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ORIGINAL RESEARCH ARTICLE

The Risk of Opioid Intoxications or Related Events and the Effect of Alcohol-Related Disorders: A Retrospective Cohort Study in German Patients Treated with High-Potency Opioid Analgesics

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Abstract

Introduction Intoxications involving prescription opioids are a major public health problem in many countries. When taken with opioids, alcohol can enhance the effects of opioids, particularly in the central nervous system. However, data quantifying the impact of alcohol involvement in opioid-related intoxications are limited.

Methods Using claims data from the German Pharmacoepidemiological Research Database (GePaRD), we conducted a retrospective cohort study based on users of high-potency opioid (HPO) analgesics during the years 2005–2009. HPO use was classified as extended-release, immediate-release or both. We calculated incidence rates (IRs) for opioid intoxications or related events as well as adjusted IR ratios (aIRR) comparing HPO-treated patients with alcohol-related disorders (ARDs) to those without ARDs overall and within each HPO category.

Results During the study period, 308,268 HPO users were identified with an overall IR of 340.4 per 100,000 person-years [95 % confidence interval (CI) 325.5–355.7]. The risk was highest when patients received concomitant treatment with extended- and immediate-release HPOs (IR 1093.8; 95 % CI 904.6–1310.9). ARDs increased the risk during HPO use by a factor of 1.7 and the highest aIRR was seen when comparing patients simultaneously exposed to extended- and immediate-release HPOs with ARDs to those without ARD also after excluding patients with potential improper/non-medical HPO use.

Conclusions Physicians should be aware of these elevated risks in HPO patients with ARDs. Active patient education by healthcare providers regarding the risk of opioid intoxications or related events due to alcohol in conjunction with HPOs is warranted.

Key Points

The risk of opioid intoxications or related events among users of high-potency opioid (HPO) analgesics was highest when patients received extended- and immediate-release products simultaneously.

Alcohol-related disorders (ARD) displayed the highest effect for this combined HPO treatment also after excluding patients with potential improper/non-medical HPO use.

1 Introduction

High-potency opioids (HPOs) are essential drugs in the management of acute and chronic pain [1–3]. Although therapy with these drugs is generally considered safe, overdose and intoxication are serious, potentially fatal complications resulting mainly from respiratory depression and apnoea [4]. Overdoses involving prescription opioids have been increasingly reported in the USA and Canada

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and are considered a major public health problem there [5–7]. According to the Centers for Disease Control and Prevention, more people in the USA die from overdoses of prescription opioids than from cocaine and heroin combined [8]. These findings are accompanied by reports of increasing misuse/non-medical use of prescription opioids [9]. To date, evidence of deaths resulting from the use of prescribed opioid drugs or the non-medical use of these analgesics remains limited in Europe [10, 11].

The role of alcohol in opioid poisonings has been widely reported [12–14] under the assumption that alcohol enhances the effects of opioids, particularly in the central nervous system (CNS) through pharmacodynamic interactions [15], but data quantifying the impact of alcohol involvement in opioid-related intoxications are limited [16]. Additionally, potential pharmacokinetic interactions have been reported for extended-release dosage forms when co-ingested with alcohol, resulting in unintended, rapid release of the entire amount or a significant fraction of the extended-release drug over a short period of time (so-called 'dose-dumping') [17]. In 2011, a review on a possible pharmacokinetic interaction of oral extended-release HPOs with alcohol was completed by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) [18]. The CHMP concluded that overall the benefits of extended-release HPOs outweighed their risks but recommended a harmonised warning in the Summary of Product Characteristics (SPC) and package leaflets that concomitant use of alcohol might increase the undesirable effects and should be avoided. However, as the CHMP mainly reviewed the results of laboratory studies and gathered information from studies in human volunteers, the impact of these findings in real-life settings remains unclear.

Against the background of rising opioid prescription rates in Germany [19], the objectives of this study were to (i) estimate incidence rates (IRs) of opioid intoxications or related events in German patients treated with HPO analgesics; and (ii) compare the risk of intoxication in HPO users diagnosed with alcohol-related disorders (ARDs) to that in those without ARDs. ARDs served as a proxy for a high-risk group with alcohol abuse, as investigated in a recent study estimating the ARD prevalence among HPO users and in the general German population [20]. To examine if the risks differed with respect to the mode of release, HPO use was classified as extended-release, immediate-release or both, with a special focus on extended-release products.

2 Methods

This retrospective cohort study was based on data from the German Pharmacoepidemiological Research Database (GePaRD) established by the Leibniz Institute for Prevention Research and Epidemiology-BIPS. The database contains data from four statutory health insurance providers (SHIs) covering more than 17 million insured members from all over Germany. The population contained in this database represents approximately 20 % of the German population and in previous studies the data have been shown to be representative for Germany with respect to age, sex, hospitalisations and drug use [21–23]. GePaRD data include demographic characteristics for each person, information on hospitalisations and outpatient physician visits, as well as outpatient prescription data. Hospital data encompass information about the periods of hospitalisation, diagnostic and therapeutic procedures, and the reasons for admission and discharge, with the main discharge diagnosis reflecting the condition mainly responsible for hospital admission. Claims of outpatient physician visits are reimbursed on a quarterly basis and contain diagnoses, treatments and procedures. All diagnoses from the in- and outpatient setting are based on the German modification of the *International Classification of Diseases*, 10th revision (ICD-10-GM). Prescription data are limited to reimbursable drugs and include prescribing and dispensation dates, the amount of substance prescribed and information on the prescribing physician. They are linked to a reference database providing information on the Anatomical Therapeutic Chemical (ATC) code, the defined daily dose (DDD), generic and trade name. Drugs that are purchased over the counter (OTC) and private prescriptions are not contained in the database. With a few exceptions, the same applies to in-hospital medication.

