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Significant toxicity following an increase in poisonings with designer benzodiazepines in the Netherlands between 2010 and 2020

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ABSTRACT

Background: Designer benzodiazepines (DBs) are an emerging class of new psychoactive substances. While structurally derived from pharmaceutical benzodiazepines, their toxicological profile is less clear. We investigated time trends in the rate of DB poisonings and their clinical toxicity.
Methods: A retrospective observational study was performed on the incidence rate of DB poisonings, relative to all recreational drug poisonings reported to the Dutch Poisons Information Center (DPIC) from 2010 to 2020. Time-trend analysis was performed using Poisson regression. A prospective cohort study was performed on toxicity of DBs, including the Poisoning Severity Score, from January 2016-June 2019. Data was collected through telephone interviews.
Results: Between 2010 and 2020, the DPIC was consulted on 142 DB exposures. The incidence rate of DB exposures increased from 0.1% to 4.3%, with a year effect estimate of 1.35 (95% CI [1.14;1.54]). Twenty different DBs were reported, mostly etizolam (33%), clonazolam (17%), and flunitrazolam (8%). During consultation (often shortly after exposure), poisoning was graded moderate-severe in 29% of cases (n = 146). In the prospective cohort sample with follow-up (n = 22), 86% of cases (n = 19) showed a moderate-severe poisoning. The severity of poisoning did not differ between mono- and mixed intoxications. Frequently reported symptoms in the prospective cohort sample included drowsiness (86%), confusion (59%), and agitation (55%). Coma was observed in seven cases (32%) and respiratory depression requiring mechanical ventilation in five cases (23%).
Conclusion: The rate of DB poisonings reported to the DPIC strongly increased from 2010 to 2020, indicating increased (ab)use of DBs. Most DB exposures resulted in moderate-severe toxicity with neurological effects.

1. Introduction

New psychoactive substances (NPS), also known as designer drugs, are synthesized to mimic the effects of common recreational drugs. Until 2021, around 830 NPS were notified to the European Monitoring Centre for Drugs and Drug addiction (EMCDDA) (EMCDDA, 2021a). Designer benzodiazepines (DBs) are a rapidly emerging class of NPS consisting of pharmaceutical benzodiazepine derivatives (Carpenter et al., 2019). Regulations for DBs differ among countries. Two categories of DBs can be identified. Firstly, DBs that were exclusively designed for recreational purposes, like diclazepam and flubromazolam. These substances are controlled in some countries but not (yet) in others. Secondly, DBs that were originally created as pharmaceuticals but were never approved for medical use or were withdrawn from the market in most countries, such as etizolam and phenazepam (Moosmann and Auwärter, 2018). Currently, the EMCDDA and the United Nations Office on Drugs and Crime (UNODC) monitor around 30 DBs, from both categories (EMCDDA, 2021a; UNODC, 2020).

Due to their addictive potential, pharmaceutical benzodiazepines are controlled in many countries. Moreover, restrictions apply to prescribing pharmaceutical benzodiazepines, resulting in decreased dispensing to patients (FDA, 2020; Guina and Merrill, 2018; Stichting Farmaceutische Kengetallen, 2020). Simultaneously, the use of DBs has increased (Carpenter et al., 2019; EMCDDA, 2021b). DBs can be easily

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purchased via the internet and on the black market (Moosmann and Auwärter, 2018). Common reasons for use include self-treatment of insomnia and recreational purposes. DBs are often combined with other recreational drugs to enhance the euphoric effects of stimulants, reduce unwanted side effects of stimulants and hallucinogens, and alleviate withdrawal of recreational drugs like opioids (Bäckberg et al., 2019; Shafi et al., 2020).

The basic chemical structures of DBs resemble those of pharmaceutical benzodiazepines (Moosmann and Auwärter, 2018). Pharmaceutical benzodiazepines are positive allosteric modulators of the $GABA_A$ receptor; they enhance the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) on this receptor resulting in depression of the central nervous system (CNS) (Moosmann and Auwärter, 2018). During overdose, this results in sedation, confusion, and in severe cases, coma (Bounds and Nelson, 2020).

While DBs have structural similarity to pharmaceutical benzodiazepines, their pharmacology and toxicology is less clear. This applies especially to the DBs designed for recreational purposes as these have not been tested (in humans) before introduction on the drug market. Few case reports describe their toxicology, and effects similar to those observed during pharmaceutical benzodiazepine poisonings (e.g. drowsiness) were reported. Moreover, atypical symptoms like agitation have been reported (Bäckberg et al., 2019; EMCDDA, 2021b; Łukasik--Głębocka et al., 2016; O'Connell et al., 2015). Fatal poisonings with DBs are rare and mostly involve mixed intoxications with other CNS depressants (Carpenter et al., 2019; EMCDDA, 2021b).

Although isolated health incidents with DBs are increasingly reported in literature, recent epidemiological studies on DB poisonings are lacking. Moreover, clinical toxicological data on DBs is limited to occasional case reports and self-reported experiences on drug user fora (Moosmann and Auwärter, 2018). Therefore, we studied (time) trends in poisonings with DBs reported to the Dutch Poisons Information Center (DPIC) between 2010 and 2020, and we prospectively assessed the clinical toxicity of DBs in a cohort of poisoned patients.

