3-Methylmethcathinone (3-MMC) Poisonings: Acute Clinical Toxicity and Time Trend Between 2013 and 2021 in the Netherlands

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Study objective: The synthetic cathinone 3-methylmethcathinone (3-MMC, or metaphedrone) has recently gained popularity. We studied the numbers of 3-MMC poisonings over time and the clinical effects following poisonings with 3-MMC.

Methods: We performed a retrospective study on the numbers of self-reported 3-MMC poisonings to the Dutch Poisons Information Center (DPIC) from 2013 to June 2021. For poisonings reporting 3-MMC only, the symptoms were extracted and the Poisoning Severity Score (PSS) was determined. From 2016 to June 2019, a prospective cohort study on poisonings reporting only 3-MMC was performed, in which details on the clinical courses were collected through telephone interviews.

Results: From 2013 to June 2021, the DPIC was consulted on 184 3-MMC poisonings. The number of poisonings increased from 1 in 2013 to 70 in the first half of 2021. In 84 poisonings with only 3-MMC (46%), sympathomimetic symptoms were commonly reported, including tachycardia (n=29, 35%), hypertension (n=17, 20%), and agitation (n=16, 19%). The initial PSS was usually minor (n=37, 44%) to moderate (n=39, 46%). Five patients (6%) experienced severe effects, including 3 patients experienced severe hypertension (systolic blood pressure >180 mmHg; n=3) and nonfatal cardiac arrest (n=1). Sympathomimetic symptoms (n=8) were also reported in the prospective cohort study. The percentage of moderate poisonings increased (n=6, 75%), and 1 (13%) severe poisoning was observed. Analytical confirmation of 3-MMC exposure was performed in 2 cases.

Conclusion: The number of 3-MMC poisonings reported to the DPIC has increased over time. Most poisonings with 3-MMC resulted in moderate toxicity and involved sympathomimetic effects, while severe effects were observed in 5 cases. [Ann Emerg Med. 2022;80:203-212.]

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INTRODUCTION

Background

Synthetic cathinones are a popular class of new psychoactive substances.[1,2] These substances are structurally related to cathinone, an amphetamine-like sympathomimetic amine that naturally occurs in the leaves of the *Catha edulis* plant, which is known as khat.[3] Up to 2021, more than 150 unique synthetic cathinones were monitored in Europe.[1] Although synthetic cathinones were initially considered legal alternatives for classical recreational drugs, several of these substances are now under international regulatory control. This includes the popular synthetic cathinone 4-methylmethcathinone (4-MMC, or mephedrone) that exerts effects comparable to those of amphetamine and 3,4-methylenedioxymethamphetamine (MDMA).[4] Multiple severe and fatal 4-MMC poisonings led to a European ban in 2010.[5,6] Its structural analog 3-methylmethcathinone (3-MMC, or metaphedrone) has been available on the drug market since 2012 and has gained popularity as a substitute for 4-MMC.[6,7] Currently, the legal status of 3-MMC varies; in many European countries, the United States, and China, it has been a controlled substance for several years now.[6,8] In contrast, 3-MMC was banned only recently in the Netherlands,[9] while in other countries, it is legally and easily available online or in headshops.

Data on the prevalence of 3-MMC use are scarce.[10,11] Among Dutch citizens who attend dance parties ("clubbers"), the popularity of 3-MMC has recently

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Editor's Capsule Summary

What is already known on this topic

Misuse of the amphetamine-like synthetic cathinone 3-methylmethcathinone (3-MMC) is rising. Its medical effects only partially known.

What question this study addressed

The authors describe the effects of 3-MMC with retrospective and prospective cohorts from the Netherlands.

What this study adds to our knowledge

The number of 3-MMC poisonings increased from 1 in 2013 to 70 in just the first half of 2021. In 84 poisonings reporting use of 3-MMC only, sympathomimetic symptoms were commonly reported including tachycardia, hypertension, and agitation. Five patients (6%) experienced severe effects, including severe hypertension and nonfatal cardiac arrest.

