INCIDENCE AND PREDICTORS OF DRUG OVERDOSES AMONG A COHORT OF >10,000 PATIENTS TREATED FOR SUBSTANCE USE DISORDER

AARHUS BSS
CENTER FOR RUSMIDDELFORSKNING, KØBENHAVN
PSYKOLOGISK INSTITUT
AARHUS UNIVERSITET

LISBON ADDICTIONS
24. OKTOBER 2019

BIRGITTE THYLSTRUP
LEKTOR

TEAM

Birgitte Thylstrup

Abdu Kedir

Morten Hesse

Centre for Alcohol and Drug Research,
Aarhus University

Christian Tjagvad

Norwegian Centre for Addiction, University of Oslo

BACKGROUND

- Fatal drug overdoses increase globally, largely due to prescription drug overdoses, in particularly to opioids (Martins et al., 2015)
- Fatal and non-fatal overdoses often occur among out-of-treatment users, but also during opioid maintenance treatment (Tjagvad et al., 2016; Walley et al., 2013)
- Non-fatal overdoses more prevalent and associated with somatic problems - cardiac and muscular problems, cognitive impairment, renal failure, injuries, increasing risk of early death including fatal overdose (Rowe et al., 2017; Caudarella et al., 2016; Thylstrup et al., 2015)

