DANISH MEDICAL JOURNAL

Original Article

Prevalence and characteristics of tramadol-induced seizures in young adult emergency admissions

Anders Valentin A. Nielsen[1], Casper Kierulf Lassen[1], Dilek Cakar[2], Jakob Christensen[3, 4], Mads Lind Ingeman[2], Andreas Halgreen Eiset[1] & Eva Aggerholm Sædder[1, 5]

1) Department of Clinical Pharmacology, Aarhus University Hospital, 2) Emergency Department, Aarhus University Hospital, 3) Department of Neurology, Aarhus University Hospital – Affiliated member of Epi-CARE, 4) Department of Clinical Medicine, Aarhus University, 5) Department of Biomedicine, Aarhus University, Denmark

Dan Med J 2025;72(8):A02250108. doi: 10.61409/A02250108

ABSTRACT

INTRODUCTION. Tramadol is an opioid analgesic used to treat moderately severe pain. Overuse and recreational use of tramadol may cause seizures, but the extent of this problem remains unclear. This study evaluates admissions with tramadol-induced seizures (TIS) among young adults admitted to the emergency department (ED).

METHODS. A cross-sectional study was conducted on all patients aged 15-30 years with a seizure diagnosis admitted to the ED at Aarhus University Hospital from 1 January 2021 to 31 December 2022. Data were retrieved from a retrospective medical records review.

RESULTS. We identified 232 unique patients with 352 seizure admissions; 41 patients (17.7%) (38 male (92%)) with 62 admissions secondary to TIS. The mean (± standard deviation) age of persons with TIS was 20.34 years (± 3.19) compared to 21.88 years (± 4.45) for those with other seizure aetiologies (p = 0.00947). The median tramadol dose was 200 mg (range: 50-1,200 mg, IQR: 50-300 mg). A subgroup of 12 patients accounted for 33/62 (53%) of total TIS admissions. Concomitant cannabis use was common and was reported in 40% of TIS admissions. Among the 62 TIS admissions, only two patients had a prescription for tramadol. The mean time spent in the ED was 5.74 hours (± 5.12). A CT of the brain was performed in 33/62 (53%) of TIS admissions. A total of 31 ambulatory follow-up neurological evaluations were conducted.

CONCLUSIONS. Tramadol is a frequent cause of seizures among young adults admitted to the ED. Targeted interventions to reduce recreational use among young adults are urgently needed.

FUNDING. None.

TRIAL REGISTRATION. Not relevant.

Tramadol is a synthetic opioid analgesic with a weak affinity for the μ-opioid receptor. It is approximately ten times less potent than codeine and 6,000 times less potent than morphine [1]. In addition to its opioid agonist effects, tramadol inhibits neuronal reuptake of norepinephrine and serotonin.

Tramadol is metabolised in the liver via cytochrome P450 (CYP450) enzymes into four major metabolites: O-desmethyltramadol (M1), N-desmethyltramadol (M2), N,N-didesmethyltramadol (M3) and N,O-didesmethyltramadol (M5) [2]. The opioid receptor-mediated analgesic effects are mainly attributed to the active metabolite M1, whereas the inhibition of norepinephrine and serotonin reuptake is caused by the parent drug

Open Access under Creative Commons License CC BY-NC-ND 4.0

[1]. Unlike other opioids, the analgesic action of tramadol is only partially inhibited by the opioid agonist naloxone [1].

The main adverse effects of tramadol include nausea, vomiting, sweating, itching, constipation and headaches, most of which are dose dependent. Common symptoms of overdose include tachycardia, coma, central nervous system depression and respiratory depression. A less common, but important adverse reaction is seizures, which have been reported in patients receiving both therapeutic doses and in tramadol overdoses [3].

The precise mechanism of tramadol-induced seizures (TIS) remains unclear, but high concentrations of tramadol may antagonise gamma-aminobutyric acid (GABA)-ergic receptors [4]. A meta-analysis showed that the occurrence of seizures was dose-dependent, with higher incidences in males and individuals with drug abuse and subsequent overdose [3]. Naloxone administration was not associated with TIS in persons with tramadol use [3], and TIS did not correlate with plasma tramadol concentration in four studies [5-8]. In the meta-analysis, all studies investigated a mix of intentional overdose, recreational abuse, replacement therapy for other opioids and accidental poisoning, and some of the discrepancies in the reported frequency of TIS may be explained by drug dependency and tolerance in the study population [3].

