Epidemiological Study

Opioid Prescription in Switzerland: Appropriate Comedication use in Cancer and Noncancer Pain

Maria M. Wertli, MD, PhD[1,2], Ulrike Held, PhD[2,3], Andri Signorell, MSc[4], Johann Steurer, MD[2], Eva Blozik, MD[4,5], and Jakob M. Burgstaller, MD, PhD[2]

From: [1]Department of General Internal Medicine, Bern University Hospital, University of Bern, Bern, Switzerland; [2]Horten Center for Patient Oriented Research and Knowledge Transfer, Department of Internal Medicine, University of Zürich, Zürich, Switzerland; [3]Department of Biostatistics, Epidemiology, Biostatistics and Prevention Institute, University of Zürich, Zürich, Switzerland; [4]Department of Health Sciences, Helsana, Dübendorf, Switzerland; [5]Division of General Practice, University Medical Centre Freiburg, Freiburg, Germany

Address Correspondence:
Maria M. Wertli, MD, PhD
Division of General Internal Medicine, Bern University Hospital, University of Bern
Freiburgstrasse 16p
CH-3010 Bern, Switzerland
E-mail: Maria.Wertli@insel.ch

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Background: In Europe, limited information on the use of opioids is available.

Objectives: To assess how guideline recommendations to manage opioid-related adverse events were followed in cancer- and noncancer-related opioid use.

Study Design: Analysis of health insurance data of one of the major health insurers in Switzerland.

Setting: All opioid claims between 2006 and 2014.

Methods: Opioid episodes were cancer-related when cancer treatments were used within ± 3 months of the first opioid claim. Recurrent strong episodes were defined as ≥ 2 opioid claims with at least one strong opioid claim. Episode duration were acute (< 90 days), subacute, or chronic (≥ 120 days/≥ 90 days + ≥ 10 claims).

Results: Out of 591,633 opioid episodes 76,968 (13%) were recurrent episodes: 94% were noncancer related (83% in recurrent episodes) and 6% cancer related (17% recurrent). Chronic opioid use was observed in 55% (noncancer) and 58% (cancer) recurrent episodes. Recommended laxatives were used in 50% noncancer and in 67% cancer episodes. Antiemetic drugs were used in 54% noncancer and in 83% cancer episodes. Not recommended coprescription of benzodiazepines was observed in 34% recurrent noncancer and 46% cancer episodes.

Limitations: No clinical information was available to assess the indication for opioid use.

Conclusions: In this study, opioids were primarily used outside the context of cancer-related treatment. In noncancer-related opioid use, we found a substantial higher proportion without recommended laxative and antiemetic medications. Coprescription of benzodiazepines may increase the risk for opioid overdose and was present in one-third of the noncancer episodes and in almost every second cancer episode.

Key words: Pain medications, opioids, nonopioids, benzodiazepines, health insurance claims data, cancer pain, noncancer pain, chronic opioid use, adverse events prevention, guideline recommendations

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Opioids are effective for the treatment of acute strong pain, cancer pain, or for symptom relief at the end of life. According to the World Health Organizations (WHO) pain relief ladder, a stepwise increase of the pain treatment intensity is recommended (1,2). Nonopioids are the first choice for mild (5-44 mm on a 100 mm Visual Analog Scale [VAS]) (3) to moderate pain (VAS 45-74 mm); when the pain is insufficiently controlled, weak opioids (e.g., tramadol, codeine) are recommended. Strong opioids (e.g., morphine, fentanyl) should be used for strong pain (VAS 75-100 mm) (2). Although the WHO pain relief ladder was developed to improve cancer pain treatment, the stepwise treatment approach has also been widely adopted for noncancer pain.

The aim of pain treatment is to improve quality of life in patients. However, for noncancer pain, increasing evidence indicate that strong opioids are no more effective than nonopioid pain medications (4-6), but potentially decrease quality of life because of side effects (e.g., obstipation, nausea, dizziness, and potential addiction) (6-9). Further, long-term opioid use was associated with an increased risk for major trauma, addiction, and overdose (9). Therefore, treatment guidelines for chronic noncancer pain recommend the use of strong opioids as second-line drugs, only when alternative options result in insufficient pain control (10-12). Despite these recommendations, strong opioids are increasingly used in chronic noncancer pain, and their use has reached enormous dimensions in North America (13-15) and in some European countries (16-18). In Switzerland, the use of strong opioids has more than doubled between 2006 and 2013, with a wide variation across Swiss geographic areas (18).