2. Methods

2.1. Study design and setting

The DPIC provides a continuously operated information service on the management of (suspected) poisonings to health care professionals. All telephone inquiries are recorded. During an inquiry, an electronic case report form is completed with anonymous data on the patient, exposure, and clinical characteristics, which is stored in the DPIC database. The DPIC relies on self-reported exposures and focusses on acute poisonings. No information on comorbidities is collected during inquiry. Since follow-up is not routinely performed, the outcome of most cases is unknown.

This study consisted of two parts: (1) a retrospective observational study analyzing DPIC inquiries on DB exposures from 2010 to 2020 and (2) a prospective cohort study from January 2016 to June 2019. The latter was carried out similar to the methods described by Hondebrink et al. (Hondebrink et al., 2018) and Nugteren-van Lonkhuyzen et al. (Nugteren-van Lonkhuyzen et al., 2020). In short, cases with a DB exposure for which the DPIC was consulted were included. Follow-up interviews were performed with the physician and/or patient to collect additional information. 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 this study.

2.2. Definition DBs

We defined DBs as benzodiazepines that are not registered as pharmaceuticals in the Netherlands (Table 1), including both benzodiazepines designed for recreational purposes and benzodiazepines registered as pharmaceuticals in other countries. Benzodiazepines registered as pharmaceuticals in the Netherlands are controlled by the Dutch Opium Law. Most DBs registered as pharmaceuticals in other countries, but not in the Netherlands, are also controlled by the Dutch Opium Law. However, DBs designed for recreational purposes are not controlled by the Dutch Opium Law (Table 1).

2.3. Participants

2.3.1. Retrospective observational study - analysis of inquiries (2010–2020)

The DPIC database was queried for cases with exposure to DBs from 2010 to 2020. Both mono- and mixed intoxications were included. Mixed intoxications involved cases with concomitant exposure to non-therapeutic medication, $>$ 2 standard units of alcohol, and other recreational drugs. One case may have $>$ 1 DB exposure since occasionally several variants were consumed. For time-trend analysis, the number of exposures was analyzed.

2.3.2. Prospective cohort study (January 2016-June 2019)

All cases with exposure to DBs for which the DPIC was consulted from January 2016 to June 2019 were included, also these with other concomitant exposure(s). Cases included in the prospective cohort study were also included in the retrospective observational study. At first consultation, information required for the treatment of the patient was provided and patient identity was unknown to the DPIC. Subsequently, the DPIC requested the participation of the physician in a follow-up interview by telephone. Furthermore, the patient was asked to participate by their physician. If a patient was willing to participate, the physician provided the patient's contact information. Informed consent was obtained orally and voice recorded before the interview with the patient.

2.3.3. Recidivists

Occasionally, the DPIC was called more than once about the same patient presenting with multiple DB poisonings on separate occasions (recidivist). Recidivists were identified based on geographic location, gender, age, weight, and DB exposure. As the DPIC does not collect patient identifiers (e.g. date of birth), it was not possible to identify recidivists with certainty. For the retrospective observational study, recidivists were included once in descriptive analysis of patient characteristics (e.g. age) using data from the first inquiry. To prevent bias, one exposure for each specific DB per unique patient was included in time-trend analysis and description of the incidence of specific DBs. Recidivists have inquiries on different DB exposures at different moments in time. Consequently, recidivists were included multiple times in descriptive analysis of other exposure characteristics (e.g. co-exposures) and clinical course (e.g. severity of poisoning); once for each case. A case refers to a unique poisoning event. For the prospective cohort study, the recidivists were also included once in descriptive analysis of patient characteristics. All cases with follow-up were included in the other analyses as well (Table 2). In the retrospective observational study, four recidivists were identified; one with 22 cases, one with four cases, one with three cases, and one with two cases. In the prospective cohort study, one recidivist with four cases was identified.

2.4. Data collection

2.4.1. Retrospective observational study - analysis of inquiries (2010–2020)

Anonymous data from the DPIC inquiries was collected for all cases reported from 2010 to 2020. From the case report form, information on patient characteristics (e.g. age, gender), exposure characteristics (e.g. specific DB, co-exposures), and clinical course (e.g. symptoms) was extracted.

Table 1
Overview of common designer benzodiazepines (DBs): legal status in the Netherlands and current registration as pharmaceutical outside the Netherlands.