Previous GePaRD studies focusing on HPO use examined the utilisation of fentanyl [24] and estimated the ARD prevalence in HPO patients and in the general German population [20].

The study period was from 1 January 2004 to 30 November 2009 to avoid incomplete data for hospitalisations including the turn of the year of 2009. All patients with at least one dispensation of an HPO after having been insured continuously for at least 6 months were included. Cohort entry was defined as the prescription date of the first HPO and cohort exit was set to either (i) the end of the insurance period (including death); (ii) hospitalisation with a main discharge diagnosis of an index event indicating opioid intoxication; or (iii) the end of the study period, whichever occurred first.

During time in cohort, HPO exposure periods were constructed assessing all prescriptions of HPOs approved for pain therapy, including buprenorphine, fentanyl, hydromorphone, morphine, levomethadone, oxycodone, oxycodone in combination with naloxone, pethidine, piritramide and pentazocine [see Online Resource (Electronic Supplementary Material 1) for further details]. These agents are considered step III opioids in the pain ladder

provided by the World Health Organization (WHO) [25] and are included in the German Narcotics Drugs Act. Products licensed for opioid replacement therapy such as brands containing levomethadone or buprenorphine in combination with naloxone were not included in our study. As GePaRD does not provide prescribed daily doses, the intended duration of treatment was estimated for each dispensation. For extended-release products the recommended dosage schemes provided by the SPC were used to calculate the duration. Overlapping supplies in patients receiving a new dispensation while they supposedly still had medication were handled as follows: in cases where patients received the same therapy (defined by same substance, route of administration, mode of release and strength), stockpiling was assumed, i.e. the new dispensation started on the day after the end of the preceding prescription; and if a change in therapy occurred, stockpiling was eliminated [26] and the new dispensation was supposed to start immediately [27]. For immediate-release opioids, which are presumably used for dose titration or to manage breakthrough pain in addition to baseline treatment [3, 28], we assumed that (i) daily doses equalled half of the DDD of the respective substance; and (ii) prescriptions started immediately. To account for patients' specific dosage schemes, such as splitting tablets, a grace period of 14 days was allowed for extended- and immediate-release HPOs, i.e. 14 days were added to each estimated duration of supply. Overlapping exposure of extended- and immediate-release HPOs was allowed.

HPO exposure during time in cohort was classified as displayed in Fig. 1. If patients received low-potency opioids (LPOs) such as tramadol or tilidine in combination with naloxone while treated with HPOs, exposure time was classified as HPO and LPO use. The mode of release was addressed by categorising HPO use as extended-release, immediate-release or both. On account of our focus on the use of extended-release products, exposure was further classified as treatment with transdermal or extended-release oral HPOs and also on a substance basis.

The outcome of interest was a main discharge diagnosis of opioid intoxications or related events (see Online Resource, Electronic Supplementary Material 2). Besides diagnoses referring to opioid intoxication/poisoning [29] and common overdose symptoms such as acute respiratory failure or coma [4], we also included other related events associated with opioid use such as periodic breathing [30]. By restricting our analysis to main discharge diagnoses we ensured inclusion of only the severe events leading to hospitalisation. Intoxications due to street drugs such as heroin were not included and nor were hospitalisations because of suicidal poisonings.

Patients' characteristics were examined in the 6 months preceding cohort entry. A main reason for HPO therapy is cancer pain; however, opioid therapy for chronic non-cancer pain has increased substantially [19, 24]. A patient was assumed to receive HPOs for cancer pain if he or she had at least one hospital or outpatient diagnosis of cancer in the 6 months preceding cohort entry. As some of the more unspecific intoxication codes may also result from underlying diseases, diagnoses indicating major respiratory impairment such as chronic obstructive pulmonary disease or asthma were included in the analysis.

Patients were defined as having an ARD if they had at least one outpatient or hospital diagnosis indicating alcohol dependence or alcohol abuse or at least one dispensation of acamprosate or disulfiram. Further details can be found in a previous study estimating the prevalence of ARDs in German patients treated with HPOs approved for pain therapy [20].

A patient was assumed to have substance use disorders (see Online Resource, Electronic Supplementary Material 5) if at least one respective hospital or outpatient diagnosis was observed. As conditions related to abuse or addictions are assumed to be under-represented in claims data [31] and, additionally, might be recognised late, ARDs and substance use disorders were examined in the 6 months before cohort entry and during time in cohort. Furthermore, we assessed opioid shopping within four consecutive quarters during cohort time using two different approaches. First, according to Hall et al., we defined patients as opioid shoppers if they received prescriptions for HPOs from five or more physicians [32]. Second, we used the "four plus four" criterion of Katz et al. classifying all patients with at least four prescribing physicians and four or more pharmacies dispensing HPOs as opioid shoppers [33].

We calculated IRs and crude IR ratios (IRR) comparing HPO-treated patients with ARDs to those without ARDs with corresponding 95 % confidence intervals (CIs). Using Poisson regression, we additionally adjusted the IRRs (aIRRs) for age, sex, substance use disorders/opioid shopping, cancer and respiratory disease (GENMOD procedure; SAS®, version 9.3, SAS Institute Inc., Cary, NC, USA).

