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Individuals Dying of Overdoses Related to Pharmaceutical Opioids Differ from Individuals Dying of Overdoses Related to Other Substances: A Population-Based Register Study

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Abstract

Background: Pharmaceutical opioid (PO) overdose deaths have increased in many Western countries. There are indications that those dying from a PO overdose differ from those dying from other types of overdoses. These differences might pose a challenge as the majority of current preventive measures are tailored toward those with the characteristics of "conventional" overdose deaths. ***Objective:*** We investigated differences in the characteristics of persons who died from PO overdoses compared to all other overdoses. ***Material and Methods:*** Using the Norwegian Cause of Death Registry, we retrieved information on overdoses classified according to ICD-10 and identified PO overdoses (T40.2; T40.4) and all other overdoses (T40.X; T43.6) in 2010–2019. By linking data from nationwide registers, we analyzed data on opioid dispensations and the history of mental and behavioral disorders. 1,224 persons were registered with PO overdoses and 1,432 persons with other overdoses. ***Results:*** Persons in the PO overdose group were older and were more frequently women (35.0% vs. 20.5%) than persons with other overdoses. They had a higher prevalence of chronic pain (35.8% vs. 13.2%), history of cancer (8.1% vs. 1.8%), filled prescriptions of analgetic opioids more frequently the month before death (38.8% vs. 12.0%), and used threefold higher doses of prescribed opioids compared to individuals in all other overdose group (66 vs. 26 oral morphine equivalents/day). In the PO overdose group, oxycodone and fentanyl were more frequently dispensed, while codeine was more frequently dispensed in the other overdose groups. A lower proportion of those in the PO overdose group had recorded diagnoses of substance use disorders, schizophrenia, and hyperkinetic disorder compared to the other overdose groups. ***Conclusion:*** Persons dying from overdoses on POs often differ from the population targeted by existing prevention strategies, as they are more frequently older women with chronic pain and using high doses of prescription opioids.

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Introduction

In the previous two decades, the use of pharmaceutical opioids (PO) has increased substantially, especially in North America, but also to a lower degree in some European countries [1, 2]. This is of great public health concern, as increased PO access and use have subsequently been associated with increases in opioid use disorders and associated overdose deaths [1, 3–8].

Norway has had a consistently higher prevalence of filled opioid prescriptions than the other Scandinavian countries [9]. In 2020, about 555,000 persons – 10% of the general population – were dispensed analgesic opioids in Norway [10]. Outpatient use of oxycodone has markedly increased, and in 2020, more than 63,000 persons filled prescriptions for oxycodone [10]. At the same time, there has been an increase in PO overdose deaths, and since 2016, this has been the most common cause of overdose deaths in Norway [8].

There have been indications that those dying from PO overdoses differ from people dying from other types of overdoses [7]. These differences are important to identify and may cause concern, as the majority of current overdose interventions are tailored toward those with the more "conventional" characteristics of illicit drug users. To address this issue, we examined and compared background characteristics, filled opioid prescriptions, and morbidity (diagnoses of chronic pain, cancer, and mental and behavioral disorders) between those dying from PO overdoses and all other overdoses in Norway between 2010 and 2019.

Material and Methods

Data Sources

This study was based on data from four nationwide healthcare registers in Norway. Individual-level register data were linked using the unique personal identification number assigned to all individuals living in Norway.

The Cause of Death Registry

Information on cause of death and date of death was drawn from the Cause of Death Registry. The diagnoses are coded according to the International Classification of Diseases (ICD version 10).

The European Monitoring Center for Drugs and Drug Addiction (EMCDDA) selection B^+ criteria of drug-induced deaths were used to define the overdoses. These criteria are based upon ICD-10 codes and are operated by selecting deaths where the underlying causes are either (1) mental and behavioral disorders caused by illicit drug use (diagnoses F11–F12, F14–F16, F19), or (2) accidental poisoning (X41, X42), intentional poisoning (X61, X62, X64), or poisoning of undetermined intent (Y11, Y12) by opium (T40.0), heroin (T40.1), other opioids (T40.2), methadone (T40.3), other synthetic opioids (T40.4), cocaine (T40.5), other and unspecified narcotics (T40.6), cannabis (T40.7), lysergide (T40.8), other and unspecified psychodysleptics (T40.9), or psychostimulants (T43.6). PO overdoses were identified through the ICD-10 codes T40.2 and T40.4, and other overdoses through the codes T40.X and T43.6.

