BJA

British Journal of Anaesthesia, xxx (xxx): xxx (xxxx)

doi: 10.1016/j.bja.2023.10.016
Advance Access Publication Date: xxx
Clinical Investigation

CLINICAL INVESTIGATION

Fatal drug overdoses in individuals treated pharmacologically for chronic pain: a nationwide register-based study

Aleksi Hamina[1,2,*], Ingvild Odsbu[3], Vidar Hjellvik[3], Torgeir G. Lid[4,5], Thomas Clausen[2] and Svetlana Skurtveit[2,3]

[1]Niuvanniemi Hospital, Kuopio, Finland, [2]Norwegian Centre for Addiction Research, University of Oslo, Oslo, Norway, [3]Norwegian Institute of Public Health, Oslo, Norway, [4]Center for Alcohol and Drug Research at Stavanger University Hospital, Stavanger, Norway and [5]Faculty of Health Sciences, University of Stavanger, Stavanger, Norway

*Corresponding author. E-mail: aleksi.hamina@niuva.fi

Abstract

Introduction: Chronic pain patients may be at an increased risk for drug overdoses as a result of comorbid psychiatric disorders and treatment with risk-increasing prescription medications, such as opioids. We aimed to characterise fatal drug overdoses and investigate factors associated with the deaths among individuals who had been treated pharmacologically for chronic pain.

Methods: We included all individuals who received analgesics reimbursed for chronic pain in Norway during 2010–9 (n=569 047). Among this population, we identified all individuals with drug overdoses as cause of death (cases). Extracting data from national registries on diagnoses, filled prescriptions, and socioeconomic variables, we used a nested case-control design to compare the cases with age- and sex-matched controls from the study population.

Results: Overall, 623 (0.11%) individuals in the study population died of an overdose. Most, 66.8%, had overdosed accidentally, and 61.9% as a result of pharmaceutically available opioids. Compared with the controls (n=62 245), overdoses overall were associated strongly with substance use disorders (adjusted odds ratio 7.78 [95% confidence interval 6.20–9.77]), use of combinations of opioids, benzodiazepines and related drugs and gabapentinoids (4.60 [3.62–5.85]), previous poisoning with pharmaceuticals (2.78 [2.20–3.51]), and with living alone the last year of life (2.11 [1.75–2.54]). Intentional overdoses had a stronger association with previous poisonings with pharmaceuticals whereas accidental overdoses were strongly associated with substance use disorders.

Conclusions: This study shows the need for better identification of overdose and suicide risk in individuals treated for chronic pain. Extra caution is needed when treating complex comorbid disorders, especially with overdose risk-increasing medications.

Keywords: chronic pain; drug-induced death; fatal overdose; opioids; registry-based research; substance use disorder

Editor's key points

- Individuals with chronic pain may be at a higher than average risk for fatal overdoses due to several factors including substance use, psychiatric disorders, and prescription medication use.
- This health register-based study investigated drug-induced deaths among 569 047 individuals treated pharmacologically for chronic pain in Norway.
- The age-standardised mortality rate due to overdoses was 20.8 per 100 000 persons per year, four times that of the general population.

Received: 26 April 2023; **Accepted:** 15 October 2023

- Fatal overdoses were associated with filled prescriptions of central nervous system-depressing medication in a dose-dependent manner. For intentional overdoses, there was a stronger association with previous poisoning with pharmaceuticals, whereas for accidental overdoses the strongest association was with substance use disorders.
- These results display a need for overdose and suicide risk evaluation among chronic pain patients and calls for caution with central nervous system-depressing medication, especially when treating patients with comorbid substance use disorders.

Pain persisting longer than 3 months, or chronic pain, is a highly prevalent problem worldwide, currently affecting an estimated 30% of the global population.[1] It is frequently comorbid with psychiatric disorders, such as depression and anxiety, with a likely bi-directional relationship.[2] The same is true of alcohol and other substance use disorders, which are far more prevalent among individuals with chronic pain compared with the general population.[3] These comorbidities, in addition to more frequent access to prescription medication, may place individuals with chronic pain at an increased risk of drug overdoses.[4]

Previous research has indicated that individuals with chronic pain may have several risk factors for opioid overdoses, but many are unaware of their increased risk.[5,6] People with chronic pain are more likely to experience an overdose requiring hospitalisation compared with people without chronic pain, especially if they use prescription opioids.[7] In one small USA-based study it was estimated that one in five opioid-using chronic pain patients experiences a nonfatal overdose in their lifetime.[6] Moreover, chronic pain may be an additional risk factor for overdoses among people with opioid use disorder.[8]

Limited research exists on fatal overdoses among people with chronic pain. In addition to an unknown mortality rate, not much is known about the risk factors for overdoses and how prescription medication use affects the risk in this patient group. A previous study on patients treated with analgesic opioids found higher doses to be associated with fatal and nonfatal opioid overdoses.[9] It is also likely that other psychotropic drugs increase overdose risk,[10,11] but this has not been studied on individuals with chronic pain. Additionally, chronic pain may increase suicidal ideation and could thus hypothetically increase the risk for intentional overdoses.[12–14]

Therefore, we aimed to identify and characterise fatal drug overdoses in a nationwide study population of individuals receiving reimbursement for analgesics for chronic pain in Norway any time during 2010–9. Secondly, we aimed to investigate factors associated with fatal drug overdoses compared with age- and sex-matched controls in this study population, with emphasis on treatment with recent prescription medication. Thirdly, we examined the factors associated with intentional and accidental fatal overdoses separately.