How this is relevant to clinical practice

Emergency physicians should be alert to synthetic cathinone poisoning like 3-MMC. Currently, evidence suggests this group can be treated similarly to other sympathomimetic drugs.

increased. In 2020, 9% of Dutch clubbers reported having used 3-MMC in the previous year. With a reported lifetime use of 11% in the same population, this is indicative of recent first time 3-MMC use.[12] The published literature on the adverse health effects of 3-MMC exposure is largely limited to case reports.[6,7,11,13] Reported symptoms after 3-MMC exposure include agitation, hallucinations, tachycardia, palpations, hypertension, and hyperthermia.[6,8] These adverse effects are in line with those of 4-MMC and MDMA although the effects of 3-MMC seem to be less intense and shorter lasting. Therefore, the repeated administration of 3-MMC in a single session is common, and this may increase the risk of overdose.[14] As most case reports have involved concomitant exposures to other recreational drugs, the contribution of 3-MMC to the observed clinical course is unclear.[6,7] While several 3-MMC–related fatalities have been described in literature, clinical data on both fatal and nonfatal poisonings with only 3-MMC are lacking.[6,13,15]

Goals of This Investigation

We studied the numbers of 3-MMC poisonings reported to the Dutch Poisons Information Center (DPIC) over time, and we assessed the clinical effects following 3-MMC–only poisoning in a large sample of patients.

METHODS

Study Design and Setting

The DPIC provides a 24/7 telephone service for the management of acute poisonings, to health care professionals only, serving the entire Dutch population of 17.5 million. During every telephone consultation, an electronic case report form (eCRF) is completed and stored in the center's database. Anonymous data are routinely collected on patient (eg, age and gender) and exposure characteristics (eg, substance[s], reason for exposure) as well as on toxicity (symptoms present before or during the inquiry). The exposure data in the DPIC database generally lack analytical confirmation and are based on patient self-reports. This study consisted of 2 parts: (1) a retrospective analysis of eCRFs on 3-MMC exposures stored in the DPIC database from January 2013 to June 2021 (8.5 years) and (2) a prospective cohort study on 3-MMC–only exposures reported to the DPIC from January 2016 to June 2019 (3.5 years), as described previously.[16]

The accredited Medical Research Ethics Committee of the University Medical Center Utrecht decided that the Dutch Medical Research Involving Human Subjects Act did not apply to the prospective cohort study.

Selection of Participants

Retrospective analysis of eCRFs (January 2013 to June 2021). A database query was performed for all inquiries logged as human 3-MMC poisonings from January 2013 to June 2021. All patients with 3-MMC poisoning who were identified in the database were included. To describe the acute clinical toxicity of 3-MMC, solely 3-MMC–only poisonings (those with no other reported relevant concomitant exposures) were included. Relevant concomitant exposures were defined as all other exposures reported by the patients to the health care providers, with the exception of exposures to therapeutic medications (recommended doses) and exposures to 2 or fewer standard units of alcohol.

Prospective cohort study (January 2016 to June 2019). Detailed information on the clinical course following 3-MMC–only poisoning was collected in a prospective cohort study from January 2016 to June 2019. Patients who reported 3-MMC exposure without relevant concomitant exposures for whom the DPIC was consulted in this time period were included, regardless of whether the exposures were analytically confirmed afterward. "Exposure" was defined as the actual or suspected contact

with any substance that had been ingested, inhaled, absorbed, applied to, or injected into the body. Not all exposures reported to poison control centers result in adverse effects.[17] Patients included in the prospective cohort study were also included in the retrospective analysis of eCRFs. At each first consultation, the DPIC provided information to the health care professional regarding the treatment of the patient. At that time, the patient's identity was unknown to the DPIC. Subsequently, the DPIC requested the participation of the physician in a follow-up telephone interview. Furthermore, the patient was asked by their physician to participate. The physician provided the patient's contact information only if the patient was willing to participate. Informed consent was obtained by telephone and voice-recorded before the start of the interview with the patient, usually within 1 week after the poisoning. At that time, the patients were expected to be fully recovered.

Data Collection

Retrospective analysis of eCRFs. Anonymous data were collected from the eCRFs, including data on patient characteristics (eg, age, gender, body weight), 3-MMC exposure characteristics (eg, route of administration, dose), and symptoms reported during the DPIC consultations.

Prospective cohort study. For patients included in the prospective cohort study, we tried to collect additional data on the entire clinical course of poisoning. Only poisonings in which the physician or patient agreed to participate could be followed up to a known outcome. Additional information on 3-MMC exposure characteristics (eg, formulation, reason of exposure), clinical course (eg, symptoms, vital signs, laboratory results), and treatment (eg, hospitalization, therapy) was collected during voice-recorded telephone interviews with the physician and/or the patient. Standardized questionnaires that were tailored to the physicians or patients (translated questionnaires in Appendix E1 of Hondebrink et al,[16] https://www.annemergmed.com/article/S0196-0644(17)31382-3/) were used. Trained DPIC staff conducted the telephone interviews and completed the questionnaires. We aimed to conduct each interview within 1 week after the poisoning.