DB	Listed as illegal in Dutch Opium Law (list II*)	Registered as pharmaceutical outside the Netherlands	Countries in which specific DB is registered as pharmaceutical
3-Hydroxyphenazepam	No	No	
Clonazolam[≠]	No	No	
Clotiazepam[±≠]	Yes	Yes	Belgium, Chile, France, Italy, Japan, Luxembourg, Spain.
Cloxazolam[≠]	Yes	Yes	Argentina, Australia, Belgium, Brazil, Germany, Japan, Luxembourg, Portugal, Switzerland, Taiwan.
Deschloroetizolam[≠]	No	No	
Diclazepam[≠]	No	No	
Estazolam[±≠]	Yes	Yes	Indonesia, Japan, the Philippines, Taiwan.
Etizolam[≠]	No	Yes	Australia, Germany, India, Italy, Japan.
Flualprazolam[≠]	No	No	
Flubromazepam[≠]	No	No	
Flubromazolam[≠]	No	No	
Flunitrazolam[≠]	No	No	
Meclonazepam[≠]	No	No	
Medazepam[±≠]	Yes	Yes	Bosnia & Herzegovina, Czech Republic, Germany, Hungary, Italy, Japan, Poland, Russia, Slovakia, Spain, Thailand, Turkey.
Metizolam	No	No	
Mexazolam[≠]	No	Yes	Japan, Portugal.
Nitemazepam	No	No	
Nordazepam[≠]	Yes	Yes	Italy, Luxembourg, Singapore, Taiwan.
Phenazepam[≠]	Yes	Yes	Russia.
Pinazepam[≠]	Yes	Yes	Hong Kong, Italy, Pakistan, Singapore, Thailand.
Pyrazolam[≠]	No	No	
Tetrazepam[±≠]	Yes	No	
Triazolam[±≠]	Yes	Yes	Italy, Sweden, United States.

*List II of the Dutch Opium Law lists "soft drugs" (e.g. cannabis) that are believed to have a lower health risk than "hard drugs" scheduled on list I (e.g. cocaine). Clonazolam, diclazepam, etizolam, flualprazolam, and flubromazolam were not listed as illegal at the time of data collection, but were placed on list II of the Dutch Opium Law on the 25th of October 2021.
[±] This DB was registered as pharmaceutical in several (other) countries, but was withdrawn from the market in these countries.
[≠] This DB was reported to the DPIC between 2010 and 2020.
Note: none of the listed DBs are registered as pharmaceutical in the Netherlands.

2.4.2. Prospective cohort study (January 2016-June 2019)

Additional data was collected by telephone interviews with physicians and patients using standardized questionnaires tailored to physicians and patients (translated questionnaires in the Supplemental material). Information on patient characteristics (e.g. age, gender), exposure characteristics (e.g. DB dose, co-exposures), clinical course (e.g. symptoms, vital signs, laboratory results), and treatment (e.g. hospitalization, therapy) was collected. The interviews were conducted by trained DPIC staff. We aimed to conduct the interviews within 1 week after consultation.

2.5. Outcome measures

The primary outcomes were the DB exposure incidence rate over 2010–2020 and the severity of poisoning after DB exposure. Secondary outcomes included patient and exposure characteristics.

2.6. Data analysis

DB exposure incidence rates were calculated by dividing the annual number of all DB exposures by the annual number of all recreational drug exposures (e.g. cocaine, cannabis, NPS) reported to the DPIC. Changes in the DB exposure incidence rate over time were studied using Poisson regression with the number of DB exposures as the outcome variable, the year as the predictor, and the number of recreational drug exposures as an offset variable. The offset variable was used to correct for bias due to fluctuations in the number of recreational drug exposures over time. Because there was an indication of overdispersion, robust standard errors were used (Hondebrink et al., 2020; Omari-Baah, 2018). The result of the Poisson regression is presented as an annual effect estimate (rate ratio) with a 95% confidence interval (CI). Additionally, the number of exposures to individual DBs was studied over time.

Descriptive statistics were used to summarize patient characteristics (e.g. age, gender), exposure characteristics (e.g. specific DB, co-exposures), clinical course (e.g. symptoms), and treatment (e.g. hospitalization, therapy). Exposure to standard therapeutic medication and $\leq$ 2 standard units of alcohol was not considered a concomitant exposure. The clinical course was only described for cases reported to the DPIC in the acute phase of exposure. Categorical variables were assessed using frequencies and percentages. Medians with the 25th and 75th percentiles were calculated for continuous variables.

The severity of poisoning was graded with the Poisoning Severity Score (PSS). The PSS is a standardized scheme for grading the severity of poisoning allowing a qualitative evaluation of morbidity and facilitating comparability of data. Severity is graded into five levels: none, minor, moderate, severe, and fatal (IPCS/EAPCCT, 2007; Persson et al., 1998). Although the PSS has limitations, it is one of few available tools to assess the severity of poisoning in a standardized way (Cairns and Buckley, 2017; Schwarz et al., 2017). A preliminary PSS was determined for every case based on symptoms reported during the inquiry. For cases with follow-up, a second PSS was determined based on symptoms reported during the interview. PSS grading was performed individually by two investigators using anonymized data on the clinical effects only. Subsequently, results were discussed until consensus was reached. Interrater agreement on the PSS was evaluated with Cohen's κ. The initial PSS between the two raters corresponded in 96% of cases and excellent interrater agreement was demonstrated (Cohen's κ 0.93). Fisher's exact tests were used to assess statistical differences in the PSS between mono- and mixed intoxications, for all cases based on the inquiry and for cases with follow-up based on the interview. Moreover, a Fisher's exact test was used to determine whether there was a difference in the occurrence of severe poisonings compared to minor-moderate poisonings based on the inquiry and based on the interview for cases with follow-up.

Statistical analysis was executed using IBM SPSS Statistics (version 26; IBM, Armonk, NY) and R (version 4.0.0). Before analysis, identifiable data was omitted.

Table 2
Overview of the inclusion of recidivists in the data analysis of designer benzodiazepines (DBs).

