1 (2.2) | 1.000 |
| Neurological[c] | 3 (9.7) | 10 (2.5) | 0.057 | 2 (2.0) | 0.086 | 0 | 0.064 |
| Psychiatric[c] | 2 (6.5) | 44 (10.8) | 0.759 | 45 (45.0) | **<.001** | 5 (11.1) | 0.694 |
| Medication use, n (%)[c] | 7 (22.6) | 42 (10.3) | 0.067 | 29 (29.0) | 0.484[b] | 7 (15.6) | 0.438 |
| Analgesics | 0 | 1 (0.2) | 1.000 | 3 (3.0) | 1.000 | 0 | - |
| Antidepressants | 0 | 4 (1.0) | 1.000 | 5 (5.0) | 0.592 | 1 (2.2) | 1.000 |
| Anticonvulsants | 0 | 6 (1.5) | 1.000 | 1 (1.0) | 1.000 | 1 (2.2) | 1.000 |
| Antihypertensives | 0 | 2 (0.5) | 1.000 | 3 (3.0) | 1.000 | 0 | - |
| Antipsychotics | 2 (6.5) | 4 (1.0) | 0.061 | 8 (8.0) | 1.000 | 0 | 0.163 |
| Benzodiazepines | 0 | 9 (2.2) | 1.000 | 8 (8.0) | 0.197 | 0 | - |
| Bronchodilator | 0 | 4 (1.0) | 1.000 | 6 (6.0) | 1.000 | 0 | - |
| Contraception pill | 4 (12.9) | 3 (0.7) | **0.001** | 0 | **0.003** | 2 (4.4) | 0.218 |
| Dexamphetamine | 0 | 0 | - | 2 (2.0) | 1.000 | 0 | - |
| Methylphenidate | 0 | 3 (0.7) | 1.000 | 3 (3.0) | 1.000 | 0 | - |
| Proton pump inhibitor | 0 | 2 (0.5) | 1.000 | 1 (1.0) | 1.000 | 0 | - |
| Statin | 0 | 1 (0.2) | 1.000 | 0 | - | 0 | - |
| Other | 3 (9.7) | 23 (5.7) | 0.417 | 14 (14.0) | 0.761 | 3 (6.6) | 0.683 |
| Mono-intoxication, n (%)[c] | 10 (32.3) | 59 (14.5) | **0.018** | 10 (10.0) | **0.008** | NA | - |
| Multi-intoxication, n (%)[c] | 21 (67.7) | 347 (85.5) | **0.018** | 90 (90.0) | **0.008** | NA | - |
| 2C-B | 0 | 4 (1.0) | 1.000 | 0 | - | 1 (2.2) | 1.000 |
| Alcohol | 15 (48.4) | 248 (61.1) | 0.185 | 51 (51.0) | 0.839 | 31 (68.9) | 0.096 |
| Benzodiazepines | 1 (3.2) | 4 (1.0) | 0.309 | 6 (6.0) | 1.000 | 0 | 0.408 |
| Caffeine | 0 | 6 (1.5) | 1.000 | 1 (1.0) | 1.000 | 0 | - |
| Cocaine | 3 (9.7) | 91 (22.4) | 0.114 | 18 (18.0) | 0.402 | 12 (26.7) | 0.084 |
| Methamphetamine | 0 | 4 (1.0) | 1.000 | 2 (2.0) | 1.000 | 0 | - |
| GHB/GBL | 7 (22.6) | 67 (16.5) | 0.454 | 42 (42.0) | 0.058 | 12 (26.7) | 0.791 |
| Heroin | 0 | 2 (0.5) | 1.000 | 1 (1.0) | 1.000 | 0 | - |
| Ketamine | 0 | 25 (6.2) | 0.242 | 4 (4.0) | 0.572 | 6 (13.3) | 0.076 |
| Nitrous oxide | 3 (9.7) | 8 (2.0) | 0.036[a] | 1 (1.0) | 0.041[a] | 2 (4.4) | 0.393 |
| LSD/LSA | 1 (3.2) | 3 (0.7) | 0.256 | 3 (3.0) | 1.000 | 0 | 0.408 |
| Alkyl nitrite (poppers) | 0 | 3 (0.7) | 1.000 | 0 | - | 1 (2.2) | 1.000 |
| Psilocybin | 0 | 13 (3.2) | 0.612 | 1 (1.0) | 1.000 | 1 (2.2) | 1.000 |
| THC | 5 (16.1) | 79 (19.5) | 0.815 | 12 (12.0) | 0.549 | 12 (26.7) | 0.402 |
| Other | 3 (9.7) | 3 (0.7) | **0.006** | 3 (3.0) | 0.144 | 1 (2.2) | 0.298 |
| UTS, n (%)[c] | 8 (25.8) | 97 (23.9) | 0.810[b] | 23 (23.0) | 0.748[b] | 20 (44.4) | 0.098[b] |
| Amphetamine | 3 (9.7) | 12 (3.0) | 0.082 | 16 (16.0) | 0.561 | 13 (28.9) | 0.043[bd] |