Methods

This study was part of the Preventing an Opioid Epidemic In Norway - Focusing on Treatment of Chronic pain (POINT) project. The project and the study population of individuals treated for chronic pain in this study have been described in detail previously.[15] The present study utilised data from several nationwide healthcare and population registries in Norway, which were linked with a unique personal identification number. The study was approved by the Regional Committee for Medical and Health Research (registration number 2019/656/REC South-East C).

Study population and data sources

The data sources for this study include the Norwegian Prescription Database (NorPD), which is an electronic registry including all medication dispensing records from all community pharmacies in Norway.[16] Each filled prescription is registered with patient identifiers and drug information, such as the date of dispensing, Anatomical Therapeutic Chemical (ATC) codes, and dispensed amounts as defined daily doses (DDDs).[17] Treatment indication is recorded for reimbursed prescriptions.

To identify a study population of individuals with chronic pain in this study, we included all individuals registered in the NorPD who were aged 15 yr or older and had been dispensed at least one analgesic reimbursed for chronic pain during 2010–9.[10] Under this reimbursement scheme, a patient can be prescribed pain-relieving medication (i.e. opioids, non-opioids [paracetamol, nonsteroidal antiinflammatory drugs (NSAIDs)], and adjuvant analgesics [e.g. gabapentinoids, amitriptyline, carbamazepine]) for the treatment of moderate to severe chronic pain, regardless of the underlying diagnosis (Supplementary Table S1). When prescribing opioids or pregabalin, the treating physician must document the diagnosis of chronic pain, pain duration and severity in an application to the health authorities.

We identified the fatal overdoses in the study population from the Causes of Death Registry. The registry contains information on all underlying causes of death among Norwegian inhabitants, recorded with International Classification of Diseases 10th revision (ICD-10) codes. We extracted all deaths in the study population that corresponded to the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA) selection B+ definition of fatal overdoses.[18] In this definition, the underlying cause of death has to be either (1) mental and behavioural disorders caused by illicit drug use (diagnoses F11–F12, F14–F16, F19), or (2) accidental poisoning (X41, X42, X44), intentional poisoning (X61, X62, X64) or poisoning of undetermined intent (Y11, Y12, Y14) by narcotics or psychodysleptics (T40.X) or psychostimulants (T43.6).

In addition, we utilised two patient registries in this study: the Norwegian Patient Registry (NPR), which includes data on specialist healthcare services, and the Norwegian Registry for Primary Care (NRPC), which includes data on primary care services.[19] Both include data on diagnoses made by treating physicians, dates of diagnosis, and patient identifiers. Diagnoses made in the secondary healthcare are recorded according to ICD-10, and in primary healthcare according to the International Classification of Primary Care, 2nd edition (ICPC-2). Moreover, we extracted data on history of cancer from the Cancer Registry of Norway, which contains information on all incident malignancies and certain benign tumours. Socioeconomic data were received from Statistic Norway. All variable definitions and data sources for each variable are presented in Supplementary Table S2.

Study design and analysis strategy

The first dispensed medication reimbursed for chronic pain was considered study entry. First, we identified all fatal

overdoses in our study population. Thereafter, we calculated the age-standardised mortality rate of overdoses in the study population of individuals receiving analgesics reimbursed for chronic pain, calculating person-time from study entry to outcome, death attributable to other causes or end of study follow-up (December 31, 2019), whichever came first. Then we characterised the overdoses according to age, sex, and type of overdose (intentional, accidental or undetermined).

In order to study several factors that could be related to overdoses, with a focus on factors close to the time of the overdose, we utilised a nested case-control design. Each fatal overdose was matched with 100 controls within the study population of individuals who had received at least one reimbursed dispensing for chronic pain. The matching was conducted according to sex, age at study entry, and time since study entry to remove confounding by these known risk factors.[20] The date of the overdose was considered the index date for the cases and a correspondingly distant date from the study entry for the matched controls, meaning the cases and their corresponding controls had the same follow-up time. We excluded individuals who emigrated from Norway at least once or died between the study entry and the index date, to obtain unskewed follow-up time. This included one fatal overdose excluded because of emigration. The study design and assessment periods for the different factors are visually represented in Supplementary Figure S1.

Statistical analyses

Descriptive statistics are presented as proportions with 95% confidence intervals (CIs), means with standard deviations (SDs), and medians with inter-quartile ranges. We calculated the age-standardised mortality rate of overdoses in the full study population for each year adjusting for the age structure with direct standardisation utilising Eurostat's European Standard Population 2013.[21]

To investigate factors related to fatal overdose, we conducted a conditional logistic regression analysis, comparing the cases with the controls, presenting the results as odds ratios (ORs) with 95% CIs. Variables utilised in the analyses were selected according to previous literature on factors related to overdoses,[11,22,23] including medication with effects depressing the central nervous system (CNS). We had access to NRPC and NPR data starting from January 1, 2008, from which we started extracting diagnoses in primary and secondary healthcare until the index date, excluding the index date itself (Supplementary Fig. S1). Data on history of cancer from the Cancer Registry of Norway was extracted from January 1, 1990 until 1 day before the index date. Factors included in the adjusted model were education, gross income below study population median, living alone, being born outside Norway, history of cancer, kidney disease, depression, anxiety disorders, previous suicide attempt, previous poisonings with pharmaceuticals, alcohol use disorder, substance use disorders, and the following medication dispensed in the past 90 days: opioids, benzodiazepines and related drugs (BZDRs), gabapentinoids, and muscle relaxants (Supplementary Table S2). In this analysis, the dispensed medication was considered regardless of reimbursement status. Moreover, we conducted analyses to investigate factors related to accidental poisoning (X41, X42, X44) and intentional poisoning (X61, X62, X64) separately. Additional analyses investigated factors related to fatal opioid overdoses (T40.0–T40.4) and to the main outcome of all fatal overdoses stratified by sex.