Studies investigating the semiology of seizures associated with tramadol found that they commonly presented as generalised tonic-clonic seizures and were associated with electroencephalography (EEG) abnormalities in about 50% of cases [9, 10].

The incidence of TIS among individuals using tramadol at therapeutic doses (50-100 mg 3-4 times daily) ranged from 0.025% to 14.6% in nine studies [3], whereas the incidence among abusers ranged from 0.86% to 52.4% [3]. A study of 356 patients who were hospitalised with seizures found that 33 patients (9.3 %) had TIS [9]. In an Australian first-seizure outpatient clinic, TIS was identified in eight out of 98 patients (8.1%) [11].

The frequency of TIS in Danish populations remains unknown. However, emergency physicians at Aarhus University Hospital (AUH) have observed an apparent increase in the number of young adults admitted to the emergency department (ED) with TIS. The present study aims to evaluate the frequency of TIS in the ED by quantifying and characterising TIS among young patients admitted with seizures.

Methods

Study design

This was a register-based, cross-sectional study using medical records from the ED at the AUH, Central Denmark Region. Data were retrieved from the Business Intelligence (BI) data warehouse [12]. BI-data captures patient-centred information, including medical history, diagnoses, treatments and outcomes. The study data were extracted from electronic medical records and organised using Research Electronic Data Capture (REDCap) [13]. The local ethics committee approved the study, and permission was obtained to access medical records without patient consent in accordance with Danish law.

Inclusion- and exclusion criteria

The BI data warehouse was used to identify patients aged 15-30 years who were admitted to the ED between 1 January 2020 and 1 January 2022, with a diagnosis of any seizure type, as classified according to the International Classification of Diseases, tenth revision (ICD-10) [14] (Supplementary material).

All cases were reviewed for tramadol exposure by one of the authors (AVN), who assessed the relationship between seizures and tramadol intake. Cases identified as TIS by AVN were further reviewed by authors CKL, AHE and EAS to confirm the association. Cases were excluded if alternative, more probable causes of seizures

Open Access under Creative Commons License CC BY-NC-ND 4.0

were identified, such as epilepsy, brain tumour, cerebral haemorrhage, alcohol withdrawal, other drug responsible for seizures and seizures where an association with tramadol exposure was uncertain or seizures with no identified cause. To ensure data quality, 10% of the patients were randomly selected for cross-validation and double data entry, using a random number generator.

Data extraction and analyses

Data extraction included the following variables:

- Civil registration number

- Diagnosis (ICD-10)

- Age (years)

- Sex (male/female)

- Ingested tramadol dose (mg)

- Prescription available for tramadol (yes/no)

- Alcohol or recreational drug user status (yes/no)

- If recreational drug user, which drugs were used (alcohol, tramadol, other opioids, cannabis, cocaine, amphetamine and other)

- Other medication (yes/no)

- Time in the ED (hours)

- Description of seizure (loss of consciousness, amnesia, postictal state, tonic-clonic seizure)

- Clinical findings (faecal secretions, tongue bite, bladder voiding, froth from the mouth, Glasgow Coma Scale, saturation)

- Biochemical parameters (lactate, glucose, ethanol)

- Electrocardiogram (yes/no, normal/abnormal)

- CT of the brain (yes/no, normal/abnormal)

- Urine drug test (yes/no, amphetamine, methamphetamine, cannabis, opioids, methadone, benzodiazepine, ecstasy, cocaine)

- Follow-up at neurological department (yes/no)

- Electroencephalogram (yes/no, normal/abnormal).

After initial registration, all cases were reviewed by CKL and ES for validation. Data were presented and summarised using standard descriptive statistics with mean and standard deviation (SD) or median and IQR, depending on the distribution of data. Group differences were analysed using the chi-squared test for categorical variables with a significance threshold of $p < 0.05$. Statistical analyses were conducted in Microsoft Excel and R [15].