(Continues)

**TABLE 1** (Continued)

| | Study group | | | | | | |
|---|---|---|---|---|---|---|---|
| | 4-FA (N = 31) | MDMA (N = 406) | *P*-value | Amphetamine (N = 100) | *P*-value | Cross-intoxications (N = 45) | *P*-value |
| Benzodiazepines | 2 (6.5) | 35 (8.6) | 1.000 | 10 (10.0) | 0.730 | 7 (15.6) | 0.295 |
| Cocaine | 2 (6.5) | 21 (5.2) | 0.674 | 5 (5.0) | 0.669 | 10 (22.2) | 0.108 |
| Methamphetamine/XTC | 0 | 88 (21.7) | **0.004**[b] | 5 (5.0) | 0.592 | 18 (40.0) | <**0.001**[b] |
| Opiates/heroin | 0 | 1 (0.2) | 1.000 | 2 (2.0) | 1.000 | 0 | - |
| Phencyclidine | 1 (3.2) | 0 | 0.071 | 0 | 0.237 | 0 | 0.408 |
| THC | 2 (6.5) | 33 (8.1) | 1.000 | 10 (10.0) | 0.730 | 9 (20.0) | 0.183 |
| Negative | 3 (9.7) | 2 (0.5) | **0.003** | 3 (3.0) | 0.144 | 0 | 0.064 |
| LOS (min), median [IQR][a] | 141 [121-210] | 191 [131-269] | **0.023** | 181 [110-272] | 0.153 | 192 [134-258] | 0.072 |
| Admission rate, n (%)[c] | 2 (6.5) | 21 (5.2) | 0.674 | 5 (5.0) | 0.669 | 6 (13.3) | 0.460 |

Baseline characteristics of all included patients: baseline of 4-FA-intoxicated patients in comparison to MDMA-, amphetamine-, and cross-intoxicated patients. Continues variables expressed as mean (±SD), categorical variables expressed as frequency (%), non-normal continuous variables expressed as median [IQR]. *P*-values calculated with $\chi^2$, Fisher's exact, or Mann-Whitney *U* tests.

Abbreviations: LOS, length of stay in ED (min); NA, not applicable; PPI, proton pump inhibitor; UTS, urine toxicology screening.

[a]Statistical test used = Mann-Whitney *U* test.

[b]Statistical test used = $\chi^2$ test.

[c]Statistical test used = Fisher's exact test.

[d]Not significant after Benjamini Hochberg procedure; false discovery rate, 25%.

Bold value indicates statistically significant.

GCS-score was observed in 18 (31%) MDMA mono-intoxicated patients, of whom 8 had received therapeutic benzodiazepines. An ECG was obtained for 200 (49%) MDMA-intoxicated patients (28 mono-intoxications). None of the patients were diagnosed in hospital with acute cardiac pathology in the absence of major ECG abnormalities, whereas 2 out-of-hospital cardiac arrest (OHCA) patients died. Echocardiography was performed in the ED for 3 MDMA intoxicated patients, of whom 1 mono-intoxicated patient (male, age 47 year) was diagnosed with dilated cardiomyopathy, possibly related to a genetic disorder. For 32 (8%) MDMA intoxicated patients (5 mono-intoxications) a CT-scan of the head was obtained, for suspected head injury (n = 20), decreased consciousness (n = 4), hyponatremia and suspected convulsion (n = 3), and headache (n = 2). One comatose patient (female, 36 years old) was diagnosed with an intracranial hemorrhage after the ingestion of MDMA, 2 C-B, and alcohol.