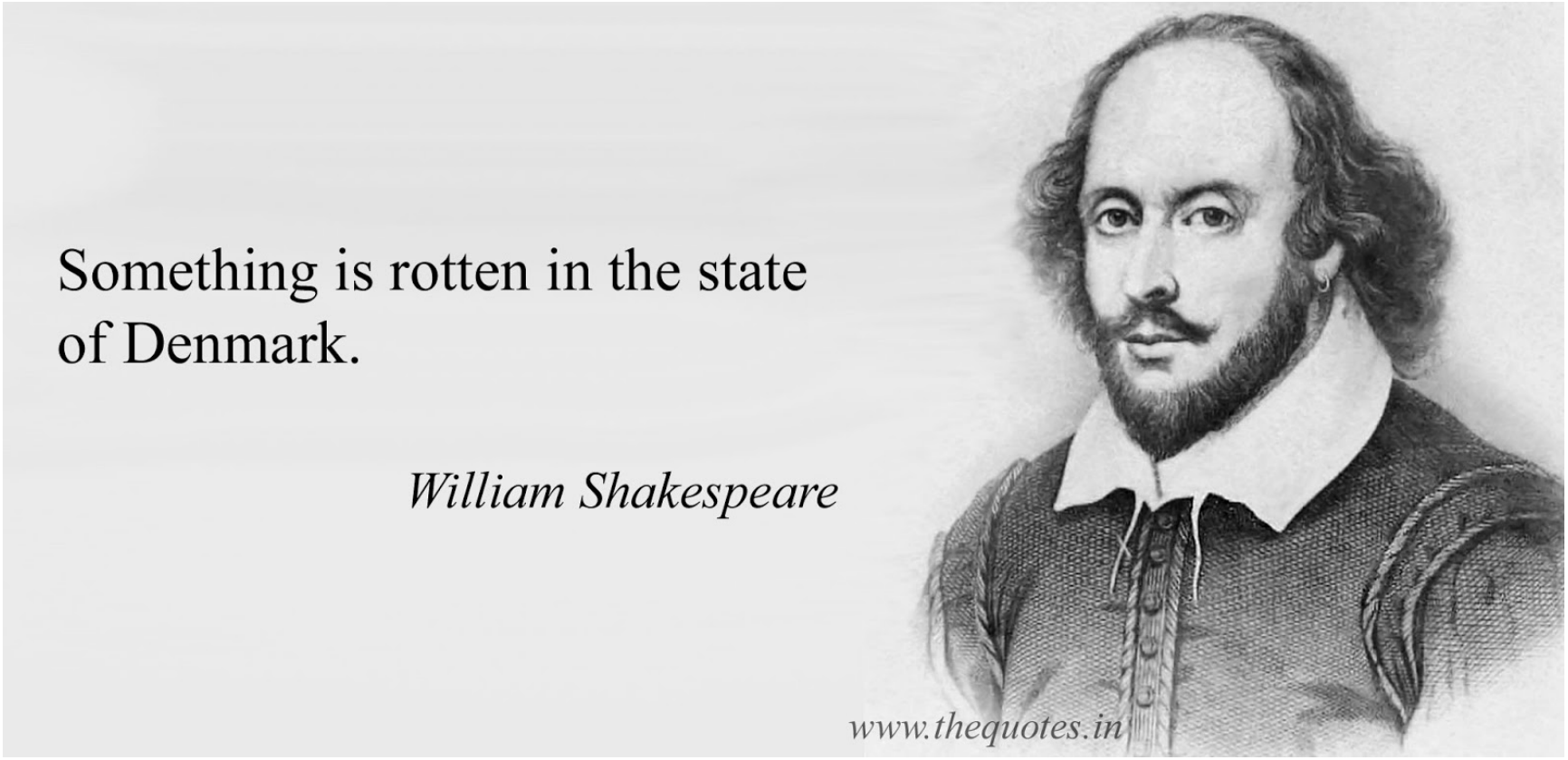
RISK FACTORS

- Substance use history, socio-demographic characteristics – age, gender, ethnicity, residence area (Brady et al., 2017; Elzey et al., 2016; Martins et al., 2015)
- Route of administration, poly-drug use, transitioning on or off drug treatment, release from prison, history of previous non-fatal overdoses (Caudarella et al., 2016; Chang et al., 2015)
- Psychiatric disorders and history of psychiatric care (Bauer et al., 2016; Brady et al., 2017)

THE STATE OF DENMARK

- 1980ties: shift from abstinence towards harm reduction, and from psychosocial approach towards medical approach (Frank et al., 2013)
- Treatment for illicit DUD, including OUD publically funded - must be initiated within two weeks
- Treatment for OUD secondary to pain treatment managed in general healthcare system (The Danish Health Authority, 2017)
- Hospital pharmacies deliver medication to clinics, and intake should be under clinical supervision 5 days per week/as take-home medication, depending on level of functioning (The Danish Health Authority, 2017)
- At enrollment, patients are referred to relevant type of treatment (methadone/buprenorphine)
- Medication record is linked to the prescribing physician, rather than to the individual patient

THE STATE OF DENMARK



THE STATE OF DENMARK

- Among countries in Europe with highest rate of fatal overdoses (EMCDDA, 2018) - more than 40 deaths per million adult population (EMCDDA, 2017)
- App. 2/3 of the deceased received methadone treatment at time of death , of which app. 3/4 did not have a supervised intake (Tjagvad et al., 2016)
- Identification of risk factors support preventive and life saving strategies

AIM

Assess incidence and predictors of non-fatal and fatal drug overdoses among patients with OUD at public DUD treatment centers in Denmark

REGISTERS

The Registry of Drug Abusers Undergoing Treatment - information on individuals enrolled in DUD treatment (Pedersen et al., 2013)

The Danish National Patient Register - hospital contacts with drug poisonings were extracted from (Lynge et al., 2011)

The Danish Cause of Death Register - general mortality register – includes underlying cause of death based on ICD-10 (Helweg-Larsen, 2011)

Statistics Denmark - the central authority on Danish statistics, Ministry of Economic Affairs (https://www.dst.dk/en/OmDS)