Additionally, we conducted a conditional logistic regression analysis of the average medication dose as a continuous variable in the past 90 days before the index date among the users of the medication in question. Opioid, BZDR, gabapentinoid, and muscle relaxant average doses were measured in DDDs per day, and opioid doses were also measured in oral morphine milligram equivalents (MMEs). We calculated MMEs from the dispensed DDD amounts, taking into account the opioid agent and the route of administration.[24] The factors included in the adjusted model were the same as in the main analysis (see above).

In a *post hoc* analysis, we included pain-related diagnoses measured in the past year before index date as variables into a conditional logistic regression model, considering all fatal overdoses as the outcome. These diagnoses were previously identified as common in this population: arthrosis, back pain, and fractures.[15] To evaluate the mediating role of medications for these variables, we utilised two adjusted models in this analysis. The first model adjusted for the factors included in the main analysis with other pain-related diagnoses, excluding medication dispensing (model 1) and the second model included medication dispensing (model 2).

All analyses were conducted using R (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/

Results

The study population included 569 047 patients with at least one dispensed medication reimbursed for chronic pain. Sixty-three percent were women, and the mean age at study entry was 57.1 (SD 18.2) yr (see Hamina and colleagues[15] for more details). We identified 623 individuals (cases) who died of an overdose during 2010–9 (0.11% of the study population). The age-standardised mortality rate of overdoses during the study period was 20.8 per 100 000 persons per year.

Those who died of an overdose were on average 48.5 yr old at death (SD=13.0), and the majority, 57.3%, were men (95% CI 53.7–61.2%, *n*=357). Most overdoses, 66.8% (62.9–70.4%, *n*=416), were reported as accidental, 24.4% as intentional (21.1–28.0%, *n*=152), and 8.8% were reported having undetermined intent (6.8–11.4%, *n*=55). Opioids (illegal or pharmaceutical) were the most common underlying cause of overdose death (*n*=538, 86.4% [83.4–88.9%]). The ICD-10 codes T40.2 and T40.4, which include pharmaceutically available opioids (excluding methadone), were registered as the underlying cause in 61.9% of the cases (57.8–65.6%, *n*=385).

The 623 cases were matched with a total of 62 245 controls from the study population. The cases had, compared with the controls, a lower education level (tertiary education attainment 11.7% *vs* 20.7%, respectively) and a lower median gross annual income (270 000 Norwegian kroner [NOK] *vs* 370 000 NOK) (Table 1). They were also more likely to have lived alone (58.9% *vs* 22.7%) and were less likely to have been born outside Norway than the controls (5.9% *vs* 18.8%). Aside from a history of cancer, all measured diagnoses were significantly more

Table 1 Characteristics of the study population. IQR, inter-quartile range; NOK, Norwegian kroner; SD, standard deviation.

Variable	Individuals with overdose N=623	95% confidence interval	Controls N=62 245	95% confidence interval
Sex (men), *n* (%)	357 (57.3)	53.7–61.2	35,645 (57.3)	56.9–57.7
Mean age at index date (yr)	48.5	SD: 13.0	48.5	SD: 12.9
Socioeconomic variables				
Median gross annual income (NOK)	270,000	IQR 230,000–340 000	370,000	IQR 270,000–500 000
No data, *n* (%)	0		226 (0.4)	0.3–0.4
Highest attained education before index date, *n* (%)				
Lower secondary school or less	332 (53.3)	49.3–57.3	21,137 (34.0)	33.6–34.3
Upper secondary school	214 (34.3)	30.6–38.2	27,309 (43.9)	43.5–44.3
Tertiary education	73 (11.7)	9.4–14.6	12,881 (20.7)	20.4–21.0
No data on education	4 (0.6)	0.2–1.8	918 (1.5)	1.4–1.6
Lived alone, *n* (%)	367 (58.9)	54.9–62.8	14,112 (22.7)	22.3–23.0
No data, *n* (%)	1 (0.2)	0.0–1.0	298 (0.5)	0.4–0.5
Born outside Norway, *n* (%)	37 (5.9)	4.3–8.2	11,715 (18.8)	18.5–19.1
No data, *n* (%)	0		89 (0.1)	0.1–0.2
Diagnoses before the index date, *n* (%)				
History of cancer	58 (9.3)	7.2–11.9	4478 (7.2)	7.0–7.4
Kidney disease	35 (5.6)	4.0–7.8	1076 (1.7)	1.6–1.8
Depression	424 (68.1)	64.2–71.7	20,606 (33.1)	32.7–33.5
Anxiety disorders	75 (60.2)	56.2–64.0	14,046 (22.6)	22.2–22.9
Alcohol use disorder	218 (35.0)	31.3–38.9	3500 (5.6)	5.4–5.8
Substance use disorders	423 (67.9)	64.0–71.5	4290 (6.9)	6.7–7.1
Previous suicide attempt	132 (21.2)	18.1–24.7	1524 (2.4)	2.3–2.6
Previous poisoning with pharmaceuticals	221 (35.5)	31.7–39.4	1706 (2.7)	2.6–2.9
Chronic pain reimbursement the prior year	428 (68.7)	65.0–72.2	36,153 (58.1)	57.7–58.5
Pain-related diagnoses in the prior year, *n* (%)				
Arthrosis	60 (9.6)	7.5–12.3	6867 (11.0)	10.8–11.3
Back pain	206 (33.1)	29.4–36.9	16,080 (25.8)	25.5–26.2
Fractures	99 (15.9)	13.2–19.1	2919 (4.7)	4.5–4.9
Prescription medications dispensed 3 months before index date, *n* (%)				
Opioids	409 (65.7)	61.8–69.4	15,447 (24.8)	24.5–25.2
Benzodiazepines and related drugs	440 (70.6)	66.8–74.1	11,181 (18.0)	17.7–18.3
Gabapentinoids	228 (36.6)	32.8–40.5	5983 (9.6)	9.4–9.8
Muscle relaxants	11 (1.8)	0.9–3.2	533 (0.9)	0.8–0.9
Opioid maintenance therapy	64 (10.3)	8.1–13.0	401 (0.6)	0.6–0.7
Opioid + BZDR	326 (52.3)	48.3–56.3	5551 (8.9)	8.7–9.1
Opioid + gabapentinoid	171 (27.4)	24.0–31.2	2828 (4.5)	4.4–4.7
Opioid + BZDR + gabapentinoid	142 (22.8)	19.6–26.3	1143 (1.8)	1.7–1.9