Hypertension was observed in 30% (n = 3) of amphetamine mono-intoxicated patients. None of the amphetamine mono-intoxicated patients presented with a decreased GCS score. An ECG was obtained in 51 (51%) amphetamine intoxicated patients (4 mono-intoxications). ST-segment abnormalities, without other signs of cardiac disease, was observed once. Furthermore, hypertensive urgency was diagnosed in 2 amphetamine multi-intoxicated patients, of which 1 was diagnosed with transient atrial fibrillation (141/128 mm Hg). CT scans of the head were performed for 3 amphetamine intoxicated patients without signs of pathology.

Management in all study groups primarily consisted of administration of analgesics or benzodiazepines combined with observation. Airway intervention was necessary for 7 MDMA mono-intoxicated patients (11.9%) due to decreased consciousness caused by administered benzodiazepines or bruxism.

According to the PSS criteria, the majority of all included patients presented with minor (n = 349, 60.1%) and moderate intoxication (n = 163, 28.1%). Of the 10 mono-intoxicated 4-FA patients, 5 (50%) presented with a moderate or severe intoxication, compared to 22 (39%) of MDMA and none of the amphetamine mono-intoxicated patients (Table 3, suggesting a non-significant association toward more severe complications in 4-FA-intoxicated patients).

## 4 | LIMITATIONS

The symptomatic ED patients in this study were selected and categorized based on SRDU, possibly leading to selection bias and possible allocation to the wrong study group. Although false–positive SRDU was deemed unlikely, drugs may have contained other substances than expected. In 2018, 70.7% of MDMA tablets contained only MDMA (on average 172 mg in 2018) and in 2019, 49% of amphetamine powders contained 100% amphetamine.[19,37,38] Since the 4-FA ban, 4-FA drug samples more frequently contained the substance 4-FMA (4-fluormethamphetamine), which closely resembles 4-FA in chemical structure.[19,37,38] We acknowledge the possibility that a part of our 4-FA-intoxicated patients might have been (co)exposed to 4-FMA. Besides this, false–negative SRDU has been commonly reported, leading to missed inclusions or missed allocation to the multi- or cross-intoxication study group. Because misclassification could have led to

**TABLE 2** Baseline and vital parameters of substance mono-intoxications

| | Study group | | | | |
|---|---|---|---|---|---|
| | 4-FA N = 10 | MDMA N = 59 | *P*-value | Amphetamine N = 10 | *P*-value |
| Age in y, mean (SD)[g] | 26 ± 6 | 27 ± 10 | 0.804 | 37 ± 15 | 0.089 |
| Male, n (%)[i] | 5 (50.0) | 37 (62.7) | 0.497 | 4 (40.0) | 1.000 |
| Dutch resident, n (%)[i] | 8 (80.0) | 31 (52.5) | 0.168 | 9 (90.0) | 1.000 |
| Medical history, n (%)[i] | 1 (10.0) | 11 (18.6) | 0.679 | 8 (80.0) | **0.005** |
| Cardiovascular | 0 | 1 (1.7) | 1.000 | 2 (20.0) | 0.474 |
| Respiratory | 0 | 2 (3.4) | 1.000 | 4 (40.0) | 0.087 |
| Neurological | 0 | 3 (5.1) | 1.000 | 0 | - |
| Psychiatric | 0 | 5 (8.5) | 1.000 | 7 (70.0) | **0.003** |
| Medication use, n (%) | 2 (20.0) | 7 (11.9) | 0.609 | 6 (60.0) | 0.170 |
| UTS, n (%)[i] | 1 (10.0) | 17 (28.8) | 0.274 | 2 (20.0) | 1.000 |
| Amphetamine | 1 (10.0) | 0 | 0.145 | 2 (20.0) | 1.000 |
| Benzodiazepines | 0 | 7 (11.9) | 0.582 | 0 | - |
| Cocaine | 0 | 0 | - | 0 | - |
| Methamphetamine/MDMA | 0 | 17 (28.8) | 0.058 | 0 | - |
| Opiates/heroin | 0 | 0 | - | 0 | - |
| Phencyclidine | 0 | 0 | - | 0 | - |
| THC | 0 | 4 (6.8) | 1.000 | 0 | - |
| Negative | 0 | 0 | - | 0 | - |
| LOS (min), median [IQR][g] | 142 [105–266] | 189 [127–308] | 0.240 | 134 [89–265] | 0.912 |
| Admission rate, n (%)[i] | 1 (10.0) | 6 (10.2) | 1.000 | 1 (10.0) | 1.000 |
| Vitals present, % | 10 (100.0) | 58 (98.3) | 1.000 | 10 (100.0) | 1.000 |
| Highest RR, median [IQR][g] | 15.0 [12.0–18.0][a] | 20.0 [16.0–25.0][c] | **0.030** | 14.0 [12.0–25.0][a] | 0.264 |
| Highest sat, median [IQR][g] | 100 [99–100] | 99 [98–100][e] | 0.182 | 98 [97–99.5][b] | **0.037** |
| Highest SBP, mean ± SD[h] | 164.3 ± 30.8 | 139.2 ± 19.3[d] | **0.031** | 135.4 ± 22.1[b] | **0.033** |
| Highest DBP, mean ± SD[h] | 105.2 ± 27.1 | 86.1 ± 15.1[d] | 0.055 | 92.0 ± 14.0[b] | 0.198 |
| Highest MAP, mean ± SD[h] | 124.8 ± 27.1 | 102.7 ± 14.0[d] | **0.030** | 106.2 ± 15.8[b] | 0.085 |
| Highest HR, mean ± SD[h] | 81.5 ± 23.1 | 112.0 ± 22.3[e] | **<0.001** | 103.0 ± 17.6[b] | **0.037** |
| Highest T, median [IQR][g] | 36.7 [36.2–37.3][b] | 37.1 [36.8–37.8][d] | **0.047** | 36.8 [36.4–37.3][b] | 0.791 |
| GCS, median [IQR][g] | 15.0[15.0–15.0] | 15.0[11.5–15.0][e] | **0.030** | 15.0[15.0–15.0][f] | 0.264 |