In two sensitivity analyses we (i) restricted our outcome definition to only diagnoses indicating intoxication/poisoning (Online Resource, Electronic Supplementary Material 3); and (ii) also included more unspecific codes in a broader definition of intoxications or related events (Online Resource, Electronic Supplementary Material 4). Patients diagnosed with substance use disorders and/or fulfilling our definition of opioid shopping were excluded in a subgroup analysis. Further, we calculated IRs separately for patients with cancer and for those without respective diagnoses.

In Germany, utilisation of health insurance data for scientific research is regulated by the code of Social Law.

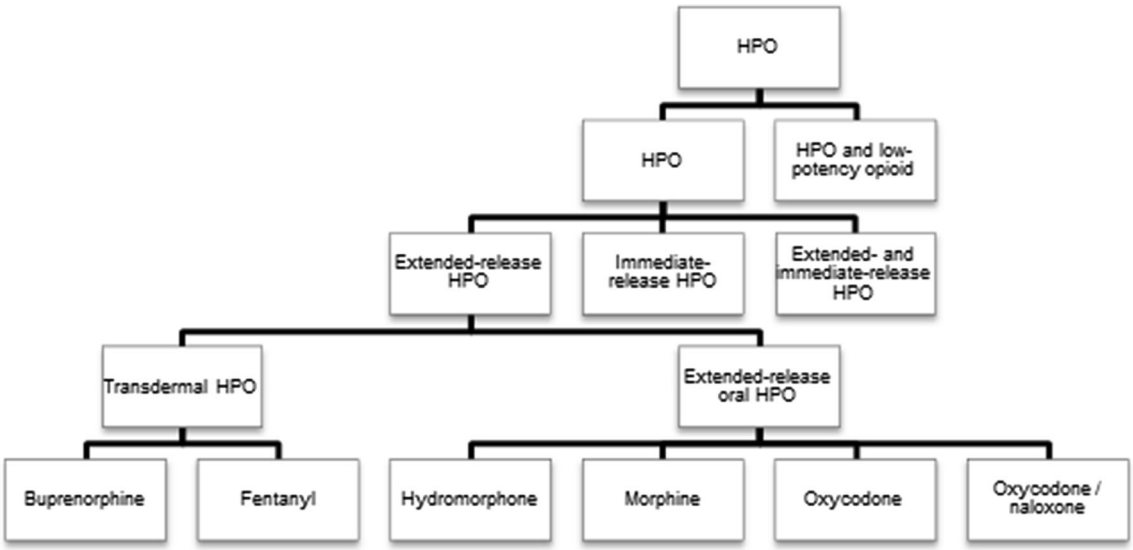

Fig. 1 Classification of high-potency opioid exposure during time in cohort. *HPO* high-potency opioid

All contributing SHIs and the regulatory authorities approved the use of the data for this study. Informed consent was not required by law because the study was based on routinely collected pseudonymised data.

3 Results

During the study period, 308,268 HPO users could be identified. The mean age at cohort entry was 68.8 years. About 65 % of patients were female and more than one-third of all patients (36.2 %) had a diagnosis of cancer (Table 1). ARDs were found in 5.4 % of HPO users. Patients diagnosed with ARDs were younger [mean age at cohort entry 62.5 (standard deviation [SD] 12.7) vs. 69.2 (SD 14.7) years] and more likely male (57.0 vs. 34.0 %) than those without ARDs. For less than 1 % of ARD patients, treatment with acamprosate or disulfiram was observed (data not shown). Substance use disorders were substantially more common among HPO patients with ARDs than in those without (20.3 vs. 5.6 %) and opioid shopping was found slightly more often (3.6 vs. 2.2 %). Overall, 12 % of HPO users were diagnosed with ARDs and/or substance use disorders or were found to be opioid shoppers. Almost three-quarters of patients received extended-release HPOs only, whereas 20 % were treated with extended- and immediate-release products. Less than 6 % of patients were only prescribed immediate-release HPOs. Nearly one-third of patients received multiple HPO substances during time in cohort (see Online Resource, Electronic Supplementary Material 6). Aside from multiple HPO use, use of fentanyl only (25.8 %) was most common, followed by treatment with morphine or oxycodone only (12.4 and 10.9 %, respectively). Patients with ARDs were slightly more likely to receive multiple HPOs than those without ARDs (34.2 vs. 32.2 %) and were far more often prescribed levomethadone only (0.9 vs. 0.3 %). On the contrary, ARD patients received only transdermal HPOs such as fentanyl or buprenorphine slightly less frequently. HPO users with cancer far more often received multiple HPOs during time in cohort than those without cancer diagnoses (39.4 vs. 28.2 %). In contrast, they were less likely to be treated with oxycodone or oxycodone/naloxone only (5.3 vs. 14.0 % and 3.0 vs. 7.2 %, respectively) [see Online Resource, Electronic Supplementary Material 7].

During time in cohort, 1978 patients (0.6 %) suffered from opioid intoxications or a related event resulting in an overall IR of 340.4 per 100,000 person-years (95 % CI 325.5–355.7). HPO treatment yielded an IR of 502.1 per 100,000 person-years (95 % CI 472.2–533.4) (see Table 2). The risk was found to be higher for males than females (611.6; 95 % CI 551.7–676.2 vs. 455.8; 95 % CI 422.0–491.6) and considerably higher in patients diagnosed with cancer than in those without cancer diagnoses (835.0; 95 % CI 753.1–923.3 vs. 409.9; 95 % CI 379.5–442.0). Concomitant use of HPOs and LPOs yielded higher risks than treatment with HPOs alone.