PARTICIPANT FLOW

Inclusion

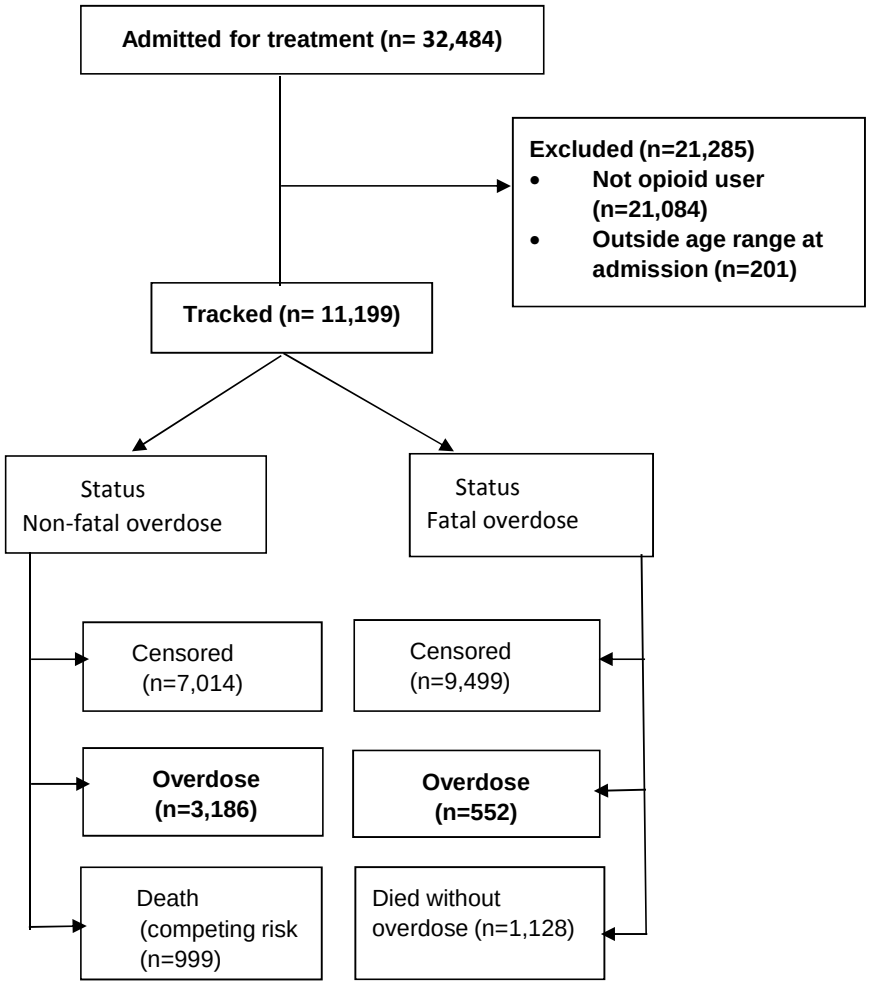
Enrollment in publicly funded DUD treatment
January 2000 - December 2010 (only available until 2010, but overdoses have remained essentially stable since 1995)
Between 18 to 75 years at admission
Reported past year use of any opioid or indicated that any opioid was the primary problem

Exclusion

Missing information on substances for both primary drug of use and past year use
Invalid date of death

Follow-up

The entire observation period from first registered enrollment to death or December 2010. First registered episode also used when multiple episodes were recorded



OUTCOMES

Fatal overdoses: classified according to the underlying causes of death (EMCDDA, 2018)

Drug overdoses (ICD-10): F11 or F19 (opioid or poly-drug related disorder), X42 (accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified), Y12 (poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified, undetermined intent)

Non-fatal overdoses (ICD-10): any hospital contact with a diagnosis of T40 (followed by any of the numbers from 0-4) and T406 (Rowe et al., 2017)

(For T406, we excluded T406A, T406B, T406C, and T406D, codes indicating that the poisoning was due to non-opioids)

Exclusion of poisonings due to drugs with little/uncertain abuse potential: nonopioid analgesics, antipyretics, antirheumatics, antiparkinsonism and other psychotropic drugs. In contrast to other studies and the definition from Center for Disease Control in the US (Rudd et al, 2016)

- 3,186 (28%) experienced a non-fatal drug overdose, 18% had at least one hospital admission, 552 (5%) died from an overdose
- Mean time at risk around 6 years (5.9 years for non-fatal and 6.7 years for fatal overdoses)
- High rates, but substantial amount of time for events to occur
- During this time, treatment providers may work to identify and intervene in high risk cases

PREDICTORS

Substance use 12 months prior to enrollment (heroin, methadone, other opioids, buprenorphine, cannabis, cocaine, amphetamine, MDMA, any problem drinking, benzodiazepines, and intravenous drug use)

Hospital admissions due to drug poisoning or DUD within the past 12 months (drug poisoning or DUD was considered if admission or discharge diagnosis was T40, F11, or F19

Sociodemographics (immigrant status, post-mandatory education/completed education beyond nine years of mandatory schooling), NEET (not in education, employment and training), living in the capital city Copenhagen.