Baseline and vitals of mono-intoxicated patients: 4-FA mono-intoxicated patients in comparison to MDMA- and amphetamine mono-intoxicated patients. Normal continuous variables expressed as mean (±SD), non-normal continuous variables expressed as median [IQR], categorical variables expressed as frequency (%). After Benjamini Hochberg procedure, all significant results remained significant; false discovery rate 20%.

Abbreviations: CRT, capillary refill time; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; HR, heart rate; IQR, interquartile ratio; LOS, length of stay in ED (min); MAP, mean arterial pressure; RR, respiratory rate; sat, saturation; SBP, systolic blood pressure; T, temperature; UTS, urine toxicology screening.

[a]n = 7.

[b]n = 9.

[c]n = 51.

[d]n = 54.

[e]n = 57.

[f]n = 8.

[g]Statistical test used = Mann-Whitney *U* test.

[h]Statistical test used = independent samples *t* test.

[i]Statistical test used = Fisher's exact test.

Bold value indicates statistically significant.

**TABLE 3** Poisoning Severity Scores

| | Study group | | | | |
|---|---|---|---|---|---|
| No. (%) | 4-FA, N = 10 | MDMA, N = 59 | *P*-value* | Amphetamine, N = 10 | *P*-value* |
| None | 2 (20.0) | 2 (3.4) | 0.097 | 2 (20.0) | 1.000 |
| Minor | 3 (30.0) | 34 (57.6) | 0.170 | 8 (80.0) | 0.700 |
| Moderate | 1 (10.0) | 14 (23.7) | 0.442 | 0 | 1.000 |
| Severe | 4 (40.0) | 8 (13.6) | 0.064 | 0 | 0.087 |
| Fatal | 0 | 1 (1.7) | 1.000 | 0 | – |

Poisoning severity scores of 4-FA mono-intoxications in comparison to MDMA and amphetamine mono-intoxications, using $\chi^2$ and Fisher's exact tests. Categorical variables expressed as frequency (%).
*Fisher's exact *P*-values.