Norwegian Prescription Database

Data on dispensed opioids were drawn from the Norwegian Prescription Database (NorPD), covering the entire Norwegian population [10]. All Norwegian pharmacies are obliged by law to send data on all dispensed drugs electronically to the NorPD, which therefore represent outpatient use of drugs.

In this study, we included data on the patients' unique (encrypted) identity number, the date of drug dispensation, and drug information (Anatomical Therapeutic Chemical [ATC] code) and defined daily doses [10]. Opioid analgesics were defined as ATC group N02A. A user of opioids was defined as a person who filled at least one prescription of an opioid during 14 days, 1 month, and 1 year before death.

Data from NorPD were also used to identify persons in opioid maintenance treatment (OMT). OMT was defined as filling at least one prescription of an opioid with ATC code N07BC and being diagnosed with opioid use disorder (F11). Chronic pain was defined as being dispensed at least one analgesic reimbursed for chronic pain [11, 12].

Norwegian Patient Registry

The Norwegian Patient Registry (NPR) is an administrative database of records reported by secondary health care, i.e., all governmental-funded specialized hospitals and outpatient services, including addiction services. The NPR includes information on patients who have been referred by a general practitioner to secondary health care. The registry covers all public specialist healthcare services in Norway, including private institutions and medical specialists contracted to the regional health authorities. Diagnoses in the NPR are registered with ICD-10 codes. In this study, we used data on diagnoses reported by hospitals and outpatient specialist clinics and substance use treatment facilities in the period 2008–2019 (Table 2).

Norwegian Registry for Primary Health Care

The Norwegian Registry for Primary Health Care is a database for reimbursement of health expenses in primary health care and contains data on each patient-related contact in primary health care. Diagnoses are coded according to the International Classification of Primary Care second version (ICPC-2) (Table 2).

The Cancer Registry

The registry contains information on all incident malignancies and certain benign tumors since 1990. We collected data on the history of malignant cancers (ICD-10 codes C00-C97) in the period 1990–2018.

Statistics Norway

Statistics Norway collects data on demographics on all residents in the country. We extracted data on highest attained education, whether the person was living alone the last year before death

Table 1. Characteristics of persons dying of overdoses in Norway 2010–2019, aged ≥16 years

	Overdose deaths		*p* value
	PO overdoses, *N* = 1,224	all other overdoses, *N* = 1,432	
Age, mean (SD)	46.6 (14.9)	39.0 (11.6)	<0.001
Women, *n* (%)	428 (35.0)	293 (20.5)	<0.001
Education, *n* (%)			
Primary school/lower secondary school	683 (55.8)	977 (68.2)	<0.001
Upper secondary school	382 (31.2)	327 (22.8)	
Higher education	139 (11.4)	97 (6.8)	
No data	17 (1.4)	22 (1.5)	
Lives alone, *n* (%)			
Yes	708 (57.9)	889 (62.2)	0.025
Immigrant background, *n* (%)			
Yes	58 (4.7)	104 (7.3)	0.033
No	1,166 (95.3)	1,327 (92.7)	
No data	0 (0.0)	1 (0.1)	
History of cancer, *n* (%)	99 (8.1)	26 (1.8)	<0.001
Chronic pain, *n* (%)	450 (35.8)	193 (13.2)	<0.001
Filled prescription of opioids			
0–14 days before death, *n* (%)	371 (30.3)	114 (8.0)	<0.001
1 month before death, *n* (%)	475 (38.8)	172 (12.0)	<0.001
1 year before death, *n* (%)	707 (57.8)	427 (29.8)	<0.001
Quantity of opioids measured as DDDs last year, mean (SD)	373 (549)	165 (365)	<0.001
Quantity of opioids measured as OMEQ per day last year, mean (SD)	66 (160)	26 (103)	<0.001
Number of opioid prescriptions during the last year, *n* (SD)	19.9 (24)	10.0 (14)	<0.001
Last filled opioid prescription before death,[a] *n* (%)			
Codeine	336 (47.5)	240 (56.2)	0.004
Tramadol	148 (20.1)	95 (22.2)	0.601
Oxycodone	110 (15.6)	37 (8.7)	0.001
Morphine	44 (6.2)	23 (5.4)	0.562
Buprenorphine	17 (2.4)	19 (4.4)	0.057
Fentanyl	31 (4.4)	9 (2.1)	0.044
Others	21 (3.0)	4 (0.9)	0.018
OMT, *n* (%)	199 (16.3)	418 (29.2)	<0.001