Coprescribing benzodiazepines in chronic opioid users was associated with an increased risk for overdose (19) and with more pain, physical, and mental disability, and increased health care use (20). Therefore, the American Society of Interventional Pain Physicians guideline recommended avoiding the combination of opioids and benzodiazepines (10). The guideline further recommended managing opioid-related side effects such as constipation and nausea. In opioid users, constipation is common and underrecognized by health care professionals (21). The preventive treatment with laxatives is recommended when opioids are started before constipation is developed (22). However, it is unclear how physicians implement these recommendations when prescribing opioids for noncancer and cancer pain.

The aims of this study were 2-fold. First, we aimed to determine how opioids were used in a Swiss population. Second, we assessed coprescribing of medications recommended or discouraged by the treatment guidelines. We hypothesized that the majority of strong opioids were used for noncancer-related pain treatment. Further, we hypothesized that patients with noncancer-related opioid use were less likely to receive treatments for constipation and nausea compared with patients with cancer pain.

Methods

We analyzed insurance claims data from one of the major health insurers in Switzerland, the Helsana health insurance group. The insurer covers 1.2 million individuals (approximately one-sixth of the Swiss population) in all 26 cantons and maintains records of all health care invoices including information about prescribed medications reimbursed by Swiss basic mandatory health insurance (23). The patient-level linked database provided information on sociodemographic data, health insurance status (e.g., additional private insurance, managed care program), prescribed drugs, health care use and its associated costs (inpatient, outpatient), and the date of death.

Swiss Regulation for Opioid Prescription

The Swiss health care system is highly decentralized with 26 Swiss administrative regions (cantons) responsible for the planning of health services and several health insurance payers on the market (23). Therefore, no centralized opioid use registry is available. Opioids cannot be purchased over the counter, and for strong opioids a special prescription (a so-called "prescription for narcotic substances") is issued on prescriptions with 3 copies including a unique identification number. One copy remains with the prescribing physician, one with the pharmacy, and one with the insurance company. Although this formal procedure is aimed at reducing the risk of abuse, there is no central database in which misuse and patients with multiple parallel prescribers can be identified.

Eligibility Criteria

We included all administrative claims data of adults who received reimbursement for at least one opioid prescription between January 2006 and December 2014. We identified opioid claims using WHO pharmacological Anatomical Therapeutic Chemical (ATC) codes (24).

Since 1999, the insurance companies reimburse the opioids that are prescribed with a drug substitution program. We excluded opioid use for the substitution of opioid dependency by using specific reimbursement codes (TarMed position 00.0155, positions specifically assigned to substitution programs in pharmacies or substitution centers for buprenorphine, methadone, heroin, and morphine). We excluded all opioid claims from the analysis of patients in which substitution codes were identified at least once (e.g., in a patient the unique code was identified in the database in 2009, then all opioids reimbursed for this person were excluded). In addition, we excluded diamorphine using the corresponding ATC-code (N07BC06 Diaphin (DiaMo Narcotics GmbH, Thun, Switzerland)). Other specific brands are used within substitution programs and for pain treatment: Sevre-Long (Mundipharma Medical Company, Basel, Switzerland) (morphine, N02AA01), Subutex (Indivior Schweiz AG, Baar, Switzerland) (N07BC01), and Temgesic (Temgesic Indivior Schweiz AG, Baar, Switzerland) (N02AE01, both buprenorphine), or L-Polamidon (Mundipharma Medical Company, Basel, Switzerland) (N07BC05) and Ketalgin (Ketalgin Amino AG, Gebenstorf, Switzerland) (N07BC02, both methadone). These medications were included in the analysis as long as no code for a substitution program was detected. We excluded patients with recurrent prescriptions of Subutex sublingual (not excluded by the earlier defined criteria) when the daily dose was > 640 mg morphine equivalent assuming that Subutex was used within an "off-label" opioid substitution.