different results in this small number of patients, the results need to be judged carefully. Therefore, SRDU is preferably complemented by laboratory confirmation;[39,40] however, because 4-FA is not implemented in the UTS, self-reported use was the only viable method to determine 4-FA intoxication. UTS also has limitations with an overall percent agreement with ultra-performance liquid chromatography of 98.1% for amphetamine and a false–positive methamphetamine result for high urine concentrations of paramethoxymethamphetamine.[27,41] Nevertheless, 3 SRDU 4-FA patients tested positive for amphetamine, although no false–positive amphetamine or methamphetamine results were found with the Triage Tox Drug screen after 4-FA use in a previous study.[27] This could be explained by false–positive SRDU, drug contamination, or false–positive UTS results. Additionally, there is missing data regarding vital signs, especially low blood pressure, that could have skewed results. Another limitation is the small sample size of mono-intoxicated patients. Differences in PSS and vital parameters might have been more pronounced if the 4-FA study group would have been larger. Last, the effects of benzodiazepines, administered by medical personnel was not included in the study because prehospital administration and timing was unreliably reported, resulting in uncorrected possible early ED or pre–hospital-administered benzodiazepines effects. Although it is less likely, it is also possible that opioids were administered by ambulance personnel.

## 5 | DISCUSSION

The aim of this study was to explore the cardiovascular symptoms and complications observed in 4-FA-intoxicated ED patients and compare these to those observed in MDMA- and amphetamine-intoxicated patients. In total, 582 patients were included reporting intoxication with 4-FA (n = 44), MDMA (n = 449), or amphetamine (n = 137). 4-FA mono-intoxicated patients presented with headache more frequently compared to MDMA and amphetamine mono-intoxicated patients (80% vs 3.3% vs 0.0%, respectively; $P < 0.001$). They also showed a lower heartrate (81.5 ± 23.1 bpm vs 112.0 ± 22.3 bpm; $P = <0.010$ vs 103.0 ± 17.6 bpm; $P = 0.037$, respectively), higher systolic blood pressure (164 vs 139 mm Hg; $P = 0.031$ vs 135 mm Hg; $P = 0.033$, respectively), and the PSS suggested a non-significant association toward more serious complications. Other cardiovascular symptoms and complications related to 4-FA mono-intoxications were comparable to MDMA and amphetamine mono-intoxications. 4-FA-induced headache was described previously.[20,34] This might be contributable to a rapid rise in arterial blood pressure,[35,36] because all patients (n = 8) that presented with hypertension lacked hypertensive history. Most patients responded well to benzodiazepines and analgesics without additional standard antihypertensive treatment.[35] However, additional antihypertensive treatment might be indicated because 4-FA can induce severe hypertensive complications, like intracranial hemorrhage and Takotsubo cardiomyopathy, in concordance with previously described case reports.[22,23] Therefore, ED physicians should be aware of potential 4-FA-induced hypertension-related cardiovascular complications and the potential need for adequate antihypertensive treatment.

Besides hypertension, a significant lower heartrate was found in 4-FA-intoxicated patients compared to MDMA and amphetamine intoxication. This was unexpected because a sympaticomimetic effect would also cause tachycardia. One possible explanation could be that 4-FA patients present with complaints other than sympaticomimetic effects (eg, headache).

The cardiovascular complications observed in 4-FA-intoxicated patients were in line with the complications reported by earlier studies[15,16,20,22,23] and comparable to the nature of complications observed in MDMA-intoxicated patients. Although the overall prevalence of complications was low, 4-FA intoxications (4/31, 12.9%) seemed to have a higher complication rate then MDMA (6/406, 1.5%) and amphetamine intoxications (2/100, 2.0%).

Three patients with self-reported 4-FA use that denied amphetamine use tested positive for amphetamine by UTS. This observation is in line with some previous studies showing that especially high concentrations of 4-FA in urine samples may cross-react with amphetamine in immunoassays, although overall immunoreactivity is poor.[11,26,27] Physicians must be aware of the lack of detection of 4-FA in UTS because UTS may result in undetected 4-FA intoxications in different emergency settings and consequent complications.[6]

An overall decrease of 4-FA intoxications has been observed since the Dutch 4-FA ban in 2017. This is in line with the decrease in 4-FA reported incidents from 15% in 2016 to 5% in 2018 in the Netherlands

and the decrease in its overall use in the EU.[8,19] Interestingly, more MDMA- and amphetamine-intoxicated patients presented at the ED after the ban, compared to before, suggesting that users might have changed their drug of choice.

In summary, 4-FA-intoxicated patients in the ED present with a significantly lower heart rate, higher systolic blood pressure, and more frequent headache, compared to MDMA and amphetamine. Other 4-FA intoxication-related ED symptoms, resemble MDMA- and amphetamine-related symptoms. Severe cardiovascular complications were observed, including hypertensive crisis (4-FA, amphetamine), transient atrial fibrillation (amphetamine), Takotsubo cardiomyopathy (4-FA), dilated cardiomyopathy (MDMA), intracranial hemorrhage (4-FA and MDMA), and OHCA (MDMA).