The most common discharge diagnosis of intoxications or related events in patients exposed to HPOs with or without additional LPO treatment was "poisoning by narcotics and psychodysleptics [hallucinogens]—other opioids" (30.0 %), followed by "acute respiratory failure" (27.9 %) and "somnolence" (20.1 %) [see Online Resource, Electronic Supplementary Material 8]. Patients with cancer had a main discharge diagnosis of "acute respiratory failure" far more often, whereas those without

Table 1 Characteristics of the study cohort of users of high-potency opioids stratified by alcohol-related disorders

Characteristics	All (n = 308,268)	ARDs (n = 16,526)	No ARD (n = 291,742)	P value
Mean age at cohort entry (SD)	68.8 (14.7)	62.5 (12.7)	69.2 (14.7)	<0.0001
Mean days of follow-up (SD)	688.5 (634.9)	743.4 (654.8)	685.4 (633.7)	<0.0001
Sex				<0.0001
Female	199,565 (64.7)	7108 (43.0)	192,457 (66.0)	
Male	108,703 (35.3)	9418 (57.0)	99,285 (34.0)	
Incident use	274,829 (89.2)	14,402 (87.2)	260,427 (89.3)	<0.0001
Cancer	111,723 (36.2)	5975 (36.2)	105,748 (36.3)	0.8109
Respiratory disease	43,884 (14.2)	3063 (18.5)	40,821 (14.0)	<0.0001
Substance use disorders/opioid shopping	25,113 (8.2)	3649 (22.1)	21,464 (7.4)	<0.0001
Substance use disorders	19,744 (6.4)	3357 (20.3)	16,387 (5.6)	<0.0001
Opioid shopping in 4 consecutive quarters	6877 (2.2)	594 (3.6)	6283 (2.2)	<0.0001
HPO prescriptions by ≥5 physicians	5936 (1.9)	500 (3.0)	5436 (1.9)	<0.0001
HPO prescriptions by ≥4 physicians and ≥4 pharmacies	1927 (0.6)	222 (1.3)	1705 (0.6)	<0.0001
HPO use during time in cohort				<0.0001
Only one HPO substance	208,749 (67.7)	10,868 (65.8)	197,881 (67.8)	
Multiple HPO substances	99,519 (32.3)	5658 (34.2)	93,861 (32.2)	
Mode of release				<0.0001
Only extended-release HPO	229,125 (74.3)	11,971 (72.4)	217,154 (74.4)	
Only immediate-release HPO	17,455 (5.7)	975 (5.9)	16,480 (5.7)	
Extended- and immediate-release HPO	61,688 (20.0)	3580 (21.7)	58,108 (19.9)	
Mean number of prescriptions (SD)	10.6 (18.1)	13.2 (22.0)	10.4 (17.9)	<0.0001

All data are presented as n (%), unless otherwise stated

ARDs alcohol-related disorders, *HPO* high-potency opioid, *SD* standard deviation

Table 2 Absolute numbers and incidence rates with 95 % confidence intervals for opioid intoxications or related events

	Opioid intoxications or related events	IR (95 % CI) for opioid intoxications or related events
HPO	1053	502.1 (472.2–533.4)
Female	672	455.8 (422.0–491.6)
Male	381	611.6 (551.7–676.2)
Cancer	380	835 (753.1–923.3)
No cancer	673	409.9 (379.5–442.0)
HPO and LPO	137	679.4 (570.4–803.2)
Female	82	598.2 (475.8–742.5)
Male	55	851.9 (641.8–1108.8)
Cancer	53	1315.6 (985.5–1720.9)
No cancer	84	520.6 (415.2–644.5)

CI confidence interval, *HPO* high-potency opioid, *IR* incidence rate, *LPO* low-potency opioid

cancer were more likely to be hospitalised because of opioid poisoning.

Opioid intoxication patients diagnosed with ARDs were younger (mean age at intoxication: 63.4 vs. 72.7 years) and more likely to be male (56.8 vs. 34.4 %) than those without ARDs (Table 3). Nearly half (48.3 %) of opioid intoxication patients with ARDs had a diagnosis of substance use disorders or were found to be opioid shoppers compared with 17 % in those without ARDs. Overall, 20.3 % of patients with intoxication were found to have substance use disorders/opioid shopping. Following intoxication, 207 patients (17.4 %) died in hospital; death occurred more often in patients without ARDs than in those with ARDs (18.0 vs. 11.9 %).

Considering the mode of release of HPO products, the IR was found to be highest when patients received extended- and immediate-release HPOs simultaneously (IR 1093.8; 95 % CI 904.6–1310.9), followed by exposure to immediate-release products only (IR 912.2; 95 % CI 708.4–1156.5), while treatment with extended-release HPOs alone yielded an IR of 454.2 per 100,000 person-years (95 % CI 424.5–485.5) (see Table 4). Transdermal HPOs showed a higher IR of opioid intoxication than oral extended-release HPOs (501.6; 95 % CI 457.7–548.5 vs. 406.9; 95 % CI 367.4–449.5). On a substance level, morphine was associated with the highest risk of intoxication followed by transdermal fentanyl, while the lowest IR was found during exposure with oxycodone in combination with naloxone.