Table 2 Logistic regression of fatal overdose in relation to average prescription medication doses. Adjusted for education, income below median, living alone, being born outside Norway, history of cancer, kidney disease, depression, anxiety disorders, previous suicide attempt, previous poisonings with pharmaceuticals, alcohol use disorder, substance use disorder, and other medications dispensed in the past 90 days. CI, confidence interval; DDD, defined daily dose; MME, morphine milligram equivalents; OR, odds ratio.

Dispensed dose in the past 90 days	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Opioids (log MME per day)	1.29 (1.25–1.32)	1.17 (1.13–1.21)
Opioids (log DDD per day)	3.65 (3.16–4.22)	1.72 (1.43–2.06)
Benzodiazepines and related drugs (log DDD per day)	2.92 (2.66–3.21)	1.53 (1.36–1.73)
Gabapentinoids (log DDD per day)	2.53 (2.23–2.86)	1.61 (1.38–1.87)
Muscle relaxants (log DDD per day)	1.24 (0.41–3.69)	1.10 (0.37–3.26)

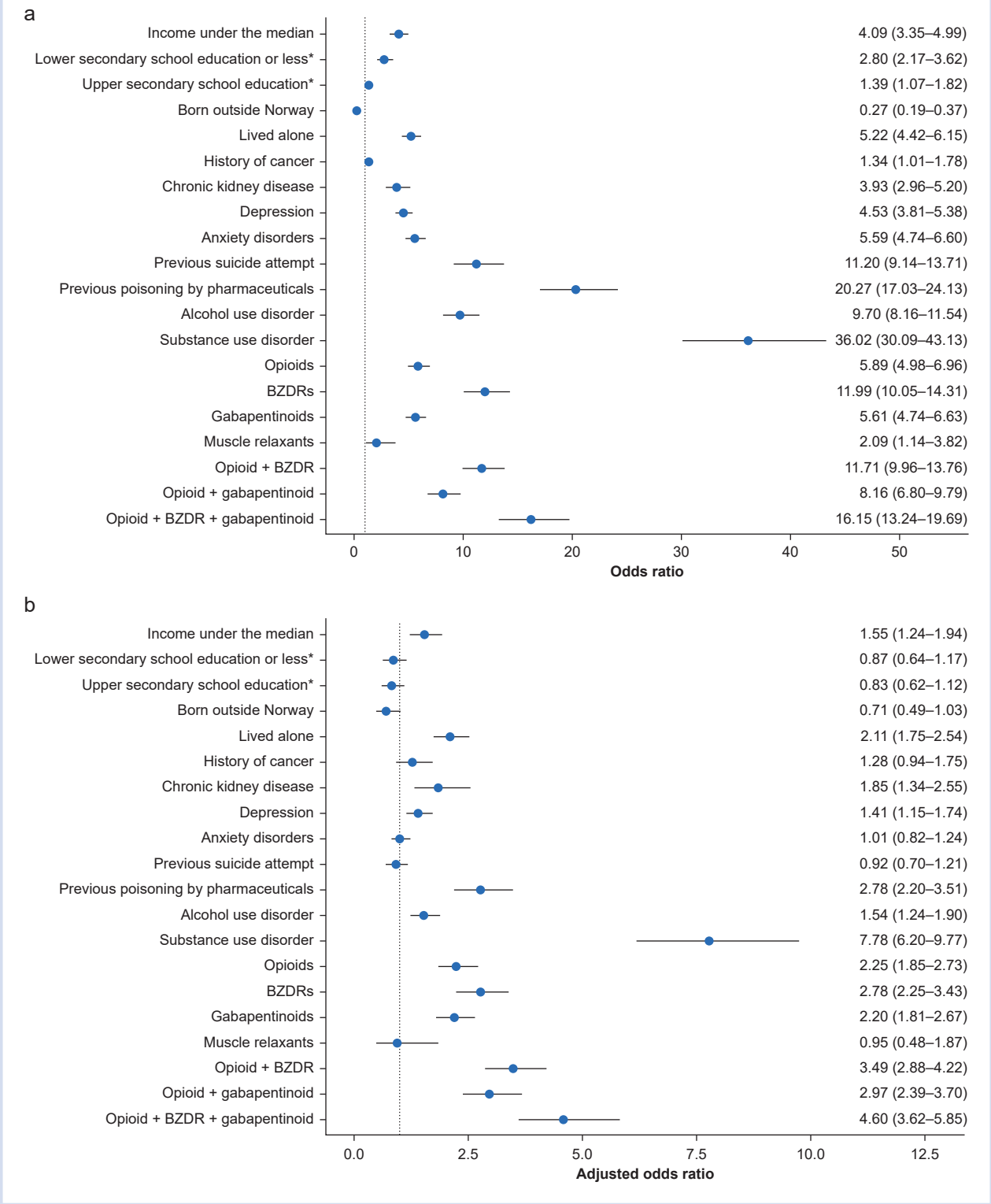

Fig 1. Factors associated with fatal overdoses in (a) non-adjusted and (b) adjusted logistic regression models. BZDR, benzodiazepines and related drugs. *Tertiary education as reference.