Analysis of Biological Samples

During the prospective cohort study, we aimed for the analytical confirmation of 3-MMC exposure from biological samples for all included patients. To achieve this, the physicians were asked whether any leftover blood or urine samples collected for diagnostic procedures during treatment were available. The leftover samples were sent to the Dutch National Institute for Public Health and the Environment and stored at −20 °C until analysis. The analysis was aimed at the detection of prescription drugs and recreational drugs. First, a general screening was performed, using ultraperformance liquid chromatography quadrupole time-of-flight mass spectrometry. After the screening, the identity of 3-MMC and absence of 4-MMC were confirmed by an ultraperformance liquid chromatography triple-quadruple mass spectrometry analysis. The identity was confirmed using a reference standard of 3-MMC. Until 2018, 3-MMC and 4-MMC could not be differentiated.

Outcomes

The primary outcome was the severity of 3-MMC poisoning. The severity of poisoning was graded using the Poisoning Severity Score (PSS). The PSS is a scoring system that classifies the severity of poisoning in a standardized manner, including 5 severity grades (none, minor, moderate, severe, and fatal). A more elaborate description of the PSS can be found in the original publication.[18] The secondary outcomes were the annual numbers of 3-MMC poisonings reported to the DPIC from 2013 to 2021, patient characteristics, and exposure characteristics.

Data Analysis

Data from the retrospective analysis of eCRFs were entered in IBM SPSS Statistics version 26 (IBM) based on the DPIC database query (Product name "3-MMC," start date "01-01-2013," end date "06-30-2021," "human only"). Data from the interviews of the prospective cohort study were entered in IBM SPSS Statistics based on the questionnaires completed by trained DPIC staff. Before the data analysis with IBM SPSS Statistics, all identifiable data were omitted.

Descriptive statistics were used to summarize the patient characteristics (eg, age, gender), 3-MMC exposure characteristics (eg, route of administration, dose), clinical courses (eg, symptoms), and treatment (eg, hospitalization, therapy) of patients with 3-MMC–only poisoning. Categorical variables were assessed using frequencies and percentages. Medians with the 25th and 75th percentiles (interquartile range [IQR]) and full ranges were calculated for continuous variables. A Mann-Whitney *U* test was used to compare the median ages of patients who snorted or ingested 3-MMC and patients who injected 3-MMC.

The severity of poisoning was graded using the PSS.[18] An initial PSS was determined for every patient based on the symptoms reported during the DPIC consultation. For each patient with follow-up (in the prospective cohort study), a second PSS was determined based on the known clinical outcome (symptoms reported during the telephone interview). The PSS grading was performed individually by

2 investigators using anonymized data on the clinical effects. Subsequently, the results were discussed until a consensus was reached. The interrater agreement on the initial PSS between the 2 raters corresponded in 87% of cases, and good interrater agreement was demonstrated (Cohen κ=0.781).

RESULTS

Retrospective Analysis of eCRFs (January 2013 to June 2021)

Epidemiology. In total, 184 poisonings with 3-MMC (with and without relevant concomitant exposures) were reported to the DPIC from January 2013 to June 2021. The annual numbers of 3-MMC poisonings increased from 1 in 2013 to 63 in 2020 (Figure 1). The majority (n=158, 86%) of the 3-MMC poisonings were reported after 2018, with 70 poisonings reported during the first half of 2021.

Characteristics of study subjects (3-MMC–only poisonings). From January 2013 to June 2021, 84 acute 3-MMC–only poisonings were reported to the DPIC, mostly by general practitioners (including regional 24/7 GP services, n=33, 39%), paramedics (n=22, 26%), and emergency departments (n=19, 23%). Predominantly male patients were involved (n=63, 75%). The median age was 25 years (IQR 21 to 33 years; range 15 to 60 years). The most common routes of exposure to 3-MMC involved ingestion (n=31, 37%), snorting (n=22, 26%), and injection (n=16, 19%). Some patients (n=5, 6%) combined different routes of exposure in a single session, and rectal exposure was also reported (n=1, 1%). The routes of exposure were unknown for 9 patients (11%). The median age was significantly lower in patients who ingested or snorted 3-MMC (median 23 years; IQR 20 to 30 years; range 15 to 54 years) than in patients who injected 3-MMC (median 40 years; IQR 32 to 43 years; range 25 to 60 years; $P<.001$). The 3-MMC was used as a powder (n=29, 35%), a liquid (n=19, 23%), and as a tablet/capsule (n=10, 12%); the 3-MMC formulations were not specified for 26 patients (31%). The median self-reported estimated dose per session was 1,000 mg (IQR 500 to 2,500 mg; range 0.3 to 6,000 mg; n=36). For 3 patients, potential 3-MMC addiction, as assessed by their physician, was reported during the initial DPIC consultation.