OMEQ, oral morphine equivalents; SD, standard deviation; DDDs, defined daily doses. [a] Among all persons who filled a prescription for opioids during the last year.

or not, and on immigrant background, defined as being an immigrant or a child to immigrant parents.

Study Population

We included all 2,656 persons aged ≥16 who died of an overdose during 2010–2019 in this study. In total, 1,224 persons were registered with PO overdoses and 1,432 persons with other overdoses.

Ethics

This study was approved by Regional Committees for Medical Research Ethics South East Norway, REK South East, approval number 2019/656/REK sør-øst C.

Analysis Strategy and Statistics

Statistical procedures included descriptive analyses (mean, standard deviation) of the study population. The χ^2 test and *t* tests were used to compare persons in the PO overdose group and the other overdose groups. Statistical analyses were performed using SPSS (version 27).

Results

The PO overdose group was on average 7 years older, included significantly more women than the other overdose groups, and had higher education and a higher proportion lived with other people (Table 1). Moreover, a

Table 2. Mental and behavioral disorder diagnoses of persons dying of overdoses in Norway 2010–2019, age ≥16 years

	Overdose deaths		*p* value
	PO overdoses, *N* = 1,224	all other overdoses, *N* = 1,432	
Mental and behavioral disorders (primary/secondary health care), *n* (%)			
Mental and behavioral disorders due to alcohol use[a]	385 (31.5)	455 (31.8)	0.860
Mental and behavioral disorders due to pharmaceutical drugs[b]	493 (40.3)	662 (46.2)	0.002
Mental and behavioral disorders due to illegal drug use[c]	658 (53.8)	1,169 (81.6)	<0.001
Schizophrenia and related disorders[d]	120 (9.8)	197 (13.8)	0.002
Hyperkinetic disorder[e]	171 (14.0)	245 (17.1)	0.027
Anxiety and related disorders, 1 year before death[f]	495 (40.4)	501 (35.0)	0.004
Depressive disorders, 1 year before death[g]	336 (27.5)	363 (25.3)	0.220

ICPC-2, International Classification of Primary Care second version; ICD-10, International Classification of Diseases version 10. [a] ICPC-2= P15/P16 or ICD-10= F10. [b] ICPC-2= P18 or ICD-10 = F13. [c] ICPC-2= P19 or ICD-10 =F11/F12/F14/F15/F18/F19. [d] ICPC-2= P72/P98 or ICD-10= F20–25/F28–29. [e] ICPC-2= P81 or ICD-10= F90. [f] ICPC-2= P01/P02/P74/P75/P78/79 or ICD-10= F40–45/F48. [g] ICPC-2= P76/P77 or ICD-10= F32–34/F38/F39.

larger proportion in the PO overdose group had a history of cancer (8.1% vs. 1.8%), and treatment for chronic pain (nonmalign) was approximately three times as frequent in the PO overdose group (35.9%) as among the other overdose groups (13.2%).

The individuals in the PO overdose group had to a much larger extent been dispensed prescribed opioids 14 days, 1 month, and 1 year before death compared to the other overdose group. The difference was most profound for the 14 days before death (30.3% compared to 8.0%) (Table 1). In addition, the mean amount of opioids dispensed during the year prior to death in the PO overdose group was more than twice the amount compared to the other overdose groups (66 vs. 26 oral morphine equivalents [OMEQ]/day). The two overdose groups had different prescribed opioids as their last opioid dispensed before death: in the PO overdose group, oxycodone and fentanyl were more frequently dispensed, while codeine was more frequently dispensed in the other overdose groups.