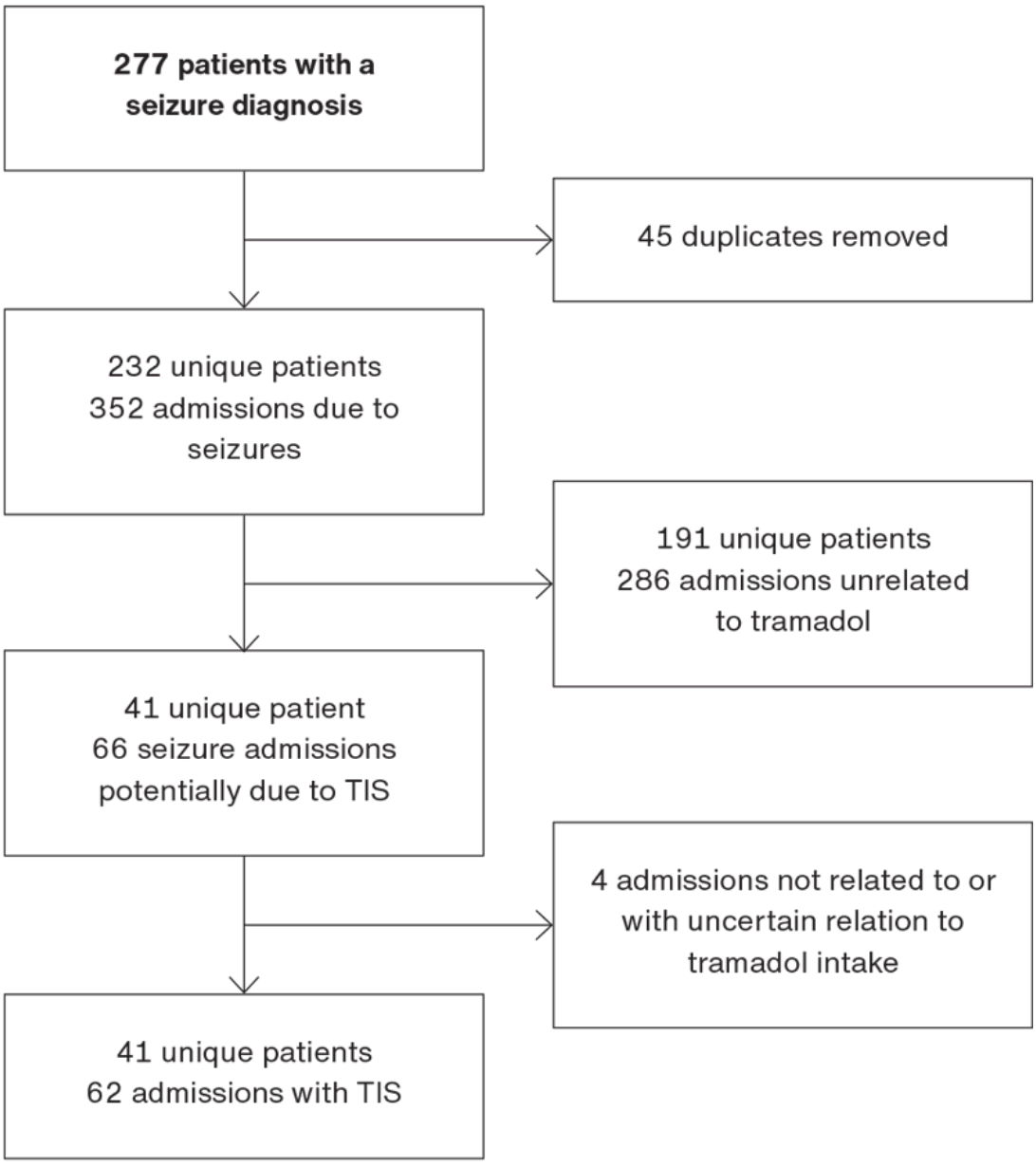
Trial registration: not relevant.

Results

Open Access under Creative Commons License CC BY-NC-ND 4.0

We identified 232 patients (61.2% male, mean age 21.6 years) with a total of 352 ED admissions for seizure diagnoses. Among these, 191 patients with 286 corresponding admissions were classified as unrelated to tramadol intake (male 54.5%, mean age 21.88 years (± 4.45)), the majority of whom had a history of epilepsy. A total of 62 seizure-related admissions attributed to tramadol exposure were identified, involving 41 patients (male 92.7%, mean age 20.34 years (± 3.19). **Figure 1** illustrates the identification and inclusion process for the study population.