Clinical effects reported during initial DPIC consultations (3-MMC–only poisonings). During the initial DPIC consultations, sympathomimetic effects, including tachycardia (n=29, 35%), hypertension (n=17, 20%), and agitation (n=16, 19%), were frequently reported (Table 1). The initial PSSs (based on the information provided during the initial DPIC consultations) were minor (n=37, 44%) to moderate (n=39, 46%) in the majority of patients (Table 1). Five patients (6%) had severe poisoning during their initial consultations, based on the presence of severe hypertension (systolic blood pressure more than 180 mm Hg; n=3), repeated convulsions (n=1), or ventricular fibrillation followed by cardiac arrest (n=1; Table 2, patient 9).

Prospective Cohort Study (January 2016 to June 2019)

Inclusions. From January 2016 to June 2019, 16 patients reporting 3-MMC–only poisoning were included in the prospective cohort study, of whom 8 were followed up and 8 were lost to follow-up (Figure 2). The main reasons for loss to follow-up were (1) unwillingness to participate (n=2, 25%) and (2) inability to reach the

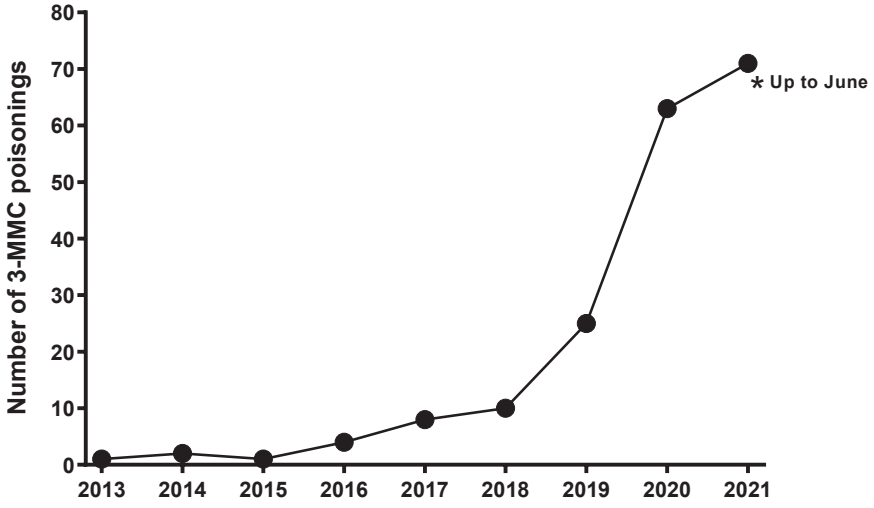

Figure 1. Numbers of 3-MMC poisonings reported to the DPIC from January 2013 to June 2021. *Only the number of 3-MMC poisonings in the first half of the year (up to and including June) is included for 2021.

Table 1. Acute clinical toxicity during 3-MMC–only poisoning reported to the DPIC.

	2013–2021		Cohort study: 2016–2019	
	All patients*: based on consultation, n=84		Patients with follow-up: based on interviews, n=8	
	N	(%)	n	%
Symptoms present	81	(96)	8	(100)
PSS				
None	3	(4)	0	(0)
Minor	37	(44)	1	(13)
Moderate	39	(46)	6	(75)
Severe	5	(6)	1	(13)
Cardiovascular†				
Tachycardia	29	(35)	5	(63)
Hypertension	17	(20)	4	(50)
Chest pain	15	(18)	4	(50)
Palpitations	14	(17)	2	(25)
ECG abnormalities	3	(4)	2	(25)
Cardiac arrest	1	(1)	0	(0)
Neurologic‡				
Muscular effects	7	(8)	3	(38)
Drowsiness	7	(8)	3	(38)
Headache	5	(6)	2	(25)
Convulsions	4	(5)	0	(0)
Dizziness	4	(5)	2	(25)
Insomnia	3	(4)	2	(25)
Psychotropic				
Agitation	16	(19)	6	(75)
Anxiety	10	(12)	3	(38)
Hallucinations	5	(6)	1	(13)
Confusion	1	(1)	3	(38)
Other§				
Gastrointestinal distress	11	(13)	3	(38)
Perspiration	6	(7)	4	(50)
Hyperthermia	4	(5)	3	(38)
Dyspnea	4	(5)	3	(38)
Tachypnea	1	(1)	3	(38)
Dry mouth/throat/nose	2	(2)	4	(50)