frequent among the deceased compared with the controls, the largest differences being in alcohol use disorder (35.0% *vs* 5.6%), substance use disorders (67.9% *vs* 6.9%), previous suicide attempts (21.2% *vs* 2.4%), and previous poisonings with pharmaceuticals (35.5% *vs* 2.7%), respectively. Back pain was frequent both among the deceased (33.1%) and the controls (25.8%). Of the deceased, 68.7% had received at least one medication reimbursed for chronic pain during the past year, compared with 58.1% of the controls.

The prevalence of medication dispensed in the past 90 days was generally more frequent among the deceased when compared with the controls (Table 1). The difference between the cases and the controls was most pronounced for BZDRs (70.6% *vs* 18.0%), opioid maintenance therapy (10.3% *vs* 0.6%), and combinations of opioids with other medication. Among the deceased, analgesic opioids were dispensed to 65.7% (n=409), of whom 95.1% (n=389) were not new users, having also had a dispensing the previous year (91–456 days before the index date). In contrast, 24.8% of the controls (n=15 447) had opioid dispensings, of whom 84.6% (n=13 071) were not new users.

In both the univariate and multivariate logistic regression models, the strongest association with overdose deaths overall was found for substance use disorders (adjusted OR, aOR 7.78 [95% CI 6.20–9.77]), previous poisoning with pharmaceuticals (aOR 2.78 [2.20–3.51]), for BZDRs, especially in combination with opioids and gabapentinoids (aOR 4.60 [3.62–5.85]), and for living alone (aOR 2.11 [1.75–2.54]) (Fig. 1). Similar results were found in the sex stratified logistic regression analysis (Supplementary Table S3) and the analysis on fatal opioid overdoses (Supplementary Table S4).

In the analysis of average dose during the past 90 days, a near linear dose-response relationship was found on a logarithmic scale for nearly all the studied drugs (Table 2). For opioids, every two-fold increase in dose corresponded to an aOR for overdoses of 1.17 (95% CI 1.13–1.21) measuring MMEs per day and of 1.70 (1.41–2.04) in DDD per day. For every two-fold increase in BZDR dose, the aOR was 1.53 (1.36–1.73) and for gabapentinoids 1.61 (1.38–1.87).

Accidental fatal overdoses (n=416) had the strongest association with substance use disorders, (aOR 11.78 [95% CI 8.79–15.79]), whereas for intentional fatal overdoses (n=152) this association was weaker (aOR 2.38 [1.53–3.70]) (Table 3). Intentional fatal overdoses were more strongly associated with the use of medication, especially opioids (aOR 4.96 [3.17–7.77]) and opioids with BZDRs (aOR 7.92 [5.30–11.85]), whereas these associations were weaker for accidental fatal overdoses (opioids aOR 1.77 [1.40–2.24] and opioids with BZDR aOR 2.56 [2.02–3.23]). Similarly, in the adjusted model, income below the median was significantly associated with accidental, but not intentional fatal overdoses (aORs 1.56 [1.18–2.07]) and 1.13 [0.74–1.73], respectively), as was alcohol use disorder (1.64 [1.27–2.13] and 0.98 [0.61–1.59]). Previous suicide attempts and history of cancer were significantly associated with intentional (aORs 1.91 [1.13–3.22] and 1.98 [1.15–3.39]), but not accidental overdoses (aORs 0.83 [0.59–1.16] and 1.17 [0.77–1.77]).

In the *post hoc* analysis, which included pain-related diagnoses, fractures and back pain were associated with fatal overdoses when adjusting for factors other than the dispensing of medication (model 1) (fractures aOR 1.99 [1.55–2.55]; back pain aOR 1.27 [1.05–1.53]) (Supplementary Table S5). Further adjusting by medications dispensed attenuated these associations (fractures aOR 1.57 [1.21–2.03]; back pain aOR 0.93 [0.77–1.14]). Arthrosis was not associated with fatal overdoses in the crude or adjusted models.

Discussion

In our analysis of a nationwide study population of individuals treated pharmacologically for chronic pain, we found a high rate of age-standardised fatal overdoses that was four-fold the national average.[25] In addition to a high prevalence of alcohol and substance use disorders, other psychiatric morbidity, and indicators of socioeconomic disadvantage, overdoses were associated with dispensing of CNS-depressing medication in a dose-dependent manner. For intentional overdoses, we observed a stronger association with previous poisoning with pharmaceuticals and with filled prescriptions of opioids alone or in combination with BZDRs. At the same time, the strongest association with accidental overdoses was with substance use disorders.

The findings on the association between dispensed medications and overdose deaths is supported by previous research in which higher prescribed opioid doses among chronic pain patients and co-prescribing of gabapentinoids have been found to correlate with opioid overdoses.[9,10] Our results on the high mortality rate of fatal overdoses among individuals who were treated for chronic pain compared with the general population and of the high correlation of overdose deaths with prescription medication are cause for concern. The results of our *post hoc* analysis also indicate that prescription medication mediates the association between pain-related diagnoses, especially back pain, and fatal overdoses. Further research should be conducted to study the association between fractures and overdoses.