Data analysis	Retrospective analysis of inquiries (2010–2020)	Prospective cohort study (January 2016-June 2019)
Time-trend analysis	One exposure for each specific DB per unique patient, n = 142 exposures	–
Descriptive statistics		
Patient characteristics	Once for each unique patient, n = 122 patients	Once for each unique patient, n = 19 patients
Exposure characteristics: specific DB exposures reported	One exposure for each specific DB per unique patient, n = 142 exposures	Exposures of all cases with follow-up, n = 26 exposures
Exposure characteristics: other	All cases, n = 149 cases	All cases with follow-up, n = 22 cases
Caller	All cases, n = 149 cases	All cases with follow-up, n = 22 cases
Clinical course	All cases* , n = 146 cases	All cases with follow-up, n = 22 cases

*Three cases were excluded from the analysis of the clinical course as the Dutch Poisons Information Center (DPIC) was not contacted in the acute phase of exposure, but after the patients ceased chronic DB use.
Exposures, patients, and cases reported to the DPIC between 2010 and 2020 were included in the retrospective analysis of inquiries, so including exposures of patients, patients, and cases with follow-up.
The term 'case' refers to a unique poisoning event, so one patient can contribute with several cases.

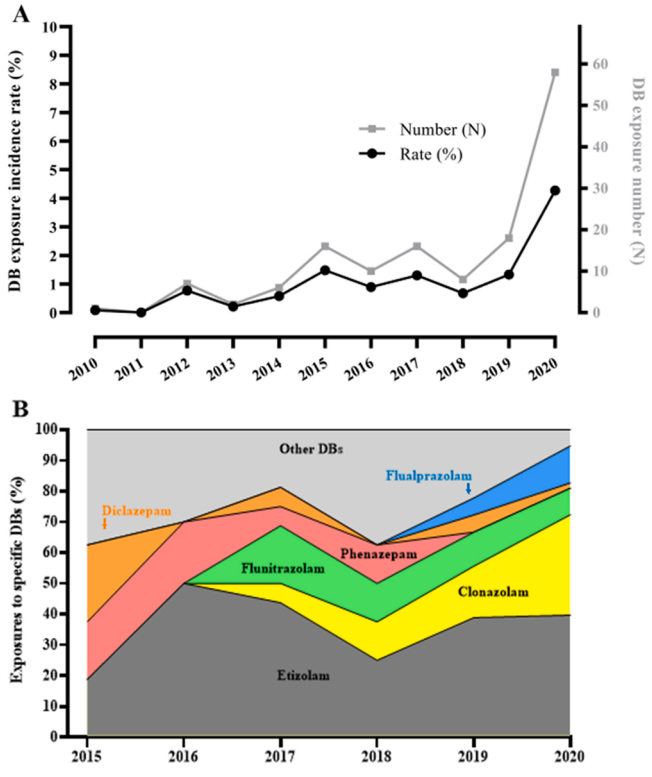

Fig. 1. Epidemiology of designer benzodiazepine (DB) exposures reported to the Dutch Poisons Information Center (DPIC). **A.** Incidence rate and number of DB exposures reported to the DPIC from 2010 to 2020. Incidence rates of DB exposures were calculated relative to all recreational drug exposures reported to the DPIC. **B.** Exposures to the most prevalent DBs reported to the DPIC between 2015 and 2020 in proportions. View online for color printing. Note: proportions were calculated per year, not per month. See Table S2 in the Supplementary material for a complete overview of the specific DBs reported to the DPIC between 2010 and 2020. One exposure for each specific DB per unique patient was included (Table 2).

Table 3
Specific designer benzodiazepine (DB) exposures reported to the Dutch Poisons Information Center (DPIC) between 2010 and 2020.

Specific DB	2010–2020 All exposures* , n = 142, n (%)	Cohort study: 2016–2019 Exposures of cases with follow-up¥, n = 26, n (%)
Etizolam	47 (33)	11 (42)
Clonazolam	24 (17)	3 (12)
Flunitrazolam	11 (8)	5 (19)
Phenazepam	10 (7)	2 (8)
Diclazepam	8 (6)	1 (4)
Flualprazolam	8 (6)	0 (0)
Nordazepam	7 (5)	0 (0)
Tetrazepam	5 (4)	0 (0)
Estazolam	4 (3)	0 (0)
Flubromazolam	4 (3)	3 (12)
Pyrazolam	2 (1)	1 (4)
Other (n = 1)	9 (6)	0 (0)
Unknown	3 (2)	0 (0)

Other DBs that were reported once included: clotiazepam, cloxazolam, deschloroetizolam, flubromazepam, meclonazepam, medazepam, mexazolam, pinazepam, and triazolam.
* All exposures refers to exposures reported to the DPIC between 2010 and 2020 of 122 unique patients, so including exposures of patients with follow-up (Table 2).
¥ Exposures of all 22 cases with follow-up were included, so including all exposures of the recidivist (19 unique patients; Table 2).

Table 4
Patient and exposure characteristics of patients/cases with a designer benzodiazepine (DB) exposure reported to the Dutch Poisons Information Center (DPIC) between 2010 and 2020.