Comparing patients with ARDs to those without, the highest aIRR was seen in patients exposed to extended- and immediate-release HPOs (aIRR 2.6; 95 % CI 1.6–4.5) and

Table 3 Characteristics of patients with opioid intoxications or related events during exposure with high-potency opioids (with or without additional treatment with low-potency opioids) stratified by alcohol-related disorders

Characteristics	All ($n = 1190$)	ARDs ($n = 118$)	No ARD ($n = 1072$)	P value
Mean age at intoxication (SD)	71.8 (13.6)	63.4 (12.7)	72.7 (13.4)	<0.0001
Mean days of follow-up (SD)	442.7 (494.3)	592.7 (533.6)	426.2 (487.2)	0.0015
Sex				<0.0001
Female	754 (63.4)	51 (43.2)	703 (65.6)	
Male	436 (36.6)	67 (56.8)	369 (34.4)	
Cancer	433 (36.4)	40 (33.9)	393 (36.7)	0.5539
Respiratory disease	227 (19.1)	33 (28.0)	194 (18.1)	0.0096
Substance use disorders/opioid shopping	241 (20.3)	57 (48.3)	184 (17.2)	<0.0001
Substance use disorders	217 (18.2)	53 (44.9)	164 (15.3)	<0.0001
Opioid shopping in 4 consecutive quarters	41 (3.5)	10 (8.5)	31 (2.9)	0.0016
HPO prescriptions by ≥5 physicians	34 (2.9)	10 (8.5)	24 (2.2)	0.0001
HPO prescriptions by ≥4 physicians and ≥4 pharmacies	17 (1.4)	6 (5.1)	11 (1.0)	0.0004
Death	207 (17.4)	14 (11.9)	193 (18.0)	0.0950

All data are presented as *n* (%), unless otherwise stated

ARDs alcohol-related disorders, *HPO* high-potency opioid *SD* standard deviation

those receiving immediate-release products only (aIRR 2.0; 95 % CI 1.0–4.1). Among extended-release HPOs, ARDs increased the risk of opioid intoxication for all products except buprenorphine (overall aIRR 1.5; 95 % CI 1.2–2.0).

Excluding patients with substance use disorders/opioid shopping yielded mostly lower IRs of opioid intoxications or related events (Table 5), with an overall estimate of 489.9 (95 % CI 457.5–524.1) per 100,000 person-years in patients treated with HPOs. For the simultaneous use of extended- and immediate-release HPOs, however, a higher IR of 1287.0 (95 % CI 1040.0–1574.9) was found. Accordingly, the highest aIRR comparing patients with ARDs with those without was observed for this group of patients (2.9; 95 % CI 1.6–5.3).

Including only hospitalisations for intoxication/poisoning in our first sensitivity analysis yielded a substantially lower risk during HPO use (IR 166.5 per 100,000 person-years; 95 % CI 149.5–184.9). Differences between the risk in patients with cancer and those without (213.1; 95 % CI 172.8–260.0 vs. 153.5; 95 % CI 135.1–173.6, respectively) were far less pronounced than in the main analysis. As observed in the main analysis, treatment with extended-release HPOs alone yielded the lowest IR. In contrast to the main analysis, however, the risk was found to be higher when patients received immediate-release HPOs only than with the combined use of extended- and immediate-release products (Online Resource, Electronic Supplementary Material 9). Considering this tighter outcome definition, no differences were found when comparing transdermal products to oral extended-release HPOs. During HPO exposure, ARDs increased the risk of intoxication by a factor of 1.7, as observed for the main outcome definition.

Our second sensitivity analysis based on a broader outcome definition yielded a higher overall IR of intoxications or related events of 651.8 per 100,000 person-years (95 % CI 617.7–687.3) during HPO exposure. As in the main analysis, the risk was found to be highest among those treated simultaneously with extended- and immediate-release HPOs (IR 1320.2; 95 % CI 1111.3–1557.0). With respect to extended-release products, morphine revealed the highest IR, whereas the lowest risk was found for oxycodone in combination with naloxone. Likewise, ARDs showed similar increases for intoxication as found in the main analysis.

4 Discussion

In this study, we examined the risk of opioid intoxications or related events in a large cohort of over 300,000 HPO users, not restricting the study population to specific diagnoses for HPO use. Almost 95 % of patients received extended-release HPOs, suggesting that the majority were treated for chronic pain conditions for which German guidelines give preference to extended-release HPOs in both cancer and non-cancer pain [3, 28].

ARDs increased the risk of opioid intoxications or related events for all groups, with the exception of buprenorphine, a partial opioid agonist that is reported to have a wide safety margin [34, 35]. The highest effect of ARDs on intoxications was observed in patients using concomitantly extended- and immediate-release HPOs. This combination is normally used for complex pain conditions that are difficult to control. While dosage schemes

Table 4 Incidence rates, crude and adjusted incidence rate ratios and 95 % confidence intervals for opioid intoxications or related events among patients with and without alcohol-related disorders receiving high-potency opioids