Several national and international guidelines emphasise the preference of non-pharmacological treatment over pharmacotherapy in the treatment of chronic pain, especially when it comes to opioids.[26–29] Our results in individuals treated pharmacologically for chronic pain can thus be considered to be in line with these guidelines, although our results regarding prescribed medicines need to be confirmed in subsequent studies in other populations and study designs. Regardless, recommending non-pharmacological treatment for chronic pain and its comorbid psychiatric disorders should be further facilitated. The risk of overdose should be considered when prescribing pharmacotherapy, and patients treated with medication that is associated with more overdoses should be made aware of this risk.

The 623 overdoses characterised here represent 23% of all overdose deaths in Norway during 2010–9.[25] Compared with national averages, the proportion of women and the average age at death were higher among the deceased in our study population, although the majority of the deceased in both groups were men.[30] This can likely be explained by the characteristics of our study population and of chronic pain populations overall, which consist disproportionately of women and older adults.[31] Similarly, the proportion of intentional overdoses and of pharmaceutically available opioids as the underlying cause was higher in our study population than at the national level.[30] In Norway, heroin-related deaths have decreased during the past decade, whereas deaths attributed to pharmaceutically available opioids have increased.[23] Our previous research shows that fatal overdoses attributable to pharmaceutically available opioids differ from other overdose deaths in terms of patient characteristics and morbidity,

Table 3 Factors associated with intentional (n=152) and accidental overdoses (n=416). Adjusted for education, income below median, living alone, being born outside Norway, history of cancer, kidney disease, depression, anxiety disorders, previous suicide attempt, previous poisonings with pharmaceuticals, alcohol use disorder, substance use disorders, and drugs dispensed in the past 90 days. CI, confidence interval; OR, odds ratio.

	Intentional overdoses		Accidental overdoses	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Education				
Lower secondary school or less	1.32 (0.85–2.05)	0.62 (0.36–1.05)	3.84 (2.72–5.42)	1.07 (0.72–1.59)
Upper secondary school	0.95 (0.61–1.48)	0.73 (0.44–1.22)	1.70 (1.18–2.44)	0.96 (0.65–1.43)
Tertiary education	Reference	Reference	Reference	Reference
Income below median	2.43 (1.68–3.51)	1.13 (0.74–1.73)	4.60 (3.59–5.89)	1.56 (1.18–2.07)
Lived alone	4.36 (3.13–6.07)	2.29 (1.57–3.34)	5.25 (4.29–6.42)	1.92 (1.53–2.42)
Born outside Norway	0.37 (0.2 0–0.70)	1.21 (0.62–2.35)	0.27 (0.18–0.4)	0.68 (0.44–1.07)
History of cancer	1.75 (1.07–2.85)	1.98 (1.15–3.39)	1.29 (0.89–1.86)	1.17 (0.77–1.77)
Kidney disease	3.32 (1.86–5.92)	1.99 (1.03–3.87)	3.89 (2.73–5.55)	1.75 (1.17–2.61)
Depression	5.53 (3.84–7.96)	1.60 (1.02–2.52)	4.49 (3.64–5.54)	1.47 (1.14–1.90)
Anxiety	5.88 (4.19–8.26)	1.16 (0.75–1.79)	5.45 (4.46–6.67)	0.90 (0.70–1.15)
Previous suicide attempt	19.24 (13.25–27.93)	1.91 (1.13–3.22)	9.59 (7.43–12.39)	0.83 (0.59–1.16)
Previous poisoning with pharmaceuticals	26.37 (18.7–37.21)	4.37 (2.74–6.99)	18.82 (15.16–23.35)	2.30 (1.73–3.07)
Alcohol use disorder	6.86 (4.69–10.05)	0.98 (0.61–1.59)	10.49 (8.51–12.92)	1.64 (1.27–2.13)
Substance use disorders	16.64 (11.85–23.37)	2.38 (1.53–3.70)	46.92 (37.14–59.29)	11.78 (8.79–15.79)
Dispensed medications in the past 90 days				
Opioids	12.85 (8.55–19.3)	4.96 (3.17–7.77)	4.81 (3.94–5.88)	1.77 (1.40–2.24)
Benzodiazepines and related drugs	17.34 (11.61–25.89)	3.84 (2.43–6.08)	10.91 (8.83–13.46)	2.49 (1.93–3.20)
Gabapentinoids	6.47 (4.64–9.01)	2.18 (1.47–3.23)	5.76 (4.69–7.06)	2.28 (1.80–2.89)
Muscle relaxants	2.42 (0.76–7.73)	0.71 (0.19–2.68)	1.93 (0.91–4.11)	0.90 (0.39–2.11)
Opioids with benzodiazepines and related drugs	21.58 (15.19–30.65)	7.92 (5.30–11.85)	9.59 (7.86–11.7)	2.56 (2.02–3.23)
Opioids with gabapentinoids	11.68 (8.29–16.45)	4.00 (2.63–6.08)	7.91 (6.31–9.9)	2.86 (2.18–3.75)
Opioids, gabapentinoids, and benzodiazepines and related drugs	22.55 (15.59–32.63)	6.59 (4.16–10.44)	15.67 (12.24–20.05)	4.24 (3.15–5.71)

although there is also overlap in the characteristics of these groups.[22] In addition, the current results demonstrate that well-known risk factors for overdoses, such as diagnosis of substance use disorders, previous poisonings, and use of certain prescription medication combinations, also have the strongest association with fatal outcomes among individuals treated for chronic pain. Our findings on the high prevalence of substance use disorders among cases may also partly be explained by the aging of those with substance use disorders in Norway.[32] This population suffers from an extensive somatic burden,[32] including chronic pain, and could potentially be at a particularly high risk for fatal overdoses, when prescribed risk-increasing medications.[8] For healthcare professionals, this underlines the need to be cautious when treating comorbid pain and substance use disorders, and to utilise the strategies outlined by treatment guidelines for high-risk individuals: prioritise non-pharmacological treatment, use careful consideration of the advantages and disadvantages of prescribing, prescribe the lowest effective dose, follow up treatment closely, and have a predetermined strategy for tapering opioids and benzodiazepines and related drugs.[27,29,33,34]