Opioids and Morphine Equivalent Dose

Weak opioids included oral or rectal opioid formulations with a morphine conversion factor of ≤ 0.3: N02AA59 (codeine and combinations), N02AX01 (tilidine), N02AX02 (tramadol), and N02AX06 (tapentadol). Strong opioids included all other opioids not defined as weak (see Appendix 1 for full list of ATC codes and opioid substances).

We converted each reimbursement of an opioid medication (referred to hereafter as a "claim") to a total amount of substance. To account for the different potencies of opioids, the morphine equivalent dose (MED) was calculated for each opioid (weak and strong) as follows: strength of opioid drug in milligrams per unit x quantity of units per reimbursed package x number of packages x conversion factor for morphine equivalents. The equianalgesic conversion factors are estimates and cannot account for individual variability in genetics and pharmacokinetics. Wherever available, we used conversion factors provided by the Swiss Agency for Therapeutic Products (Swissmedic, agency comparable to the US Food and Drug Administration) or based on the CONSORT classification (CONsortium to Study Opioid Risks and Trends) (25). Further, we consulted the literature relevant to the topic and a clinical pharmacologist. We calculated the morphine equivalent dose per claim (single claim) or episode (multiple claims) by dividing the total MED dose by the number of days between each prescription (21).

The MED calculation for patches was assumed that one patch delivers opioids over a time provided by the manufacturer. For example, fentanyl patches deliver the dispensed (and bioavailable) micrograms per hour over 72 hours. The calculation of the total bioavailable MED dose in milligrams equals (mcg/hour [according to the package reimbursed] x 72 hours x number of patches per package x number of packages reimbursed x 100 [fentanyl conversion factor])/1,000. The total MED in milligrams for one package containing 10 fentanyl patches that each delivers 12 mcg per hour is calculated as follows: 12 mcg x 72 hours x 10 patches x 100 = 864,000 mcg/1000 = 864 mg. For transdermal buprenorphine patches, the assumption is that one patch delivers the dispensed (and bioavailable) micrograms per hour over 96 hours. The total MED dose in milligrams equals (mcg/hour [according to the package reimbursed] x 96 hours x number of patches per package x number of packages reimbursed x 95 [buprenorphine conversion factor])/1,000.

Opioid Episodes

We calculated the episode durations in days using the difference between the claim date of the initial dispensation and the run-out date of the last prescription dispensed plus one day (25). The daily dose was calculated by dividing the total MED per dispensed package by the duration of the episode. In case of several claims, we calculated the run-out date based on the average daily dose between the last 2 dispensation dates. In case of a single claim, we used the defined daily dose provided by the WHO ATC based on the assumed average maintenance dose per day for a drug used for its main indication in adults (24). We categorized opioid episodes based on the duration in acute (< 90 days), subacute (≥ 90 to < 120 days or < 10 claims), and chronic (≥ 90 days and ≥ 10 claims or ≥ 120 day supply of opioids) (25).

Outcomes of Interest

The main outcome of interest was the coprescription of medications recommended or discouraged by treatment guidelines in cancer- and noncancer-related opioids in recurrent opioid use. We further compared the characteristics of cancer- and noncancer-related opioid users.

Definition of Cancer and Noncancer Episodes

We defined an episode to be cancer related if it was within 3 months before and after the start of an opioid treatment, and one of the prespecified ATC or TarMed codes for cancer disease was detected. Underlying malignant disease was defined using ATC codes for malignant disease and TarMed positions related to cancer-specific treatments or interventions (see Appendix 2 for the full list of definitions). Episodes were noncancer related in all other episodes.

Comedications

Comedications were categorized into 3 groups based on the recommendations of treatment guidelines (11):

- Medications not recommended by treatment guidelines: benzodiazepines (N05BA) and stimulants (N06B).
- Medications recommended by treatment guidelines to treat side effects: medications for constipation (e.g., sterculia, lactulose, magnesium carbonate; A06A), antiemetics (e.g., ondansetron; A04A), and propulsive acting drugs (e.g., metoclopramide, domperidone; A03F).
- Medications that may be indicative of mood disorders: antidepressants (N05A), psychotic drugs (N06C), and medications for bipolar disorders (N05AN).