FIGURE 1 Flow chart illustrating identification, screening and inclusion of patients with tramadol-induced seizure (TIS).



Compared to patients with seizures unrelated to tramadol, the final study population consisted almost exclusively of male patients, **Table 1.** Although the study only included patients aged 15-30 years, patients with

Open Access under Creative Commons License CC BY-NC-ND 4.0

TIS were slightly, but statistically significantly, younger than patients in the non-tramadol group (–1.54 years (95% CI: –2.7; –0.4), p = 0.00947).

Among the 41 patients admitted with TIS, 12 (29.3%) had multiple admissions. All of these patients were male; see **Table 2**. Of the 62 total TIS admissions, 33 (53.2%) occurred in the 12 patients who had multiple admissions during the study period. The remaining 29 admissions (46.8%) involved patients with an isolated TIS admission.

TABLE 2 Overview of the admission patterns among the 41 patients with tramadol-induced seizures.

Admission occurrences per patient, n	Patients (n = 41)	Admissions, total (n = 62)
1, n (%)	29 (70.7)	29 (46.8)
2-5		
2, n (%)	7 (17.1)	14 (22.6)
3-5[a], n (%)	5 (12.2)	19 (30.6)
Subtotal, n/N (%)	12/41 (29.3)	33/62 (53.2)

a) Patients had to be pooled into 1 group to ensure their anonymity.

Among the 62 TIS admissions, clinical features included tongue bite in six cases (9.7%), bladder voiding in three cases (4.8%) and frothing at the mouth in eight cases (12.9%). Brain CTs were performed in 33 of the 62 admissions, with no abnormal findings reported. Notably, 60 of the 62 TIS admissions (96.8%) involved patients without a prescription for tramadol. Concomitant cannabis use was identified in 25 (40.3%) of the 62 TIS

Open Access under Creative Commons License CC BY-NC-ND 4.0

admissions. The median reported tramadol dose was 200 mg (IQR: 50-1,200 mg).

A subset of 16 patients (36.6%) underwent EEG evaluation, with abnormal findings reported in six cases (37.5%). An overview of the data collected from the 62 admissions is presented in **Table 3.**

TABLE 3. Description of data collected in relation to the 62 admissions due to tramadol-induced seizure. The distribution of diagnosis codes for hospital admissions is available in the supplementary material.

Tramadol dose intake, median (IQR) [range], mg[a]	200 (50-300) [50-1,200]
Prescribed tramadol by a physician, n/N	2/62
Reported history of drug usage, n/N	
Alcohol	4/62
Cannabis	25/62
Tramadol	27/62
Other opioid	3/62
Cocaine	4/62
Amphetamine	1/62
Symptoms, n/N	
Reported loss of consciousness	43/62
Postictal at arrival to hospital	32/62
Clinical findings, n/N	
Faecal secretion	0/62
Tongue bite	6/62
Bladder voiding	3/62
Froth around the mouth	8/62
Lactate concentration, mean ± SD, median (IQR) mmol/l	4.59 ± 2.76, 3.80 (2.7-6.5)
Time spent in the emergency department, mean ± SD, median (IQR) [range], h	5.74 ± 5.12, 4 (2-6) [2-24]
Blood ethanol level evaluated	0 of the performed blood tests were positive
Urine drug screening performed, n/N	11/62
Findings, n:	
0 drugs detected	2
Cannabis	6
Opioids	5
Benzodiazepines	1
Was not detected in any test	Ecstasy, cocaine, methamphetamine, methadone
Brain CT performed, n/N	33/62
ECG performed, n/N	43/62
Follow-up, neurological exam, n/N	31/59[b]
EEG, n/N	
Performed	16/31
Abnormal findings	6/16

ECG = electrocardiogram, EEG = electroencephalogram; IQR =interquartile range; SD = standard deviation.
a) 5 admissions (8.1%) had missing values on tramadol dose.
b) Data for 3 admissions not available.