Opioid use	Overall		Patients with ARDs	Patients without ARDs	Patients with vs. without ARDs	
	Opioid intoxications or related events	IR (95 % CI) for opioid intoxications or related events	IR (95 % CI) for opioid intoxications or related events	IR (95 % CI) for opioid intoxications or related events	Crude IRR (95 % CI)	Adjusted IRR (95 % CI)[a]
HPO	1053	502.1 (472.2–533.4)	791.7 (642.7–964.8)	483.9 (453.7–515.6)	1.6 (1.3–2.0)	1.7 (1.4–2.1)
Extended-release HPO	868	454.2 (424.5–485.5)	650.0 (507.6–819.8)	442.3 (412.2–474.1)	1.5 (1.1–1.8)	1.5 (1.2–2.0)
Transdermal HPO	480	501.6 (457.7–548.5)	538.0 (354.6–782.8)	499.6 (454.6–547.8)	1.1 (0.7–1.5)	1.2 (0.8–1.7)
Buprenorphine	63	332.6 (255.6–425.5)	234.3 (28.4–846.4)	337.2 (257.9–433.2)	0.7 (0.0–1.6)	0.9 (0.2–3.9)
Fentanyl	417	543.3 (492.4–598.0)	600.3 (388.5–886.1)	540.0 (487.9–596.2)	1.1 (0.7–1.6)	1.2 (0.8–1.7)
Oral extended-release HPO	388	406.9 (367.4–449.5)	746.1 (542.1–1001.7)	384.6 (345.0–427.4)	1.9 (1.4–2.6)	1.9 (1.4–2.7)
Hydromorphone	67	449.6 (348.4–570.9)	1056.2 (482.9–2004.9)	412.8 (313.4–533.6)	2.6 (0.9–4.3)	2.4 (1.2–5.0)
Morphine	174	556.9 (477.3–646.1)	841.2 (506.4–1313.6)	534.8 (453.9–625.9)	1.6 (0.9–2.3)	1.7 (1.1–2.9)
Oxycodone	115	312.2 (257.7–374.7)	541.1 (279.6–945.2)	297.5 (242.8–360.8)	1.8 (0.8–3.0)	1.6 (0.9–3.0)
Oxycodone/naloxone	32	258.9 (177.1–365.5)	703.7 (191.7–1801.7)	237.5 (157.8–343.2)	3.0 (0.2–6.2)	2.9 (1.0–8.7)
Immediate-release HPO	68	912.2 (708.4–1156.5)	1730.4 (829.8–3182.2)	843.5 (640.5–1090.4)	2.1 (0.8–3.5)	2.0 (1.0–4.1)
Extended- and immediate-release HPO	117	1093.8 (904.6–1310.9)	2161.5 (1259.1–3460.7)	1009.1 (821.0–1227.3)	2.1 (1.1–3.3)	2.6 (1.6–4.5)
HPO and LPO	137	679.4 (570.4–803.2)	1287.8 (786.6–1988.9)	628.7 (519.9–753.4)	2.1 (1.1–3.0)	2.2 (1.3–3.6)

Incidence rates are expressed per 100,000 person-years

ARDs alcohol-related disorders, *CI* confidence interval, *HPO* high-potency opioid, *IR* incidence rate, *IRR* incidence rate ratio, *LPO* low-potency opioid

[a] Adjusted for age, sex, substance use disorders/opioid shopping, cancer and respiratory disease (SAS® GENMOD procedure)

Table 5 Incidence rates, crude and adjusted incidence rate ratios and 95 % confidence intervals for opioid intoxications or related events among patients with and without alcohol-related disorders receiving high-potency opioids, excluding patients with substance use disorders/opioid shopping

Opioid use	Overall		Patients with ARDs	Patients without ARDs	Patients with vs. without ARDs	
	Opioid intoxications or related events	IR (95 % CI) for opioid intoxications or related events	IR (95 % CI) for opioid intoxications or related events	IR (95 % CI) for opioid intoxications or related events	Crude IRR (95 % CI)	Adjusted IRR (95 % CI)[a]
HPO	847	489.9 (457.5–524.1)	665.7 (500.1–868.6)	481.3 (448.3–516.0)	1.4 (1.0–1.8)	1.4 (1.1–1.9)
Extended-release HPO	707	442.1 (410.1–476.0)	513.3 (363.2–704.5)	438.7 (406.1–473.2)	1.2 (0.8–1.6)	1.2 (0.9–1.7)
Transdermal HPO	413	501.1 (453.9–551.8)	507.0 (300.5–801.3)	500.8 (452.6–552.7)	1.0 (0.5–1.5)	1.1 (0.7–1.8)
Buprenorphine	59	354.2 (269.6–456.9)	328.4 (39.8–1186.3)	355.2 (269.0–460.1)	0.9 (0.0–2.3)	1.2 (0.3–4.8)
Fentanyl	354	538.3 (483.6–597.3)	544.0 (310.9–883.4)	538.0 (482.2–598.5)	1.0 (0.5–1.6)	1.1 (0.7–1.8)
Oral extended-release HPO	294	379.7 (337.5–425.6)	519.4 (317.3–802.2)	372.3 (329.6–419.1)	1.4 (0.8–2.0)	1.4 (0.9–2.3)
Hydromorphone	47	391.2 (287.4–520.2)	732.7 (199.6–1876.0)	374.9 (271.3–505.0)	2.0 (0.1–4.5)	2.0 (0.7–5.6)
Morphine	134	541.2 (453.5–641.0)	798.1 (398.4–1428.0)	526.1 (437.2–627.7)	1.5 (0.6–2.5)	1.7 (0.9–3.1)
Oxycodone	85	283.4 (226.4–350.4)	199.3 (41.1–582.6)	287.8 (228.9–357.3)	0.7 (0.0–1.5)	0.6 (0.2–2.0)
Oxycodone/naloxone	28	262.4 (174.4–379.3)	474.8 (57.5–1715.0)	253.7 (165.7–371.7)	1.9 (0.0–5.1)	1.8 (0.4–7.6)
Immediate-release HPO	46	856.3 (626.9–1142.2)	1096.8 (226.2–3205.4)	843.4 (610.4–1136.1)	1.3 (0.0–2.7)	1.3 (0.4–4.3)
Extended- and immediate-release HPO	94	1287.0 (1040.0–1574.9)	3260.4 (1736.0–5575.5)	1173.0 (931.5–1457.9)	2.8 (1.3–4.5)	2.9 (1.6–5.3)
HPO and LPO	102	660.0 (538.2–801.2)	817.0 (328.5–1683.3)	650.8 (526.6–795.6)	1.3 (0.3–2.2)	1.3 (0.6–2.9)