Categorical predictor indicating previous drug treatment versus no previous drug treatment, or missing information on previous drug treatment based on admission form

SOCIODEMOGRAPHICS

		Non-fatal overdoses		**Fatal overdoses**	
	Percentage	Sub hazard ratio	P-value	Sub hazard ratio	P-value
Female gender	**25%**	**1.41(1.28-1.55)**	0.000	*0.68(0.55-0.84)*	0.000
Age (mean/standard deviation)	34.0/10.0	*0.97(0.96-0.97)*	0.000	1.00(0.99-1.01)	0.502
NEET*	**81%**	**1.18(1.04-1.34)**	0.011	1.24(0.96-1.60)	0.096
Living without partner	**77%**	**1.19(1.06-1.33)**	0.003	**1.27(1.00-1.60)**	0.046
Born outside Denmark	10%	0.84(0.71-1.01)	0.064	*0.50(0.33-0.74)*	0.000
No post-mandatory education	**96%**	1.02(0.82-1.26)	0.864	1.09(0.72-1.67)	0.675
Living in Copenhagen	21%	0.95(0.84-1.08)	0.463	**1.33(1.08-1.63)**	0.007

* Not in education, employment or training.

PAST YEAR SUBSTANCE USE

		Non-fatal overdoses		**Fatal overdoses**	
	Percentage	Sub hazard ratio	P-value	Sub hazard ratio	P-value
Heroin	**58%**	**1.11(1.00-1.24)**	0.033	1.01(0.84-1.22)	0.900
Methadone	**45%**	**1.11(1.01-1.22)**	0.040	1.08(0.89-1.29)	0.437
Other opioids	19%	1.00(0.88-1.13)	0.097	0.90(0.71-1.15)	0.415
Buprenorphine	11%	1.00(0.86-1.15)	0.946	0.89(0.66-1.20)	0.462
Cannabis	**49%**	*0.84(0.76-0.93)*	0.001	0.87(0.72-1.06)	0.172
Cocaine	23%	1.03(0.92-1.16)	0.601	0.92(0.72-1.16)	0.476
Amphetamine	16%	0.94(0.81-1.08)	0.383	1.01(0.75-1.35)	0.966
MDMA	6%	*0.66(0.51-0.85)*	0.001	0.65()0.37-1.14	0.133
Alcohol	26%	**1.16(1.03-1.29)**	0.011	1.08(0.88-1.33)	0.476
Benzodiazepines	**30%**	**1.15(1.03-1.28)**	0.011	1.22(0.99-1.50)	0.057
Intravenous drug use	**71%**	**1.57(1.38-1.77)**	0.000	**1.43(1.12-1.82)**	0.004
Hospitalized for T40 (followed by any of the numbers from 0-4 and 6)	4.4%	**2.29(1.95-2.69)**	0.000	**1.68(1.32-2.14)**	0.000

Posisoning due to drugs with substance abuse potential

TREATMENT

		Non-fatal overdoses		**Fatal overdoses**	
	Percentage	Sub hazard ratio	P-value	Sub hazard ratio	P-value
Admission year (mean/standard deviation)	2004.0/3.3				
Drug treatment					
Drug free treatment	31%	Reference		Reference	
Buprenorphine treatment	10%	*0.75(0.62-0.91)*	0.003	*0.68(0.42-0.96)*	0.032
Methadone treatment	**46%**	0.92(0.82-1.04)	0.171	0.94(0.75-1.17)	0.582
Missing information	13%	1.07(0.93-1.24)	0.314	0.93(0.71-1.23)	0.617
Treatment status					
Previously treated	**57%**	Reference		Reference	
Never treated	40%	*0.88(0.80-0.97)*	0.013	0.86(0.71-1.05)	0.675
Missing information	3%	0.81(0.61-1.06)	0.129	1.39(0.90-2.14)	0.134