*"All patients" refers to all 3-MMC–only poisonings reported to the DPIC between January 2013 and June 2021 and includes patients with follow-up.
†Tachycardia: heart rate more than 100 beats/min; hypertension: systolic blood pressure more than 140 mm Hg.
‡Muscular effects include muscle twitching/spams, myalgia, and jaw clenching.
§Gastrointestinal distress includes abdominal pain, nausea, and vomiting; hyperthermia: body temperature more than 37.5 °C/99.5 °F; tachypnea: respiratory rate more than 20 breaths/min.

physician or the patient (n=4, 50%). The interviews were performed approximately 1 week after poisoning (median 7 days; IQR 3 to 11 days; range 1 to 18 days).

Characteristics of study subjects (3-MMC–only poisonings). All followed-up patients were men (n=8, 100%), with a median age of 21 years (IQR 19 to 44 years; range 18 to 60 years). The reported routes of exposure were injection (n=4, 50%), ingestion (n=3, 38%), and snorting (n=1, 13%). 3-MMC was used as a liquid (n=5, 63%), a powder (n=2, 25%), and as a tablet/capsule (n=1, 13%). Four patients (50%) administered 3-MMC at multiple time points during a

Table 2. Clinical outcomes of 3-MMC–only poisonings, in order of PSS.

No.	Clinical outcome	Treatment	Reported exposure(s)	Measured exposure	PSS
		Prospective cohort study			
1*	Agitation, anxiety, chest pain, tachycardia (HR 123 bpm), ECG abnormalities (prolonged QRS [110 ms] and prolonged QTc [474 ms]), hypertension (BP 210/142 mm Hg), tachypnea (RR 40 /min), perspiration, dry mouth/throat/nose, mydriasis. Laboratory: increased pH (7.59, minor), decreased calcium (1.20 mmol/L), increased GGT (71 U/L).	Presented to ED, benzodiazepine.	4500 mg 3-MMC (liquid) injection.	Blood: positive for 3-MMC (172 ng/ml).	Severe
2*	Agitation, confusion, chest pain, tachycardia (HR 150 bpm), hypertension (BP 144/99 mm Hg), tachypnea (RR 21 /min), perspiration, bruxism, phlebitis. Laboratory: increased ASAT (58 U/L, minor), increased ALAT (65 U/L, minor), increased GGT (123 U/L).	Presented to ED, admitted to general medical ward (>5 days), benzodiazepine.	1000 mg 3-MMC (liquid) injection.	X	Moderate
3	Agitation, anxiety, confusion, dizziness, amnesia, drowsiness, insomnia, hyperthermia (exact body temperature unknown), palpitations, tachycardia (exact HR unknown), tachypnea (exact RR unknown), dyspnea, anorexia, myalgia, paresthesia, jaw clenching, perspiration, dry mouth/throat/nose.	Presented to ED.	Unknown amount of 3-MMC (liquid) injection.	X	Moderate
4	Hyperthermia (38.6°C/101.5°F), tachycardia (HR 109 bpm), extravasation, infection, and pain at injection site. Laboratory: decreased sodium (132 mmol/L).	Presented to ED, admitted to nursing ward (4 days), amoxicillin/clavulanic acid.	Unknown amount of 3-MMC (liquid) injection.	X	Moderate
5	Agitation, anxiety, chest pain, hypertension (exact BP unknown), red skin, mydriasis.	Presented to ED.	330 mg 3-MMC (powder) ingestion.	X	Moderate
6	Agitation, hallucinations, headache, dizziness, drowsiness, insomnia, hyperthermia (37.6°C/99.7°F), dyspnea, anorexia, muscle twitching/spasms, tremor, paresthesia, paralysis of arm, swollen/cold arm, pale skin, dry mouth/throat/nose. Laboratory: increased CK (357 U/L, minor).	Presented to ED, admitted to medium care unit (<24 hours), benzodiazepine, paracetamol.	2500 mg 3-MMC (capsules) ingestion.	Blood: positive for 3-MMC or 4-MMC (discrimination was impossible).	Moderate
7‡	Confusion, headache, dizziness, amnesia, drowsiness, fainting, palpitations, chest pain, ECG abnormalities (prolonged QRS [105 ms], prolonged QTc [460 ms], early repolarization), hypertension (BP 145/82 mm Hg), dyspnea, nausea, anorexia, muscle twitching/spasms, jaw clenching, tongue bite, perspiration, pale skin, blue lips, dry mouth/throat/nose, miosis. Laboratory: decreased O_2 saturation (92%), decreased phosphate (0.54 mmol/L).	Presented to ED, admitted to medium care unit (<24 hours), nitroglycerine (intravenous).	Unknown amount of 3-MMC (liquid) ingestion.	Blood: negative for 3-MMC, positive for 4-fluoroamphetamine.	Moderate