Characteristic	2010–2020 All patients*, n = 122, n (%)	Cohort study: 2016–2019 Patients with follow-up, n = 19, n (%)
Gender		
Male	73 (60)	12 (63)
Female	49 (40)	7 (37)
Age, years		
≤ 12	2 (2)	0 (0)
13–17	10 (8)	0 (0)
18–34	80 (66)	18 (95)
≥ 35	22 (18)	1 (5)
Unknown	8 (7)	0 (0)
Characteristic	**All cases*±, n = 149, n (%)**	**Cases with follow-up±, n = 22, n (%)**
Number of DBs used		
1	131 (88)	19 (86)
≥ 2	17 (11)	3 (14)
Unknown	1 (1)	0 (0)
Co-exposure¥		
Medication	38 (26)	6 (27)
Alcohol	33 (22)	4 (18)
Recreational drugs	41 (28)	10 (45)
No co-exposure	66 (44)	7 (32)
Caller		
General practitioner	42 (28)	3 (14)
Ambulance	25 (17)	2 (9)
Emergency	32 (21)	4 (18)
department (ED)	10 (7)	3 (14)
Hospital (non-ED)	18 (12)	4 (18)
Psychiatry	22 (15)	6 (27)
Other/multiple callers		

*All patients/cases refers to unique patients/cases reported to the DPIC between 2010 and 2020, so including patients/cases with follow-up (Table 2).
± Due to recidivists, the number of cases is higher than the number of unique patients. Recidivists were incorporated with > 1 case (Table 2).
¥ Co-exposure did not include exposure to standard therapeutic medication and ≤ 2 units of alcohol.

3. Results

3.1. Retrospective observational study - analysis of inquiries (2010–2020)

3.1.1. Time-trend analysis

From 2010–2020, 142 DB exposures and 12,704 recreational drug exposures were reported to the DPIC. Around 10% of DB exposures were reported from 2010 to 2014, while the majority of exposures was reported from 2015 onwards. The DB exposure incidence rate increased from 0.1% in 2010 to 4.3% in 2020. The largest increase was observed between 2019 (1.3%) and 2020 (4.3%) (Fig. 1A). Poisson regression analysis showed a significant increase in the annual DB exposure incidence rate, with a year effect estimate (rate ratio) of 1.35 (95% CI [1.14;1.54]).

Exposures to 20 different DBs were reported to the DPIC. The most frequently reported DBs were etizolam (n = 47, 33%), clonazolam (n = 24, 17%), flunitrazolam (n = 11, 8%), phenazepam (n = 10, 7%), flualprazolam (n = 8, 6%), and diclazepam (n = 8, 6%) (Table 3). Nine different DBs were notified from 2010 to 2014, including nordazepam and phenazepam. From 2015 onwards, the number of reported variants increased to 16, including relatively new DBs like clonazolam and flualprazolam (Supplementary material; Table S1). The presence of specific DBs fluctuated over time (Fig. 1B). Etizolam was first reported in 2015, accounting for 20% of all DB exposures that year. From 2015 onwards, 25%− 50% of all DB exposures concerned etizolam. While clonazolam was first reported in 2017, it accounted for 33% of all DB exposures in 2020. Moreover, exposures to flunitrazolam and flualprazolam were first notified in 2017 and 2019 respectively and regularly reported since then (11% and 11% of all DB exposures), while phenazepam was only notified between 2015 and 2018.

3.1.2. Poisoning characteristics

From 2010–2020, a total of 149 cases involving 122 unique patients were reported to the DPIC. Most inquiries originated from general practitioners (n = 42, 28%) and emergency departments (n = 32, 21%, Table 4). More males than females were involved (n = 73, 60%). Only a minority of patients were < 18 years of age; most patients were aged between 18 and 34 years (n = 80, 66%; median: 25 years [p25-p75: 19–32 years]).

Exposure to > 1 DB was reported in 17 cases (11%), and other concomitant exposures were reported in 83 cases (56%, Table 4). In 41 cases (28%), DBs were combined with other recreational drugs, mostly involving other NPS, cannabis, and amphetamine (Table 4, Supplementary material; Table S2).

Nearly all cases concerned acute poisonings (n = 146), while three cases involved withdrawal symptoms after chronic DB use. During inquiry, adverse effects were reported in 124 cases (85%). Frequently reported adverse effects during inquiry included drowsiness (n = 91, 62%) and dysarthria (n = 21, 14%) in both mono- and mixed intoxications (Table 5). The PSS was graded as minor (n = 83, 57%) to moderate (n = 29, 20%) in the majority of cases (Table 5). Five mono-

Table 5
Clinical course after designer benzodiazepine (DB) exposure based on data collected during inquiries to the Dutch Poisons Information Center (DPIC) between 2010 and 2020 and during interviews in a prospective cohort study between 2016 and 2019.