Definition of Comorbidities

We used an adapted version of the chronic disease score (CDS) (26,27) to categorize comorbidities into chronic infections, inflammatory disease, renal disease, endocrine disease, diabetes, pulmonary diseases, liver failure, organ transplant, neurologic disease, cardiac disease, hyperlipidemia, glaucoma, acid peptic disease, thyroid disease, and gout (details of the codes are provided in Appendix 3). The CDS has been shown to be associated with health care use (28,29).

Statistical Methods

Descriptive statistics included median and interquartile range (IQR) for the continuous parameters, and percentages for the categorical parameters. Differences with respect to continuous variables such as age or dose were analyzed with a nonparametric analysis of variance (Kruskal–Wallis test for continuous variables). The chi-square tests were used to test categorical variables for independency. In cases in which both the response and grouping variable had 2 levels, we used the Fisher exact test. Statistical analysis was performed using the computing environment R software (R Foundation for Statistical Computing, Vienna, Austria), a freely available system for statistical computation and graphics environment (https://www.r-project.org/) (30). The following R packages were used: DescTools, mvtnorm, foreign, Rcpp, RDCOMClient, and tcltk.

Ethics Approval and Consent to Participate
This study is based on administrative deidentified insurance claims data handled in compliance with privacy law and regulations. According to the local ethical committee (ethical committee of the canton, Zürich, Switzerland) no institutional review board approval was required. The study was conducted following the principles of good clinical practice and in accordance with the Declaration of Helsinki.

Results

Between January 2006 and December 2014, we identified out of 2,561,558 insured persons 365,116 persons with opioid claims. Overall, we analyzed 591,633 opioid episodes (Table 1; in 66% one episode, in 34% 2 or more episodes); 35,404 episodes (6.0%) were cancer related and 556,229 (94.0%) were noncancer related. The median age was 60.0 years (IQR 44.0-74.0), 59.9% were women, 19.3% had supplementary voluntary private insurance, and 27.3% were in a managed care program. Overall, the episode was acute in 81.3%, subacute in 2.7%, and chronic in 16.0%. In 29.1% of episodes strong opioids were used. Laxative drugs were used in 14.9%, antiemetics in 20.8%, and propulsive drugs in 11.3%. Benzodiazepines were used in 12.6% and stimulants in 0.3%.

The majority of cancer-related episodes included the prescription of strong opioids (61.7 vs. 27.0% in noncancer pain) and a higher overall MED dose was used (median 1,342.0 vs. 323.2 mg MED). The majority of episodes were acute in cancer and noncancer episodes (range between 60.3% and 85.3%). Chronic episodes of strong opioids were observed in 35.0% of cancer and in 23.3% of noncancer episodes.

Table 1. *Baseline characteristics for all opioid claims reimbursed between January 2006 and December 2014.*