Incidence rates are expressed per 100,000 person-years

ARDs alcohol-related disorders, *CI* confidence interval, *HPO* high-potency opioid, *IR* incidence rate, *IRR* incidence rate ratio, *LPO* low-potency opioid

[a] Adjusted for age, sex, cancer and respiratory disease (SAS® GENMOD procedure)

for the extended-release baseline treatment are usually determined by the treating physician, dosing frequency for the immediate-release products might be adapted by the patient based on the actual pain status, thereby increasing the risk of intoxications or related events in situations of too frequent use.

ARDs significantly increased the risk of intoxications in users of oral extended-release HPOs, but not in patients treated with transdermal HPOs. This finding points to a pharmacokinetic interaction between the oral formulations and alcohol possibly resulting from an unintended, more rapid release of the drug, as discussed in the review conducted by the CHMP [18]. The effect of ARDs on intoxications or related events decreased for most of the groups after excluding patients with substance use disorders/opioid shopping. However, a significant and even higher effect was still observed for patients treated with extended- and immediate-release HPOs concomitantly, underlining the vulnerability of this group of patients.

Looking at intoxications in the different HPO user groups without taking ARDs into account, the highest IR was found in patients concomitantly receiving extended- and immediate-release products. Excluding patients with substance use disorders/opioid shopping from this group yielded an even higher IR, indicating a risk also in patients in whom proper HPO use is likely. Increased risks for this group of patients were also reported by a recent US analysis, which concluded that overdose risk did not differ among patients prescribed extended- or immediate-release opioids alone, but was significantly higher when both were used concomitantly [36]. In our study, treatment with immediate-release HPOs alone yielded substantially higher IRs than the sole use of extended-release products. Characterised by a rapid onset, immediate-release HPOs may promote opioid misuse and dependency [37]. Supporting this assumption, excluding patients with substance use disorders/opioid shopping from this group decreased the IR of intoxication.

During use of only extended-release products, a higher IR of intoxications or related events was observed for transdermal HPOs than for oral products. Excluding patients with substance use disorders/opioid shopping yielded lower rates for oral extended-release products but not for transdermal HPOs, suggesting that the high rates of intoxication observed for transdermal products might not be associated with improper use. These findings are supported by warnings, especially for transdermal fentanyl to be used only in opioid-tolerant patients [38, 39], underlining the importance of cautious prescribing of these products [24, 40]. The low risk we observed for extended-release oxycodone in the overall cohort as well as in the subgroup was remarkable since this HPO has been associated with abuse and overdose in North America that led to the introduction of abuse-deterrent preparations [41–43]. Compared with other oral HPOs, in our study oxycodone was prescribed far less often to cancer patients, and thus was possibly used at lower dosages. Overall, a comparison with other studies on a substance level is hampered by the fact that while in Germany extended-release HPOs are used far more often than immediate-release products [19], they only account for a very small proportion of prescriptions in the USA [29].

Compared with treatment with HPOs alone, additional use of LPOs yielded a higher risk of intoxication. This combination is not included in the WHO pain ladder, which recommends switching to HPOs if pain is still persisting or increasing despite LPO treatment [25], and thus might indicate improper pain therapy.

Overall, these findings do not point to a higher intoxication risk associated with extended-release compared to immediate-release HPOs. In contrast, extended-release and long-acting (ER/LA) opioids have been the subject of a Risk Evaluation and Mitigation Strategy (REMS) initiated by the US Food and Drug Administration (FDA) [16, 39] aimed at reducing serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics. In this context, the FDA recently approved class-wide labeling changes, including that ER/LA opioids should be reserved for use in patients for whom alternative treatment with non-opioid analgesics or immediate-release opioids are not an option [44].

Our study revealed higher IRs for intoxications or related events in patients with cancer than in those without, though the difference diminished when considering the tighter outcome definition of only intoxication/poisoning. Treatment of breakthrough pain in cancer patients might have been associated with the necessity of immediate treatment and potentially higher doses, which was also hinted at by a recent study [27]. Examining the association of the maximum prescribed daily opioid dose and the dosing schedule with the risk of opioid overdose death, the authors found that high daily doses and the use of as-needed medication only were associated with a high risk of overdose [27]. Additionally, co-morbid conditions such as renal failure often found in cancer patients can increase the risk of intoxication [45].