	2010–2020		Cohort study: 2016–2019	
	All cases* : based on inquiries, n = 146		Cases with follow-up: based on interviews, n = 22	
	Mono-intoxications, n = 64, n (%)	Mixed intoxications, n = 82, n (%)	Mono-intoxications, n = 7, n (%)	Mixed intoxications, n = 15, n (%)
Symptoms present	52 (81)	72 (88)	7 (100)	15 (100)
PSS				
None	9 (14)	4 (5)	0 (0)	0 (0)
Minor	36 (56)	47 (57)	1 (14)	2 (13)
Moderate	12 (19)	17 (21)	3 (43)	6 (40)
Severe	5 (8)	8 (10)	3 (43)	7 (47)
Fatal	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	2 (3)	6 (7)	0 (0)	0 (0)
Central nervous system				
Drowsiness	41 (64)	50 (61)	7 (100)	12 (80)
Fainting/syncope	8 (13)	7 (9)	2 (29)	4 (27)
Coma	3 (5)	7 (9)	2 (29)	5 (33)
Dizziness	2 (3)	3 (4)	4 (57)	4 (27)
Headache	1 (2)	3 (4)	1 (14)	4 (27)
Amnesia	0 (0)	2 (2)	4 (57)	7 (47)
Dysarthria	9 (14)	12 (15)	5 (71)	2 (13)
Ataxia	3 (5)	5 (6)	1 (14)	3 (20)
Agitation	5 (8)	4 (5)	4 (57)	8 (53)
Confusion	3 (5)	4 (5)	5 (71)	8 (53)
Respiratory[±]				
Bradypnea	1 (2)	1 (1)	3 (43)	1 (7)
Tachypnea	0 (0)	1 (1)	0 (0)	3 (20)
Respiratory depression[≠]	1 (2)	6 (7)	1 (14)	4 (27)
Cardiovascular[¥]				
Bradycardia	2 (3)	3 (4)	2 (29)	2 (13)
Tachycardia	2 (3)	6 (7)	1 (14)	6 (40)
Hypotension	5 (8)	3 (4)	2 (29)	1 (7)
Hypertension	0 (0)	0 (0)	0 (0)	2 (13)
Other				
Vomiting	1 (2)	4 (5)	0 (0)	2 (13)

Cases with exposure to > 1 DB, standard therapeutic medication, and/or ≤ 2 units of alcohol were analyzed as mono-intoxications.
*All cases refers to unique cases reported to the DPIC between 2010 and 2020, so including cases with follow-up (Table 2). Three cases were excluded from the analysis of the clinical course as the DPIC was not contacted in the acute phase of exposure, but after the patients ceased chronic DB use.
[±] Bradypnea: respiratory rate < 12 breaths/min; tachypnea: respiratory rate > 20 breaths/min.
[≠] Requiring mechanical ventilation.
[¥] Bradycardia: heart rate < 60 beats/min; tachycardia: heart rate > 100 beats/min; hypotension: systolic blood pressure < 90 mm Hg and/or diastolic blood pressure < 60 mm Hg; hypertension: systolic blood pressure > 140 mm Hg.

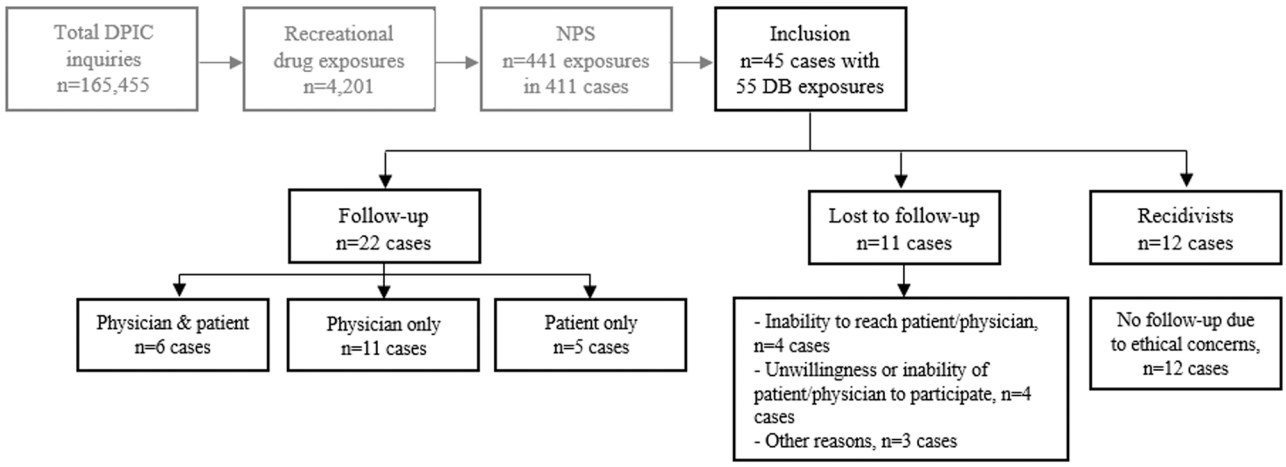

Fig. 2. Flow-chart of inclusion in the prospective cohort study. The total number of inquiries to the Dutch Poisons Information Center (DPIC) from January 2016 to June 2019 is shown, as well as the number of exposures to recreational drugs, new psychoactive substances (NPS) and designer benzodiazepines (DBs). Follow-up was obtained in 22 cases with 26 DB exposures involving 19 unique patients (4 cases of 1 patient; recidivist).

intoxications (8%) and eight mixed intoxications (10%) were graded as severe due to coma and/or respiratory depression requiring mechanical ventilation (n = 12, 92%) or pronounced bradycardia (n = 1, 8%). These included poisonings with clonazolam (n = 3, 23%), etizolam (n = 3, 23%), phenazepam (n = 2, 15%), tetrazepam (n = 2, 15%), diclazepam (n = 1, 8%), flubromazolam (n = 1, 8%), and a combination of cloxazolam and mexazolam (n = 1, 8%). The PSS did not differ between mono- and mixed intoxications (p = 0.332).