	Total	Cancer		Noncancer		*P* Value
		Weak	Strong	Weak	Strong	
		n (%), median [IQR]				
Episodes, n	591,633	13,525 (2.3)	21,879 (3.7)	405,686 (68.6)	150,543 (25.4)	
Age	60.0 [44.0, 74.0]	66.0 [54.0, 75.0]	64.0 [50.0, 74.0]	57.0 [43.0, 72.0]	65.0 [49.0, 78.0]	< 0.001
Gender, female	354,119 (59.9)	8,512 (62.9)	12,279 (56.1)	242,847 (59.9)	90,481 (60.1)	< 0.001
Insurance, p/hp	113,951 (19.3)	3,512 (26.0)	5,490 (25.1)	72,395 (17.8)	32,554 (21.6)	< 0.001
Managed care	161,275 (27.3)	3,430 (25.4)	6,288 (28.7)	111,492 (27.5)	40,065 (26.6)	< 0.001
Number of claims	1.0 [1.0, 2.0]	1.0 [1.0, 3.0]	2.0 [1.0, 9.0]	1.0 [1.0, 2.0]	1.0 [1.0, 4.0]	< 0.001
Strong opioids, n	172,422 (29.1)	-	21,879 (100.0)	-	150,543 (100.0)	
Weak opioids, n	464,031 (78.4)	13,525 (100.0)	7,634 (34.9)	405,686 (100.0)	37,186 (24.7)	< 0.001
MED total	144.0 [72.0, 572.0]	200.0 [100.0, 600.0]	1,342.2 [35.3, 8,449.2]	109.0 [75.0, 300.0]	323.2 [19.8, 2,300.0]	< 0.001
Duration (days)	6.0 [5.0, 43.0]	11.0 [5.0, 69.0]	44.0 [2.0, 201.0]	6.0 [5.0, 22.0]	5.0 [2.0, 101.0]	< 0.001
Duration type						< 0.001
Acute	480,719 (81.3)	10,571 (78.2)	13,191 (60.3)	345,964 (85.3)	110,993 (73.7)	
Subacute	16,216 (2.7)	460 (3.4)	1,023 (4.7)	10,233 (2.5)	4,500 (3.0)	
Chronic	94,698 (16.0)	2,494 (18.4)	7,665 (35.0)	49,489 (12.2)	35,050 (23.3)	
Comedications						
Antiemetic drugs	122,784 (20.8)	4,512 (33.4)	16,456 (75.2)	38,476 (9.5)	63,340 (42.1)	< 0.001
Propulsive drugs	66,750 (11.3)	2,434 (18.0)	9,709 (44.4)	24,529 (6.0)	30,078 (20.0)	< 0.001
Spasmolytic drugs	1,417 (0.2)	37 (0.3)	72 (0.3)	852 (0.2)	456 (0.3)	< 0.001
Laxative drugs	88,419 (14.9)	2,270 (16.8)	9,896 (45.2)	29,949 (7.4)	46,304 (30.8)	< 0.001
Benzodiazepines	74,545 (12.6)	2,236 (16.5)	6,740 (30.8)	39,838 (9.8)	25,731 (17.1)	< 0.001
Stimulants	1,309 (0.2)	24 (0.2)	155 (0.7)	681 (0.2)	449 (0.3)	< 0.001
Paracetamol	180,439 (30.5)	5,300 (39.2)	12,585 (57.5)	108,410 (26.7)	54,144 (36.0)	< 0.001
Metamizole	87,194 (14.7)	2,343 (17.3)	8,726 (39.9)	41,749 (10.3)	34,376 (22.8)	< 0.001
NSAIDs	86,947 (14.7)	1,877 (13.9)	3,887 (17.8)	62,481 (15.4)	18,702 (12.4)	< 0.001
Muscle relaxants	59,141 (10.0)	1,065 (7.9)	3,020 (13.8)	41,534 (10.2)	13,522 (9.0)	< 0.001
Bisphosphonates	17,678 (3.0)	795 (5.9)	2,711 (12.4)	7,452 (1.8)	6,720 (4.5)	< 0.001
PPI	155,541 (26.3)	4,402 (32.5)	10,915 (49.9)	93,038 (22.9)	47,186 (31.3)	< 0.001
Comorbidities						
Chronic infection	15,991 (2.7)	508 (3.8)	1,937 (8.9)	6,206 (1.5)	7,340 (4.9)	< 0.001

Table 1 con't. *Baseline characteristics for all opioid claims reimbursed between January 2006 and December 2014.*

	Total	Cancer		Noncancer		*P* Value
		Weak	Strong	Weak	Strong	
	n (%), median [IQR]					
Inflammatory disease	106,606 (18.0)	3,971 (29.4)	11,081 (50.6)	63,477 (15.6)	28,077 (18.7)	< 0.001
Renal disease	1,757 (0.3)	67 (0.5)	186 (0.9)	727 (0.2)	777 (0.5)	< 0.001
Endocrine disease	2,164 (0.4)	178 (1.3)	932 (4.3)	480 (0.1)	574 (0.4)	< 0.001
Diabetes	30,313 (5.1)	853 (6.3)	1,582 (7.2)	19,090 (4.7)	8,788 (5.8)	< 0.001
Pulmonary disease	31,229 (5.3)	836 (6.2)	2,200 (10.1)	18,072 (4.5)	10,121 (6.7)	< 0.001
Liver failure	13,188 (2.2)	391 (2.9)	1,699 (7.8)	4,652 (1.1)	6,446 (4.3)	< 0.001
Organ transplant	2,112 (0.4)	90 (0.7)	195 (0.9)	1,105 (0.3)	722 (0.5)	< 0.001
Neurologic disease	9,075 (1.5)	189 (1.4)	511 (2.3)	4,262 (1.1)	4,113 (2.7)	< 0.001
Cardiac disease	152,029 (25.7)	4,594 (34.0)	10,770 (49.2)	87,953 (21.7)	48,712 (32.4)	< 0.001
Hyperlipidemia	44,505 (7.5)	1,148 (8.5)	2,082 (9.5)	27,968 (6.9)	13,307 (8.8)	< 0.001
Glaucoma	10,079 (1.7)	286 (2.1)	715 (3.3)	5,100 (1.3)	3,978 (2.6)	< 0.001
Thyroid disease	16,109 (2.7)	448 (3.3)	901 (4.1)	9,343 (2.3)	5,417 (3.6)	< 0.001
Gout	9,186 (1.6)	358 (2.6)	860 (3.9)	5,218 (1.3)	2,750 (1.8)	< 0.001