TAKE HOME

- High rates of non-fatal and fatal overdoses after first registered treatment
- Time to risk allows for time for action
- Predictors for overdoses in Denmark similar to other studies
- Non-fatal and fatal overdoses - somewhat different risk factors, but interrelated and related to substance use history
- Risk related to methadone, heroin, and benzodiazepines (not surprising, given their synergistic respiratory depressant effects)
- Cannabis or MDMA use predicted lower risk of non-fatal overdose (random findings?)
- Especially patients with previous hospitalizations for non-fatal overdose and/or who inject drugs, and live alone should be monitored closely
- Relevant monitoring combined with relevant psychosocial support
- Informing and educating opioid users in risk factors and preventive measures

THANK YOU FOR LISTENING

Study to be published this year in *Journal of Alcohol and Drug Dependence*

We hope to soon follow up with publications on the impact of picking up methadone and buprenorphine from the pharmacy – who is prescribed to receive MAT at the pharmacy (is it the right target group or does it involve people at risk?)

LIMITATIONS

- Registers are only as good as the data that were put into them
- Some questions at enrollment are optimal (e.g. past year use)
- Some treatment episodes have missing information and leave open whether patients were in treatment at time at risk (e.g. dates of discharge)
- No access to contributing causes of death lead to conservative estimate of fatal overdoses
- No access to non-fatal overdoses handled by paramedics or leading to medical care
- Definitions of fatal overdoses, handling of the deceased, and coding of information varies between regions and time
- Diagnostic codes vary in terms of specificity and sensitivity in relation to overdoses (X42 will almost always indicate that the death was due to accidental overdose, whereas Y12, F11 or F19 involve uncertainty
- Risk factors may differ for later cohorts, but were consistent recent literature

REFERENCES

Bauer, L.K. et al. 2016. Characteristics of Homeless Adults Who Died of Drug Overdose: A Retrospective Record Rev. *J. Health Care Poor Underserved* 27, 846-859.

Bohnert, A.S.B. et al. 2012. Risk of Death From Accidental Overdose Associated With Psychiatric and Substance Use Disorders. *Am. J. Psychiat.* 169, 64-70.

Brady, J.E. et al. 2016. Risk markers for fatal and non-fatal prescription drug overdose: a meta-analysis. *Inj. Epidemiol.* 4, 24.

Caudarella, A., et al., 2016. Non-fatal overdose as a risk factor for subsequent fatal overdose among people who inject drugs. *Drug Alcohol Depen.* 162, 51-55.

Chang, Z. et al., 2015. Substance use disorders, psychiatric disorders, and mortality after release from prison: a nationwide longitudinal cohort study. *Lancet Psych.* 2, 422-430.

Elzey, M.J. et al. 2016. Patient Characteristics and Outcomes in Unintentional, Non-fatal Prescription Opioid Overdoses: A Systematic Review. *Pain physician* 19, 215-228.

EMCDDA, 2018. European Drug Report 2018: Trends and Developments. Publications Office of the European Union, Luxembourg.

EMCDDA, 2017. Denmark, Country Drug Report 2017. Publications Office of the European Union, Luxembourg.

Martins, S.S. et al., 2015. Worldwide Prevalence and Trends in Unintentional Drug Overdose: A Systematic Review of the Literature. *Am. J. Public Health* 105, 2373-2373.

Rowe, C. et al. 2017. Performance Measures of Diagnostic Codes for Detecting Opioid Overdose in the Emergency Department. Acad. Emerg. Med. 24, 475-483.

Rudd, R. A. et al. 2016. Increases in Drug and Opioid Overdose Deaths—United States, 2000–2014. American Journal of Transplantation, 64, 1378-1382.

Tjagvad, C. et al., 2016. Methadone-Related Overdose Deaths in a Liberal Opioid Maintenance Treatment Programme. *Eur. Addiction Res.* 1, 249-258.

Thylstrup, B., et al., 2015. Cardiovascular disease among people with drug use disorders. *Int. J. Public Health* 60, 659-668.

Walley, A.Y. et al., 2013. Opioid overdose prevention with intranasal naloxone among people who take methadone *J. Subst. Abuse Treat.* 44, 241-247

CENTER FOR RUSMIDDELFORSKNING,
KØBENHAVNSK INSTITUT
AARHUS UNIVERSITET