Withdrawal symptoms after chronic DB use were known in two out of three cases and involved convulsions after cessation of clonazolam and etizolam. Furthermore, sleeplessness was reported in one of the cases.

3.2. Prospective cohort study (January 2016-June 2019)

In total, 45 cases with 55 DB exposures were included in the prospective cohort study. Follow-up was obtained in 22 cases (49%) with 26 DB exposures involving 19 unique patients (Fig. 2). Interviews were conducted with the physician (n = 11), patient (n = 5), or both (n = 6; 12 interviews) with a median of six days after exposure (p25-p75: 4–12 days). Eleven cases (24%) were lost to follow-up. Furthermore, 12 cases (27%) were not followed-up because these involved recidivists (see 2.3.3.).

3.2.1. Patient and exposure characteristics

More males than females were involved (n = 12, 63%, Table 4). All 19 patients with follow-up were adults with a median age of 27 years (p25-p75: 25–30 years).

Exposure to > 1 DB was reported in three cases (14%), and other concomitant exposures were reported in 15 cases (68%), most often involving other recreational drugs (Table 4, Supplementary material; Table S2).

Most DB exposures involved etizolam (n = 11, 42%) and flunitrazolam (n = 5, 19%, Table 3). DBs were mainly used as tablets (n = 17, 65%), but liquids (n = 5, 19%), powders (n = 2, 8%), and blotters (n = 2, 8%) were also reported. Most exposures were oral (n = 24, 92%), including sublingual administration using blotters (n = 2, 8%). The reported dose of DBs differed substantially between the specific DBs (e.g. 100 mg for etizolam and 1–2 mg for flubromazolam were reported, Supplementary material; Table S3).

DB exposure was intentional in 20 cases (91%). DBs were used to sleep or reduce stress (n = 10, 45%), as a suicide attempt (n = 8, 36%), or for recreational purposes (n = 2, 9%). Two cases (9%) involved accidental exposure in which a DB was mistaken for GHB. Twelve out of nineteen patients (63%) reported having used DBs before, of whom ten (53%) used it daily or a few times a week. DBs were often bought on the internet (n = 14, 64%) or bought/received from family or friends (n = 4, 18%). Lastly, DBs were mostly used at (a friend's) home (n = 17, 77%).

3.2.2. Clinical course

Adverse effects were reported in all 22 cases during the interview. Drowsiness (n = 19, 86%), confusion (n = 13, 59%), and agitation (n = 12, 55%) were often reported in both mono- and mixed intoxications (Table 5). In mono-intoxications, bradypnea (n = 3, 43%) and bradycardia (n = 2, 29%) were regularly observed. Tachypnea (n = 3, 20%) and tachycardia (n = 6, 40%) were relatively often reported in mixed intoxications. Severe poisoning occurred in 10 cases (45%) (Table 5, Supplementary material; Table S4) characterized by the presence of coma and/or respiratory depression requiring mechanical ventilation (n = 8, 80%) and pronounced bradycardia (n = 2, 20%). These severe poisonings included poisonings with etizolam (n = 4, 40%), flubromazolam (n = 3, 30%), flunitrazolam (n = 2, 20%), and phenazepam (n = 1, 10%). Remarkably, severe adverse effects were observed in all three cases with exposure to flubromazolam, namely coma (n = 2, 67%) and pronounced bradycardia (n = 1, 33%). The PSS did not differ between mono- and mixed intoxications (p > 0.999). A detailed description of the clinical course of cases with follow-up is provided in the Supplementary material; Table S3.

In the majority of cases, the patient presented to an emergency department (n = 17, 77%). Subsequently, the patient was hospitalized in ten cases (45%) and admitted to an intensive care unit (ICU) in seven cases (32%). Hospitalization for ≥ 2 days was necessary in seven cases (32%) (median: 2 days [p25-p75: 1–3 days]). Treatment was mainly symptomatic, including mechanical ventilation (n = 5, 23%). Activated charcoal was given in two cases (9%). Furthermore, flumazenil was administered in two cases (9%). In one of these cases, the patient who was exposed to flubromazolam, alcohol, and possibly GHB, regained consciousness after administration of flumazenil but quickly relapsed. The effect of flumazenil was unknown in the other case.

4. Discussion

Our study demonstrated a strong increase in the incidence rate of DB poisonings reported to the DPIC from 2010 onwards, especially in 2020. The majority of poisonings with a known clinical outcome were graded moderate to severe (86%), due to CNS depression.

The increase in DB poisonings can indicate an increased (ab)use of

DBs in the Netherlands, in line with reports from other countries (Bäckberg et al., 2019; Carpenter et al., 2019). Restraints on prescriptions of pharmaceutical benzodiazepines by physicians (FDA, 2020; Guina and Merrill, 2018; Stichting Farmaceutische Kengetallen, 2020) may have contributed to this. Furthermore, use of DBs is facilitated by their easy (online) accessibility and the wide range of available variants, especially in recent years (EMCDDA, 2021b). A strong increase in DB poisonings was observed in 2020, which might have been (partially) influenced by COVID-19 pandemic-related mental health issues (EMCDDA, 2021).