Table 2. Continued.

No.	Clinical outcome	Treatment	Reported exposure(s)	Measured exposure	PSS
8	Agitation, tachycardia (exact HR unknown).	Presented to ED.	Unknown amount of 3-MMC (powder) snorting.	X	Minor
		Follow-up outside timeframe prospective cohort study			
9	Agitation, hyperthermia (38.3 °C/100.9 °F), tachycardia (HR 120 bpm), ventricular fibrillation, cardiac arrest in the ambulance. Laboratory: increased CK (280 U/L, minor).	Presented to ED, admitted to intensive care unit, resuscitated, sedated (midazolam), intubated.	Unknown amount of 3-MMC (powder), unknown route of exposure, unknown amount of alcohol.	Blood: positive for 3-MMC and caffeine.†	Severe

BP, blood pressure; ED, emergency department; HR, heart rate; bpm, beats per minute; min, minute; RR, respiratory rate.
All patients were adult men. After the prospective cohort study was finalized, the DPIC continued to try to obtain outcome information of severe 3-MMC poisonings reported to the DPIC. The outcome of 1 patient was obtained from the consulting physician after completion of the prospective cohort study (patient 9).
Laboratory results were graded according to the Poisoning Severity Score (PSS).
*This concerns the same patient, involving 2 separate poisonings.
†Qualitative analyses were performed by the hospital where the patient was admitted using liquid chromatography-mass spectrometry.
‡Patient was included in the prospective cohort study as the patient fulfilled the inclusion criteria (ie, patients who reported 3-MMC exposure without relevant concomitant exposures on whom the DPIC was consulted were included).

single session of several hours. Four patients (50%) reported a dose per session, resulting in an estimated median dose of 1,750 mg (IQR 665 to 3,500 mg; range 330 to 4,500 mg). The patients who injected 3-MMC used it for sexual stimulation (n=2, 50%), to reduce stress (n=1, 25%), and for unknown reasons (n=1, 25%). In contrast, the patients who ingested or snorted 3-MMC used it for recreational purposes (n=3, 75%) and to reduce stress (n=1, 25%). The 3-MMC was mostly used at (friends') homes (n=5, 63%). The majority of patients (n=6, 75%) reported having used 3-MMC before.

Clinical course of 3-MMC poisoning (3-MMC–only poisonings). The follow-up data showed that all patients with 3-MMC–only poisoning (n=8, 100%) experienced symptoms. Sympathomimetic symptoms, including tachycardia (n=5, 63%), hypertension (n=4, 50%), chest pain (n=4, 50%), agitation (n=6, 75%), and perspiration (n=4, 50%) were frequently reported (Table 1). A detailed description of the clinical course for each patient is provided in Table 2. The PSSs based on follow-up data were moderate for most patients (n=6, 75%). Severe poisoning, characterized by the presence of severe hypertension (systolic blood pressure 210 mm Hg), occurred in 1 patient (13%). The 3-MMC was detected in a blood sample from this patient (Table 2, patient 1).

All patients (n=8, 100%) presented to the emergency department (ED), and 4 (50%) were admitted to the hospital (2 to a medium care unit, 2 to a nursing ward). Two patients were discharged within 24 hours after admission, and 2 patients were hospitalized longer because of local effects at the 3-MMC injection sites. Benzodiazepines were administered for 3 patients. Eventually, all patients recovered without sequelae.