Discussion

In this retrospective study of ED admissions, TIS accounted for 17.6% of all seizures among patients aged 15-30 years. This aligns with clinical observations, highlighting that TIS constitutes a significant proportion of seizures

Open Access under Creative Commons License CC BY-NC-ND 4.0

in this age group. Only 3% of patients with TIS had a prescription for tramadol, indicating that most cases were likely related to recreational use. This raises concerns both for the health risks to individuals, such as complications related to seizures, and for the societal costs, including unnecessary admissions, imaging and neurological evaluations. Loss to follow-up in the neurology departments was not uncommon. The results of this study underscore the need for preventive measures targeting recreational tramadol use. Notably, some TIS cases were observed at alleged therapeutic doses, suggesting that tramadol use is associated with the risk of seizures even at therapeutic doses. However, most patients reported recreational use, and reducing this behaviour could prevent many of these admissions.

In Denmark, tramadol is listed as a euphoric substance regulated by the Danish Medicines Agency. Historically regarded as a "weak" opioid with low abuse potential, its use increased significantly before it was added to the list of controlled substances in 2022. This likely resulted in a decline in prescriptions from 186,015 individuals in 2019 to 103,500 in 2023 [16].

Although the extent of tramadol abuse from prescriptions remains unclear, this study found that only two TIS cases involved patients with tramadol prescriptions. Most patients allegedly obtained tramadol through illegal purchases, sharing among peers, theft or illegal import. The Danish Customs Agency has reported an increase in illegal opioid import, including tramadol [17]. These findings suggest that medically prescribed tramadol is not a major contributor to tramadol use leading to TIS.

Nearly one-third of the patients had multiple TIS admissions, indicating a high relapse risk and inadequate preventive strategies. Rehabilitation appears challenging for this population due to numerous treatment barriers [18]. A modest increase in the number of young adults (18-24 years) receiving treatment for opioid use disorder has been reported in Denmark, as reflected in the most recent data through 2022 [19].

Limitations

Underreporting of drug use due to stigma or legal concerns likely leads to underestimation of TIS prevalence. Patients may also downplay ingested doses, complicating dose-related assessments. Moreover, in some cases, drug use was admitted only during neurological follow-up evaluations and not identified in the ED. These factors may contribute to bias, possibly leading to an underestimation of the true dosage. To avoid ambiguity, cases with unclear histories were excluded, potentially further leading to an underestimation of TIS prevalence.

Using administrative diagnostic codes to identify patients also has limitations. Some cases may have been misclassified under opioid dependency, poisoning or suicide attempt codes. Self-harm diagnoses were not included, possibly biasing against females, who exhibit higher rates of self-harm in this age group [20].

The study population of TIS patients showed an overwhelming predominance of male patients who used tramadol without tramadol prescriptions. This represents a highly selected group of young recreational tramadol users and a target for preventive measures.

Conclusions

TIS are a significant cause of seizures among young adults in the ED, predominantly affecting males. These seizures pose a serious risk to individuals and contribute to preventable healthcare costs. Recreational drug use, often involving cannabis, is common in this population, highlighting the need for broader preventive efforts, especially for patients with multiple TIS admissions. While some TIS occurred at therapeutic doses, the actual doses are likely underreported in many cases. Further research, including systematic therapeutic drug monitoring, is necessary to better understand dose-related risks and improve prevention strategies.

Open Access under Creative Commons License CC BY-NC-ND 4.0

Correspondence *Anders Valentin A. Nielsen.* E-mail: anvanl@biomed.au.dk

Accepted 16 May 2025

Published 22 July 2025

Conflicts of interest JC reports financial support from or interest in the Novo Nordisk Foundation and the Lundbeck Foundation. ES reports financial support from or interest in the Drug Committee of the Central Denmark Region. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. These are available together with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2025;72(8):A02250108