In this study, the severity of poisoning did not differ between mono- and mixed intoxications, both based on symptoms reported during inquiry and during follow-up interview. In contrast, literature has indicated that DB poisonings are more severe when patients are concomitantly exposed to other substances (Zawilska and Wojcieszak, 2019). This discrepancy may be explained by selection bias as the DPIC is mainly contacted about DB users with adverse effects.

Of the cases with follow-up with a severe poisoning (45%), only half were also severe during the inquiry (18%, Supplementary material; Table S4), indicating the importance of follow-up and application of the PSS in its intended manner (i.e. with follow-up, Persson et al., 1998). Like expected, the PSS based on symptoms reported during the inquiry underestimates the severity of poisoning (Supplementary material; Table S4).

No conclusions can be drawn on the relative toxicity of different variants of DBs. Severe poisonings occurred after exposure to different DBs. Remarkably, all flubromazolam exposures with follow-up resulted in severe poisonings although flubromazolam was only involved in three cases. The dose of flubromazolam was known in two cases, in which the patients used sevenfold a 'normal' recreational dose. However, >100 times a 'normal' recreational dose was reported in cases with exposure to other DBs, which did not result in severe poisonings (Supplementary material; Table S3) (TripSit, 2021).

After DB exposure, mainly neurological effects were observed. Many adverse effects are part of the sedative-hypnotic toxidrome, which includes drowsiness, coma, dysarthria, ataxia, confusion, bradycardia, hypotension, and bradypnea. These effects are likely caused by the positive allosteric effects on the $GABA_A$ receptor and are comparable with effects observed after pharmaceutical benzodiazepine exposure (Kang et al., 2021). In accordance with previous findings, paradoxical symptoms such as agitation and tachycardia were also reported (Łukasik-Głębocka et al., 2016; O'Connell et al., 2015; Zawilska and Wojcieszak, 2019). Although paradoxical symptoms have also been described after pharmaceutical benzodiazepine exposure, the underlying mechanism of action is unclear. However, it has been suggested that paradoxical reactions are relatively uncommon and depend on predisposing factors, like young/advanced age, genetics, or psychological disorders (Mancuso et al., 2004).

The antidote flumazenil can be used to reverse the clinical effects of pharmaceutical benzodiazepines, which also seems to be effective in the treatment of DB overdoses (Bäckberg et al., 2019; Greenblatt and Greenblatt, 2019). Repeated or continuous administration is often needed, because its half-life is shorter than that of most benzodiazepines. This study also showed that flumazenil briefly reversed the effects of the DB in one case.

Some limitations should be addressed. First, selection bias is likely as the DPIC is mainly contacted about DB users with adverse effects. Probably, these users experience more (severe) adverse effects compared to all DB users, so the frequency and severity of symptoms reported in this study is not reflective of all users. Second, while this is a relatively large study, considering the available literature on DBs, with detailed information on the clinical toxicity, the number of cases with follow-up was still small. As shown, clinical data from the inquiry underestimated the severity of poisoning since symptoms often worsened over several hours. Third, DB exposures were not analytical confirmed, possibly resulting in misclassification. However, self-reported exposures to NPS seem to be reliable (Hondebrink et al., 2018; Nugteren-van Lonkhuyzen et al., 2020). Fourth, recidivists could not be identified with certainty as no patient identifiers were reported to the DPIC. Possibly, some cases might be incorrectly (not) classified as a recidivist, but the results would probably be more biased if all cases of the recidivists were included. Finally, this study lacks detailed information on the clinical toxicity of several DBs and depended on those reported during the timeframe of the prospective cohort study.

4.1. Conclusion

The incidence rate of DB poisonings reported to the DPIC rapidly increased between 2010 and 2020, especially in 2020. This indicates increased (ab)use of DBs in the Netherlands. Over the last few years, poisonings with 20 different DBs were reported, most frequently involving etizolam and clonazolam. Follow-up was obtained in seven cases of poisoning with DBs only, of which six resulted in moderate to severe toxicity. In the other 15 cases with follow up, 13 resulted in moderate to severe poisoning, but concomitant exposures might contributed substantially to the severity. The increase in DB poisonings along with their clinical outcome is worrying. To protect public health, it is important to register and monitor (health-incidents with) DBs closely, preferably by follow-up. In general, poison control centers play an important role in toxicovigilance by detection and identification of toxic exposures, as shown in this study.

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CRediT authorship contribution statement

Sharon Essink, Johanna J. Nugteren-van Lonkhuyzen, Antoinette J. H.P. van Riel, and Laura Hondebrink designed the study. Sharon Essink, Johanna J. Nugteren-van Lonkhuyzen, and Laura Hondebrink were involved in the data collection and analysis. Sharon Essink, Johanna J. Nugteren-van Lonkhuyzen, Antoinette J.H.P. van Riel, Douwe Dekker, and Laura Hondebrink interpreted the data. Sharon Essink wrote the first draft of the article, and all authors contributed substantially to its revision. All authors approved of and contributed to the final article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2021.109244.

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