In our study, substance use disorders/opioid shopping were found in more than one-fifth of ARD patients, suggesting that co-dependence or co-abuse is quite common in this group of HPO users. The overlap of patients diagnosed with substance use disorders and meeting our definition of opioid shopping was small and indicates that HPOs can be obtained from different physicians or pharmacies without detection. In contrast to the USA where Prescription Drug Monitoring Programs [46] have been implemented in several states, there is no central registry available in

Germany that would allow identification of drug-seeking behaviours or double prescriptions of opioids for pain therapy.

The observation of higher mortality following intoxication in patients without ARD than in those with ARDs was surprising since worse outcomes might have been expected in the latter group. However, the high prevalence of substance use disorders found in patients with ARD might also be associated with a higher opioid tolerance in this group resulting in fewer fatal events.

The strengths of our study are its size of more than 300,000 HPO users and the representativeness of the data [21–23]. Due to the administrative nature of the data, no bias is introduced by non-response and coverage of all age groups is complete. Determination of exposure based on pharmacy dispensing data is considered the gold standard as recall bias can be ruled out and information is precise regarding time and product [47]. Since all opioids approved for pain therapy are available on prescription only, ascertainment of HPO exposure is assumed to be complete. Additionally, HPOs are subject to the regulations of the Narcotic Drugs Prescription Ordinance, including special prescription forms, mandatory documentations and written dosage instructions that have to be provided by prescribing physicians [48]. Providing opioids on private prescriptions not captured in GePaRD has been reported for LPOs [49] but not for HPOs.

The limitations of this study are due to the administrative nature of the underlying data. Alcohol consumption is not included in the database, and thus coding of ARDs was used as a proxy for a high-risk group with alcohol abuse which, however, did not allow an evaluation of whether opioids and alcohol were consumed simultaneously. A further drawback is that no distinction was possible between ARD patients receiving non-pharmacological treatment and those not receiving non-pharmacological treatment. Since conditions related to abuse or addictions are assumed to be under-represented in claims data [31], some undercoding may additionally be assumed if less severe ARD is not coded overall. However, the results of a previous analysis in our database estimating the ARD prevalence in HPO-treated patients were plausible and comparable with the literature [20]. By including opioid shopping, we were able to account for potential improper/non-medical HPO use that was not recorded as substance use disorder.

As GePaRD does not provide the intended duration of treatment, we implemented plausible algorithms based on recommendations in the respective SPCs. Since we additionally allowed stockpiling and included a grace period, misclassification of exposure time appears of lesser importance. Though our study did not include a review of individual patient files, which for data protection reasons is not feasible in Germany, a high validity of our outcome definition based on hospital discharge diagnoses can be assumed. Our sensitivity analyses using tighter and broader outcome definitions, yielded different IRs of intoxications but did not change our overall findings regarding the high risk associated with the simultaneous use of extended- and immediate release HPOs or immediate-release HPOs alone.

Concomitant use of benzodiazepines, which has also been related to unintentional overdoses with opioids [14, 50], was not considered in our study since sedatives/hypnotics are generally only reimbursed for short-term use in Germany [51]. As a consequence, physicians often provide these drugs on private prescriptions [52] not contained in the database. However, mental and behavioural disorders due to use of sedatives/hypnotics were included in our definition of substance use disorders and were thus accounted for in the analyses.

Socioeconomic status, which has been reported to influence opioid prescribing as well as overdose rates [53, 54], is not captured in GePaRD and thus could not be included in the analyses.

Patients with severe pain and those who are used to HPOs possibly tolerate higher opioid dosages than other persons [4]. Additionally, patients abusing opioids probably seek high doses [55]. The potential influence of dose on intoxications is controversial [56]. Several studies investigating patients receiving opioids for pain conditions reported unexpectedly high rates of overdoses and deaths when doses were increased [27, 29]. In contrast, a recent analysis using a UK medical record database maintained by general practitioners found that higher daily doses were not a risk factor for opioid overdose [55]. As pain intensity and tolerance could not be assessed in our study, we did not adjust for opioid dose. However, by excluding patients with substance use disorders/opioid shopping in a subgroup analysis, we were also able to examine intoxication risks in a more homogenous population of pain patients.

5 Conclusions

Overall, our findings indicate that ARD is indeed a safety concern in HPO-treated patients, resulting in elevated risks for opioid intoxications or related events. Additionally, our study presents important data regarding co-abuse/dependence, showing that substance use disorders and/or opioid shopping are quite common among German HPO users with ARDs, which hampers a disentanglement of both effects.

In our cohort of HPO users, patients receiving extended- and immediate-release HPOs simultaneously were at highest risk of intoxications or related events even after excluding patients with potential improper/non-medical

HPO use, indicating that careful monitoring of alcohol consumption in this group is especially advisable. In conclusion, physicians should be aware of these elevated risks in patients with alcohol consumption or ARDs receiving HPO treatment, as also reflected by the warnings provided by the SPCs and package leaflets [18]. Active patient education by healthcare providers regarding the risk of serious CNS depression when combining HPOs with alcohol [57] is warranted.

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Compliances with ethical standard

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Conflict of interest Edeltraut Garbe is running and Kathrin Jobski, Bianca Kollhorst and Tania Schink are working for a department that occasionally performs studies for pharmaceutical industries. These companies include Bayer, Celgene, GlaxoSmithKline, Mundipharma, Novartis, Purdue, Sanofi-Aventis, Sanofi Pasteur MSD and STADA. Edeltraut Garbe served in an advisory or consultancy role for Bayer-Pharma, Nycomed, GlaxoSmithKline, Schwabe, Teva and Novartis. These advisory functions were unrelated to the topic of this study.

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