Our analysis of factors associated with individuals with accidental and intentional overdoses reveals differences between these groups. The results indicate that the dispensing of prescription medication has a stronger connection with intentional overdoses than with accidental overdoses, suggesting these drugs may present a method for self-harm. There was an especially high risk found with the combination of opioids with benzodiazepines and benzodiazepine-related drugs or gabapentinoids. The results also indicate that substance use disorders play a smaller role in intentional than among accidental overdoses. A recent study from Ireland yielded similar results on both more frequent prescription medication use and the smaller role of substance use disorders in intentional *vs* non-intentional overdoses.[35] Given the possibly higher risk of suicide among people with chronic pain, it is vital that medical professionals consider the risk of self-harm when prescribing drugs that raise the risk of fatal outcomes, especially in cases presenting with comorbid depression.

Strengths and limitations

The data linkage of several nationwide and mandatory health and population registries is a major strength of this study. These registries allow for the investigation of a population unselected by region or socioeconomic status.[16] Moreover, medication dispensing records provide a better proxy measure for actual use compared with prescriptions,[36] although we cannot be certain that the dispensed medications were not left unconsumed or even diverted. Similarly, our analysis was not limited to overdoses solely attributable to pharmaceutically available drugs, and many of the cases thus represent poisoning from illicit drugs. One important limitation of this study is that the study population consists of individuals treated with analgesics, excluding those who only utilise non-pharmacological treatment and those not in medical treatment. Moreover, not everyone in the study population had been dispensed medication reimbursed for chronic pain in their last year (~69% of the cases and 58% of the controls). Those who did not receive reimbursed medication either did not have pain which required treatment, were treated with non-reimbursed analgesics or non-pharmacological methods, or did not seek medical help during this year. Finally, our data sources do not include exact information on several other factors that could affect the outcome. The NorPD does not include data on days' supply, making the estimation of treatment duration or patterns of medication use very difficult, but it is likely that these factors affect the risk of drug overdoses. Moreover, we did not have data on the cause of pain or disease and symptom severity, including pain severity, which may have created residual confounding. Our results can also be somewhat dependent on the study setting, as healthcare systems and the treatment of chronic pain may differ from country to country. However, we find it likely that our results may be most relevant in settings where opioids are commonly prescribed for chronic pain.

Conclusion

Individuals treated for chronic pain appear to be at a higher-than-average risk for fatal drug overdoses. Overdose deaths in this study population were associated with substance use disorders and other psychiatric morbidity, indicators of socioeconomic disadvantage, and frequent prescription medication use before death. These results illustrate the need for better identification of overdose and suicide risk in this population of chronic pain patients and calls for extra caution when treating complex comorbid disorders with medication that increases the risk of overdose.

Authors' contributions

Conception of the study: AH, SS
Acquisition of data: IO, SS
Data management and analysis: AH, VH
Interpretation of results: all authors
Initial drafting of manuscript: AH
Revision of the manuscript: SS, IO, VH, TC, TGL

Acknowledgements

We thank Marte Handal for her important comments on the manuscript and Ann Oldervoll for editing the language of the manuscript.

Declaration of interest

The authors declare that they have no conflicts of interest.

Funding

The Norwegian Research Council 320360 (IO, VH, and SS).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2023.10.016.

References

1. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet* 2021; **397**: 2082–97
2. Velly AM, Mohit S. Epidemiology of pain and relation to psychiatric disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **87**: 159–67
3. Ditre JW, Zale EL, LaRowe LR. A reciprocal model of pain and substance use: transdiagnostic considerations,