According to the PSS criteria, the majority of all included patients presented with minor (n = 349, 60.1%) and moderate intoxication (n = 163, 28.1%). Of the 10 mono-intoxicated 4-FA patients, 5 (50%) presented with a moderate or severe intoxication, compared to 22 (39%) of MDMA and none of the amphetamine mono-intoxicated patients (Table 3, suggesting a non-significant association toward more severe complications in 4-FA-intoxicated patients).

## AUTHOR CONTRIBUTIONS

F.M.J. Gresnigt, A. Snik, R.K. Riezebos, E.J.F. Franssen, D.W. de Lange conceived the study, designed the trial, supervised the conduct of the trial, and data collection. F.M.J. Gresnigt, A. Snik, J.W. Vanhommerig managed the data, including quality control. J.W. Vanhommerig provided statistical advice on study design and analyzed the data. F.M.J. Gresnigt, A. Snik drafted the manuscript, and all authors contributed substantially to its revision. F.M.J. Gresnigt takes responsibility for the paper as a whole.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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**How to cite this article:** Gresnigt FMJ, Snik A, Franssen EJF, Vanhommerig JW, de Lange DW, Riezebos RK. 4-Fluoroamphetamine (4-FA) intoxication results in exaggerated blood pressure effects compared to MDMA and amphetamine: A retrospective analysis. *JACEP Open*. 2022;3:e12813. https://doi.org/10.1002/emp2.12813

## APPENDIX A: Cut-off values and definitions

| Cut-off values vital parameters[40] | |
|---|---|
| Respiratory rate (RR) | 12–20/min |
| - Tachypnea | >20/min |
| - Bradypnea | <12/min |
| Blood oxygen saturation (sat) | 95%–100% |
| - Hypoxemia | <95% |
| Systolic blood pressure (SBP) | 90–140 mm Hg |
| - Hypertension | >140 mm Hg |
| - Hypotension | <90 mm Hg |
| Diastolic blood pressure (DBP) | 60–100 mm Hg |
| - Hypertension | >100 mm Hg |
| - Hypotension | <60 mm Hg |
| Mean arterial pressure (MAP) | 60–100 mm Hg |
| - Hypertension | >100 mm Hg |
| - Hypotension | <60 mm Hg |
| Heart rate (HR) | 60–100/min |
| - Tachycardia | >100/min |
| - Bradycardia | <60/min |
| Capillary refill time (CRT) | 0–2 s |
| - Prolonged | ≥ 3 s |
| Temperature (T) | 36–38.5°C |
| - Hyperthermia | >38.5°C |
| - Hypothermia | <36°C |

| Cut-off values laboratory results[41] | |
|---|---|
| Arterial blood gas | |
| pH | 7.35–7.45 |
| $pCO_2$ | 4.4–6.3 (kPa) |
| $pO_2$ | 10.0–13.3 (kPa) |
| Bicarbonate | 23–29 mmol/L |
| Base excess | (−3)–3 mmol/L |
| Saturation | 95–100 (%) |
| Lactate | 0.4–2.0 mmol/L |
| Hb | |
| - Male | 8.5–10.5 mmol/L |
| - Female | 7.5–10.0 mmol/L |
| Leucocytes | $4.0–10.5 \times 10^9$/L |
| Thrombocytes | $150–400 \times 10^9$/L |
| Creatinine | |
| - Male | 75–110 $\mu$mol/L |
| - Female | 65–95 $\mu$mol/L |
| Sodium | 135 - 145 mmol/L |
| Potassium | 3.5–4.5 mmol/L |
| Glucose | 4.1–5.6 mmol/L |
| Creatinine kinase | |
| - Male | <171 U/L |
| - Female | <145 U/L |
| CK-MB | <7 $\mu$g/L |
| Troponin-T | < 0.014 ug/L |
| (NT-pro)BNP[a] | |
| - Male | <86 ng/L |
| - Female | <130 ng/L |
| ALAT | |
| - Male | <45 U/L |
| - Female | <34 U/L |
| ASAT | <40 U/L |
| Gamma GT | |
| - Male | <60 U/L |
| - Female | <40 U/L |
| Ethanol | <0.1 $\mu$g/L |