In addition, outside the time frame of the prospective cohort study, follow-up data were obtained for a patient who had 3-MMC poisoning that was already severe upon the initial consultation with the DPIC. The 3-MMC was detected in a blood sample from this patient. The patient was resuscitated after ventricular fibrillation followed by cardiac arrest in the ambulance, then sedated, intubated, and admitted to an ICU. No underlying heart conditions that might have caused ventricular fibrillation were found. The patient recovered without sequelae (Table 2, patient 9).

LIMITATIONS

The main limitation of this study was the potential for selection bias. Regarding 3-MMC, the DPIC is mostly contacted about users who experience unexpected adverse effects specifically following recreational 3-MMC use, while this holds true for many other substances. It is likely that the users of 3-MMC for whom the DPIC was consulted experienced more severe adverse effects compared to all 3-MMC users. Therefore, the frequency of adverse effects reported are not representative of 3-MMC use in general. Furthermore, while the number of patients included in this study was large for a cohort with a specific NPS poisoning,

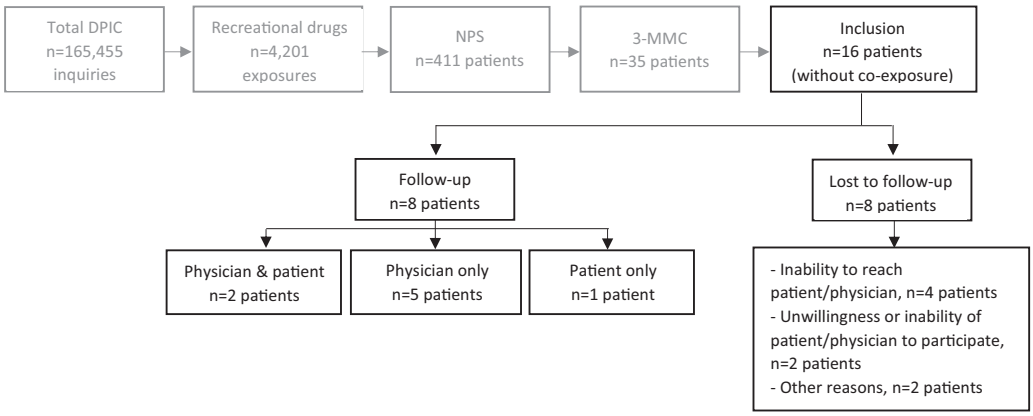

Figure 2. Flow chart of inclusions in the prospective cohort study on 3-MMC poisonings (January 2016 to June 2019). Relevant concomitant exposures were defined as all other exposures except for exposure to therapeutic medication (recommended dose) and 2 or fewer standard units of alcohol. DPIC: Dutch Poisons Information Center (DPIC); NPS: New Psychoactive Substances.

the number of patients with follow-up was small. Although information on symptoms during initial DPIC consultation provides clinical information that is currently lacking in literature, the final clinical outcomes remain unknown for the majority of 3-MMC poisonings, and late-onset severe adverse effects cannot be excluded for these patients. For the inclusion of patients, we relied on self-reported exposures to 3-MMC and other concomitant relevant exposures, as discussed above. Self-reports may possibly result in misclassification. In addition, biological samples were not available for most patients; therefore, we were unable to analytically confirm 3-MMC exposure in those patients. Obtaining biological samples is accompanied by several difficulties. As a National Poisons Information Center, we serve many different hospitals, but we lack direct patient contact and can only rely on consulting physicians for cooperation. Due to privacy laws like the General Data Protection Regulation, data sharing between health professionals has become increasingly difficult.[19-22] The degree of recall bias is expected to be low, because most interviews were performed within 1 week after poisoning.

DISCUSSION

Our study demonstrated a clear increase in the number of 3-MMC poisonings for which the DPIC was consulted, primarily during the past 2 years (2020 and 2021). Furthermore, we showed, in a relatively large cohort of 84 3-MMC–only poisonings, that the majority of patients presented with moderate (46%) to severe (6%) poisoning. In a smaller cohort of 8 patients with 3-MMC–only poisoning with known clinical outcomes, a higher percentage of patients (88%) developed moderate-to-severe poisoning compared with the entire study population. This indicates the importance of follow-up to establish the actual severity of poisoning.[18]

The rise in the number of 3-MMC poisonings that we observed from 2013 to 2021 is indicative of the increased use of 3-MMC in the Netherlands.[12] This increased use was probably facilitated by the easy (online) and legal accessibility of 3-MMC in the Netherlands during the study period (3-MMC was banned in the Netherlands in October 2021).[9] A strong increase in the number of 3-MMC poisonings was observed in 2020 and the first half of 2021. This may have been influenced by the COVID-19 pandemic due to changes in drug use behaviors, such as the home use of recreational drugs ordered online.[1,23]