clinical implications, and future directions. *Annu Rev Clin Psychol* 2019; **15**: 503–28
4. Van Draanen J, Tsang C, Mitra S, et al. Mental disorder and opioid overdose: a systematic review. *Soc Psychiatry Psychiatr Epidemiol* 2022; **57**: 647–71
5. Wilder CM, Miller SC, Tiffany E, Winhusen T, Winstanley EL, Stein MD. Risk factors for opioid overdose and awareness of overdose risk among veterans prescribed chronic opioids for addiction or pain. *J Addict Dis* 2016; **35**: 42–51
6. Dunn KE, Barrett FS, Fingerhood M, Bigelow GE. Opioid overdose history, risk behaviors, and knowledge in patients taking prescribed opioids for chronic pain. *Pain Med* 2017; **18**: 1505–15
7. Ekholm O, Kurita GP, Højsted J, Juel K, Sjøgren P. Chronic pain, opioid prescriptions, and mortality in Denmark: a population-based cohort study. *Pain* 2014; **155**: 2486–90
8. Hartz SM, Culverhouse RC, Mintz CM, et al. Association between recent overdose and chronic pain among individuals in treatment for opioid use disorder. *PLoS One* 2022; **17**, e0271379
9. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med* 2010; **152**: 85–92
10. Chen T-C, Knaggs RD, Chen L-C. Association between opioid-related deaths and prescribed opioid dose and psychotropic medicines in England: a case-crossover study. *Br J Anaesth* 2021; **127**: 789–97
11. Volkow ND, McLellan AT. Opioid abuse in chronic pain — misconceptions and mitigation strategies. *N Engl J Med* 2016; **374**: 1253–63
12. Smith MT, Edwards RR, Robinson RC, Dworkin RH. Suicidal ideation, plans, and attempts in chronic pain patients: factors associated with increased risk. *Pain* 2004; **111**: 201–8
13. Madadi P, Persaud N. Suicide by means of opioid overdose in patients with chronic pain. *Curr Pain Headache Rep* 2014; **18**: 460
14. Ilgen MA, Bohnert ASB, Ganoczy D, Bair MJ, McCarthy JF, Blow FC. Opioid dose and risk of suicide. *Pain* 2016; **157**: 1079–84
15. Hamina A, Odsbu I, Borchgrevink PC, et al. Cohort description: preventing an opioid epidemic in Norway – focusing on treatment of chronic pain (POINT) – a national registry-based study. *Clin Epidemiol* 2022; **14**: 1477–86
16. Laugesen K, Ludvigsson JF, Schmidt M, et al. Nordic health registry-based research: a review of health care systems and key registries. *Clin Epidemiol* 2021; **13**: 533–54
17. WHO Collaborating Center for Drug Statistics Methodology. Norwegian Institute of Public Health. *The anatomical therapeutic chemical classification system* 2022. Available from: http://www.whocc.no/atc_ddd_index/. (accessed 4 February 2022)
18. Statistical Bulletin 2021 — methods and definitions for overdose deaths. Available from: https://www.emcdda.europa.eu/data/stats2021/methods/drd (accessed 1 Dec 2022).
19. Bakken IJ, Ariansen AMS, Knudsen GP, Johansen KI, Vollset SE. The Norwegian patient registry and the Norwegian registry for primary health care: research potential of two nationwide health-care registries. *Scand J Public Health* 2020; **48**: 49–55
20. EMCDDA. European. *Drug report 2023: trends and developments* 2023. Available from: https://www.emcdda.europa.eu/publications/european-drug-report/2023_en. (accessed 18 August 2023)
21. European Commission. *Eurostat. Revision of the European Standard Population: report of Eurostat's task force : 2013 edition*. LU: Publications Office; 2013. Available from: https://data.europa.eu/doi/10.2785/11470. (accessed 11 January 2023)
22. Skurtveit S, Odsbu I, Gjersing L, et al. Individuals dying of overdoses related to pharmaceutical opioids differ from individuals dying of overdoses related to other substances: a population-based register study. *Eur Addict Res* 2022; **28**: 419–24
23. Gjersing L, Amundsen E. Increasing trend in accidental pharmaceutical opioid overdose deaths and diverging overdose death correlates following the opioid prescription policy liberalization in Norway 2010–2018. *Int J Drug Policy* 2022; **108**, 103785
24. Norwegian Health Economics Administration. *Morphine equivalency ratios* 2022. Available from: https://www.helfo.no/regelverk-og-takster/blareseptordningen-forhandsgodkjent-og-individuell-stonad/blaresept-og-individuell-stonad/omregningstabell-for-opioider-til-orale-morfinekvivalenter-(OMEQ). (accessed 27 December 2022)
25. Norwegian Institute of Public Health. *Tall fra Dødsårsaksregisteret for 2020* 2021. Available from: https://www.fhi.no/hn/helseregistre-og-registre/dodsarsaksregisteret/tall-fra-dodsarsaksregisteret-for-2020/. (accessed 4 February 2022)
26. IASP Presidential Task Force on Opioids. *Opioids for pain management*. International Association for the Study of Pain; 2018. Available from: https://www.iasp-pain.org/advocacy/iasp-statements/opioids-for-pain-management/. (accessed 29 May 2023)
27. National Institute for Healthcare and Clinical Excellence. *Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain* 2021. Available from: https://www.nice.org.uk/guidance/ng193/resources/chronic-pain-primary-and-secondary-in-over-16s-assessment-of-all-chronic-pain-and-management-of-chronic-primary-pain-pdf-66142080468421. (accessed 20 April 2022)
28. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain — United States, 2022. *MMWR Recomm Rep* 2022; **71**: 1–95
29. Norwegian Directorate of Health. Vanedannende legemidler [Dependence-forming medicines]. Available from: https://www.helsedirektoratet.no/veiledere/vanedannende-legemidler (accessed 21 Feb 2022).
30. Amundsen E. *Narkotikautløste dødsfall* 2021 [Drug-induced deaths 2021]. Available from: https://www.fhi.no/nettpub/narkotikainorge/konsekvenser-av-narkotikabruk/narkotikautloste-dodsfall/. (accessed 19 September 2022)
31. van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. *Br J Anaesth* 2013; **111**: 13–8

32. Medved D, Clausen T, Bukten A, Bjørnestad R, Muller AE. Large and non-specific somatic disease burdens among ageing, long-term opioid maintenance treatment patients. *Subst Abuse Treat Prev Policy* 2020; **15**: 87
33. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain — United States, 2016. *MMWR Recomm Rep* 2016; **65**: 1–49
34. National Institute for Healthcare and Clinical Excellence. *Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults* 2022. Available from: https://www.nice.org.uk/guidance/ng215. (accessed 26 December 2022)
35. Lynn E, Cousins G, Lyons S, Bennett KE. Comparing characteristics of suicide to non-suicide drug poisoning deaths, by sex, in Ireland. *J Affect Disord* 2022; **306**: 80–9
36. Larsen BA. Prescription drugs that are not dispensed. *Tidsskr Nor Laegeforen* 2020: 140

Handling Editor: Nadine Attal