| | |
|---|---|
| Laboratory tests | Laboratory tests of blood samples; included results:<br>• Arterial blood gas (pH, $pCO_2$, $pO_2$, bicarbonate, base excess, saturation, lactate)<br>• Hemoglobin<br>• Leucocytes<br>• Thrombocytes<br>• Creatinine<br>• Sodium<br>• Potassium<br>• Glucose<br>• Creatinine kinase<br>• CK-MB<br>• Troponin-T<br>• (NT-pro)BNP<br>• ALAT<br>• ASAT<br>• Gamma-GT<br>• Ethanol |
| Urine toxicology screening | Performed with the Triage TOX Drug Screen (Biosite, Bunnik, Netherlands), tests urine sample for following drugs:<br>• Amphetamine<br>• Barbiturates<br>• Benzodiazepines<br>• Cocaine<br>• Methadone<br>• Methamphetamine/XTC<br>• Opiates<br>• Phencyclidine<br>• Tetrahydrocannabinol (THC)<br>• Tricyclic anti-depressants |
| ECG | Performed in the ED and recorded in patient file; abnormalities included if described by ED physician or by re-assessing cardiologist<br>• Sinus tachycardia<br>• Sinus bradycardia<br>• Abnormal R-top progression<br>• Atrial fibrillation/flutter<br>• AV-block (1st, 2nd, 3rd degree)<br>• (incomplete) LBBB<br>• (incomplete) RBBB<br>• Inverted T-wave<br>• Left atrial enlargement<br>• Left ventricle hypertrophy<br>• Pathological Q-wave<br>• Prolonged QTc time<br>• ST-segment abnormalities<br>• U-wave<br>• Ventricular extrasystole<br>• Ventricle tachycardia<br>• Other abnormalities |

| | |
|---|---|
| Radiology exams | Performed at the ED and reported by radiologist or if unavailable ED physician<br>• Abdominal CT-scan<br>• Abdominal ultrasound<br>• Cervical spine CT-scan<br>• Chest x-ray<br>• Chest CT-scan<br>• Echocardiography<br>• Extremity x-ray<br>• Head CT-scan |
| Airway interventions | Interventions to assure patency of the airway, performed either pre-hospital or at the ED<br>• Removing foreign objects/suctioning<br>• Jaw-thrust/chin-lift<br>• Nasopharyngeal airway<br>• Oropharyngeal airway<br>• Endotracheal intubation<br>• Laryngeal mask/tube airway<br>• Cricothyroidotomy/tracheostomy<br>Including cervical spine interventions (ie, stabilization) |
| Breathing interventions | Interventions to assure adequate ventilation and gas exchange, performed either pre-hospital or at the ED<br>• Supplemental oxygen<br>• Nasal cannula/non-rebreathing mask/venturi-mask<br>• (Non-)invasive ventilation<br>• Chest tube |
| Circulation interventions | Interventions to assure adequate circulation, performed either pre-hospital or at the ED<br>• Tourniquet/clamping/pelvic stabilizing device<br>• Intravenous fluid therapy<br>• Blood transfusion<br>• Resuscitation |
| Disability interventions | Interventions to treat neurological deficits, performed either pre-hospital or at the ED<br>• Glucose administration<br>• Antidotes (ie, naloxone, flumazenil)<br>• Neurosurgery |
| Exposure interventions | Interventions performed during exposure assessment, performed either pre-hospital or at the ED<br>• Temperature management: active cooling (ie, undressing, cold infusions, ice-packs, ventilation)<br>• Temperature management: active warming up (ie, warm infusions, warm blankets, bear-hugger)<br>• Treatment of extremities (ie, sutures, wound care) |
| Observation | Watchful waiting at the ED |
| Medication | Administered medication during pre-hospital or during presentation at the ED including:<br>• Analgesics (paracetamol, NSAID, opioids)<br>• Anti-emetics<br>• Anti-epileptics<br>• Anti-hypertensives<br>• Anti-psychotics<br>• Benzodiazepines<br>• Nitroglycerin |
| Consulted specialty | Physician from another specialty consulted by ED physician to assess the patient, including cardiology, internal medicine, intensive care, neurology, psychiatry, or other |

Abbreviation: ED, emergency department.
[a]Age-dependent; lowest values displayed.