A lower frequency of mental and behavioral disorders due to illegal drug use, schizophrenia, and hyperkinetic disorders was observed in the PO overdose group compared to the other overdose groups (Table 2). In contrast, anxiety was more frequent in the PO overdose group.

Discussion

Those dying from PO overdoses represent in part a different population than those dying from other overdoses in several aspects. The PO overdose group was older and comprised of more females, had higher education, and more often lived with other people. Regarding analgesic drug use, a higher proportion was dispensed both more potent and larger amounts of analgesic opioids, and had more frequently chronic pain and a history of cancer. Furthermore, substance use disorders, apart from alcohol use disorders, were less common among the PO overdose group. The PO overdose group had more frequent anxiety disorder, but less of the other studied mental and behavioral disorders.

Our results indicate that many of those who died of PO overdoses had a history of chronic pain, as approximately 35% in the PO overdose group had received reimbursed analgesics for chronic pain. Chronic pain patients in Norway can receive opioid analgesics as reimbursed drugs, and there has been a steep increase in the number of patients receiving opioid treatment for chronic pain [11, 12]. These patients often use opioids for many years [11]. Also typical for these patients is that they are older and more often women, and that they use high-potency opioids (e.g., oxycodone) in higher doses, similar to the individuals in the PO overdose group. The changes in the outpatient opioid treatment regulations of chronic pain patients might be an underlying factor for the observed increase in overdoses caused by POs.

We found that around 50% of persons dying from PO overdoses were dispensed opioids the year before death. These persons received an average opioid dose of 66 mg OMEQ per day, corresponding to, e.g., 40 mg oxycodone per day in the year before death. Such daily opioid dose is approximately 50% higher compared to the daily opioid

dose in all patients with chronic pain receiving reimbursed opioids in Norway (personal communication Ingvild Odsbu).

There are some studies on the characteristics of persons dying from PO overdoses, but few have studied whether opioids are prescribed before death, and information on the type and amount of opioids prescribed are also lacking [13]. Similar to our study, Abassi et al. [14] found that the opioid prescription rate in USA was higher among persons dying from PO overdoses (76%) and compared the overdoses from illicit opioids (36%) in the year before death.

The impression that the PO overdoses may be comprised of a different population is further emphasized by the finding that this group has a lower proportion of individuals with a diagnosis of illicit drug use disorders. Another finding that supports these groups being different is that a lower proportion of the PO overdose group had been in OMT compared to the other overdose group. In Norway, patients recruited to OMT are primarily previous heroin users.

A major strength of the present study is the use of data from national registers including the entire Norwegian population, which minimizes selection bias. Another strength is the linkage of data from all registers on an individual level. An important limitation of our study is that we had no information on illicit drug use or prescription drugs administered to hospitalized individuals. We also lack data on important clinical factors, such as severity of depression and economic despair.

These results indicate that a new group of opioid overdoses may be emerging. This necessitates policy makers and clinicians to be more aware of the risk for overdoses, especially among chronic pain patients and patients with a history of cancer using high doses of potent POs. Targeted interventions both to reduce the use of potent opioids in the treatment of chronic pain, as well as interventions to reduce overdose risk among those who receive such treatment are needed.

Statement of Ethics

This study was approved by Regional Committees for Medical Research Ethics South East Norway, REK South East, approval number 2019/656/REK sør-øst C. Consent to participate statement was not required (Regional Committees for Medical Research Ethics South East Norway, REK), approval number 2019/656/REK sør-øst C.

Conflict of Interest Statement

Authors have no conflicts of interest to declare.

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Author Contributions

Svetlana Skurtveit designed the study. Svetlana Skurtveit and Aleksi Hamina analyzed the data and wrote the first draft of the manuscript. Svetlana Skurtveit, Ingvild Odsbu, Linn Gjersing, Marte Handal, Torgeir Gilje Lid, Thomas Clausen, and Aleksi Hamina contributed to the interpretation of data and refinement of the paper. All authors read and approved the final version of the manuscript.

Data Availability Statement

Research data are not publicly available on legal and ethical grounds. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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