doi 10.61409/A02250108

Open Access under Creative Commons License CC BY-NC-ND 4.0

Supplementary material A02250108_supplementary.pdf

REFERENCES

1. Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet. 2004;43(13):879-923. https://doi.org/10.2165/00003088-200443130-00004
2. Valian N, Sorayya M, Asadi S, et al. Preconditioning by ultra-low dose of tramadol reduces the severity of tramadol-induced seizure: contribution of glutamate receptors. Biomed Pharmacother. 2021;133:111031. https://doi.org/10.1016/j.biopha.2020.111031
3. Nakhaee S, Amirabadizadeh A, Brent J, et al. Tramadol and the occurrence of seizures: a systematic review and meta-analysis. Crit Rev Toxicol. 2019;49(8):710-723. https://doi.org/10.1080/10408444.2019.1694861
4. Hara K, Minami K, Sata T. The effects of tramadol and its metabolite on glycine, gamma-aminobutyric acidA, and N-methyl-D-aspartate receptors expressed in Xenopus oocytes. Anesth Analg. 2005;100(5):1400-1405. https://doi.org/10.1213/01.ANE.0000150961.24747.98
5. Taghaddosinejad F, Mehrpour O, Afshari R, et al. Factors related to seizure in tramadol poisoning and its blood concentration. J Med Toxicol. 2011;7(3):183-188. https://doi.org/10.1007/s13181-011-0168-0
6. Adree H, Aldabah FH, Baraka WEA, Alshazly SM. Incidence and factors influencing acute tramadol toxicity-inducing seizures in Damietta Governorate. Mansoura J Forensic Med Clin Toxicol. 2018;26(2):155-167. https://doi.org/10.21608/mjfmct.2018.47200
7. Mohammadpour A, DAshkezari MD, Farahmand B, Shokrzadeh M. Demographic characteristics and functional performance of the kidneys and hearts of patients with acute tramadol toxicity. Drug Res (Stuttg). 2019;69(4):207-210. https://doi.org/10.1055/a-0646-3918
8. Nasr MA, Mahmoud SF, Mohammad MA, El-samie HSA. A study of clinical and laboratory picture of acute tramadol toxicity in Damietta Governorate. Mansoura J Forensic Med Clin Toxicol. 2018;26(2):143-153. https://doi.org/10.21608/mjfmct.2018.47199
9. Iranmanesh F, Arvan H, Ahmadipour H, et al. Tramadol abuse-associated seizure: an epidemiological and electroencephalographic study. Int J High Risk Behav Addict. 2023;11(4):e127462. https://doi.org/10.5812/ijhrba-127462
10. Boostani R, Derakhshan S. Tramadol-induced seizure: a 3-year study. Caspian J Intern Med. 2012;3(3):484-487
11. Labate A, Newton MR, Vernon GM, Berkovic SF. Tramadol and new-onset seizures. Med J Aust. 2005;182(1):42-43. https://doi.org/10.5694/j.1326-5377.2005.tb06556.x
12. Central Denmark Region. Business intelligence data warehouse in the Central Denmark Region. www.rm.dk/om-os/organisation/it-og-digitalisering/business-intelligence (28 Sep 2024)
13. REDCap. Research Electronic Data Capture. Citations. https://projectredcap.org/resources/citations (28 Sep 2024)
14. World Health Organization. ICD-10. International Statistical Classification of Diseases and Related Health Problems: 10th Revision. Geneva: World Health Organization, 2004

15. R Core Team. The R project for statistical computing. www.R-project.org/ (28 Sep 2024)
16. Sundhedsdatastyrelsen. Fælles afregningsregister og patientregistrering for forskning. Sundhedsdatastyrelsen, 2024. https://sundhedsdatastyrelsen.dk/nyheder/2024/faerre-faar-opioider-paa-recept
17. Danish Customs Agency. Tolderne fandt knap tre tons narkotika sidste år. Danish Customs Agency, 2024. https://toldst.dk/nyheder/pressemeddelelser/tolderne-fandt-knap-tre-tons-narkotika-sidste-aar (28 Sep 2024)
18. Kosonen J, Kuusisto K. Treatment for problematic substance use in Nordic youth: a narrative review from the viewpoint of social services. Subst Abuse Treat Prev Policy. 2023;18(1):70. https://doi.org/10.1186/s13011-023-00580-9
19. Danish Health Authority. Stofmisbrugsbehandling - efterspørgsel og tilgængelighed. Narkotikasituationen i Danmark - delrapport 3, 2024. Danish Health Authority, 2024. www.sst.dk/da/udgivelser/2024/Narkotikasituationen-delrapport-3 (28 Sep 2024)
20. Moloney F, Amini J, Sinyor M, et al. Sex differences in the global prevalence of nonsuicidal self-injury in adolescents: a meta-analysis. JAMA Netw Open. 2024;7(6):e2415436. https://doi.org/10.1001/jamanetworkopen.2024.15436

Open Access under Creative Commons License CC BY-NC-ND 4.0