3-MMC inhibits the transporters of norepinephrine (NET), dopamine (DAT), and, to a lesser degree, serotonin (SERT).[6,24] As a consequence, the concentrations of these neurotransmitters increase and lead to sympathomimetic effects comparable to those seen with other recreational stimulant drugs (like MDMA and 4-MMC).[6] This is in line with our observations; in our study, the effects reported during self-reported 3-MMC–only poisonings were consistent with a sympathomimetic toxidrome, including tachycardia, hypertension, chest pain, agitation, hyperthermia, and perspiration. These observations are similar to those in other studies.[6,7] A comparable mechanism of action is described for the cathinone bupropion.[25] However, in contrast to 3-MMC, the misuse of this antidepressant is associated with a higher incidence of seizures (19.6%).[26,27] Notably, severe effects were reported occasionally in our study and have been reported previously for mixed 3-MMC poisonings.[6] So far, no fatal 3-MMC–only poisonings have been reported to the DPIC, although a few isolated fatalities have been reported.[6,13,15]

Similar to most recreational drug poisonings, the ancient phrase "treat the patient, not the poison" also applies to the

treatment of patients with 3-MMC poisoning. Supportive care and the monitoring of vital signs are recommended for patients with (moderate or severe) 3-MMC poisoning, particularly the monitoring of heart rate, blood pressure, and body temperature. Additional diagnostics, including an ECG and measurements of serum electrolytes and glucose, should be performed in more severe cases or when a patient is hyperthermic. Benzodiazepines can be administered to treat agitation and seizures, and active cooling is indicated if hyperthermia occurs.[28,29] Regular drug screening assays, like urine screening with a fluorescence-based immunoassay, do not detect 4-MMC[30,31]; and thus likely also do not detect 3-MMC. To detect 3-MMC, advanced analytical analyses involving chromatographic techniques are required. Currently, only few hospitals in the Netherlands and likely in Europe, are able to qualify and, even rarer, quantify NPS.

Analytical confirmation from biological samples was lacking for the majority of the cases presented in this study, possibly resulting in the misclassification of cases. However, self-reported exposures to NPS seem to be quite reliable in the Netherlands.[16] Notably, the Dutch government generally does not prosecute individuals for the possession or use of small amounts of drugs (for personal use), even of controlled drugs, likely increasing the reliability of self-reported drug exposures.[32] Moreover, Dutch drug checking services reported that most (89%) drug samples that were offered for testing as 3-MMC during our study period also contained 3-MMC, further indicating the reliability of self-reported exposures for this specific NPS.[33]

Interestingly, 3-MMC was used through different routes of exposure by the patients in our study. Broadly, 2 distinct patient groups were identified in both our retrospective and prospective cohorts: (1) younger patients who used 3-MMC by ingestion or snorting and (2) older patients who used 3-MMC by injection. Although our study collected limited data on the context of 3-MMC use, younger patients likely used 3-MMC in a social, nonsexual context, while injecting 3-MMC seemed to be more common during "slamsex" parties among older patients.[6,34] Slamsex refers to the injection of psychoactive substances in a sexual context ("chemsex"), most prevalent among men who have sex with men.[34] We observed that patients who injected 3-MMC were mostly middle-aged men, and 50% of these patients mentioned sexual stimulation as the reason for use in the prospective cohort study. We also observed that the injection of 3-MMC carried additional risks of complications, like infections and extravasation, which often required treatment.

In our prospective cohort study, half of the patients administered 3-MMC at different time points in a single session. This is consistent with literature indicating that the repeated administration of 3-MMC in a single session is common, as the effect duration of 3-MMC is relatively short.[14] Importantly, the repeated administration of 3-MMC likely increases the risk of overdose due to higher blood concentrations.

In conclusion, self-reported 3-MMC–only poisonings are accompanied by significant sympathomimetic effects, resulting in moderate toxicity for the majority of patients. Therefore, most patients with self-reported 3-MMC–only poisoning may require clinical evaluation and/or hospitalization. The effects of 3-MMC poisoning seem to be short-lived (24 hours or shorter), although severe adverse effects and complications of injection can prolong hospitalization. The recent increase in self-reported 3-MMC poisonings along with the possibility of moderate to severe toxicity, is worrying. Data from poison control centers are valuable for the identification and risk profiling of new psychoactive substances.

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