The Kruskal–Wallis test was used for the comparison of continuous variables, and the chi-square test was used for categorical variables. Numbers calculated based on the area of residency (canton).
Insurance type, proportion of patients with private (p)/semiprivate (hp) insurance; MED, morphine equivalents in milligram; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Recurrent Episodes

We identified 76,968 episodes with strong opioids and 2 or more reimbursed claims (Table 2); 17.3% were cancer-related and 82.7% were noncancer-related episodes. A median of 5 claims were reimbursed (noncancer 5, cancer 7) and 55.4% were chronic episodes (noncancer 55.0%, cancer 57.5%). The choice of the drug differed between cancer and noncancer-related episodes (Appendix 4). In noncancer-related episodes, oxycodone (39.4%), fentanyl (32.7%), and morphine (32.9%) were mainly prescribed. In cancer-related episodes, morphine was most frequently used (51.7%), followed by fentanyl (45.5%), and oxycodone (36.5%). The proportion of the combination oxycodone/naloxone was comparable in cancer- and noncancer-related episodes (not shown).

Use of Guideline Recommended Comedications

Laxative drugs were used in 53.2% of the episodes (50.3% noncancer, 67.1% cancer-related episodes; Fig. 1), antiemetics in 59.2% (54.2% noncancer, 82.9% cancer episodes), and propulsive drugs in 39.0% (noncancer 33.6%, cancer episodes 64.4%).

Use of Comedications Discouraged by Guidelines

Benzodiazepines were used in 35.9% (33.9% noncancer, 45.8% cancer episodes; Fig. 1). Psychostimulants were infrequently used (noncancer 0.6%, cancer 1.1%).

Medications Indicating Mood Disorders

Antidepressants were used in 36.0% (noncancer 36.4%, cancer 33.8%; Fig. 1), antipsychotic medications in 15.5% (noncancer 15.3%, cancer 16.4%), and drugs for bipolar disorders in 0.3% (noncancer 0.3%, cancer 0.2%).

Other Comedications

Paracetamol was used in 60.1% (noncancer 58.7%, cancer 66.4%; Fig. 1), metamizole in 39.9% (noncancer 37.9%,

cancer 49.4%), and nonsteroidal anti-inflammatory drugs in 22.4% (noncancer 22.4%, cancer 23.1%). Muscle relaxants were used in 14.3% (noncancer 14.7%, cancer 12.3%). Proton pump inhibitors were used in 61.2% (noncancer 58.8%, cancer 72.6%).

Table 2. *Use in medications recommended or discouraged by guidelines in recurrent opioid use.*

	Total	Noncancer	Cancer	*P* Value
	n (%), median [IQR]			
Episodes, n	76,968	63,642 (82.7)	13,326 (17.3)	
Age	71.0 [56.0, 81.0]	72.0 [56.0, 82.0]	67.0 [57.0, 76.0]	< 0.001
Gender, female	48,858 (63.5)	41,699 (65.5)	7,159 (53.7)	< 0.001
Number of claims	5.0 [3.0, 14.0]	5.0 [2.0, 14.0]	7.0 [3.0, 16.0]	< 0.001
Duration type				
Acute	28,862 (37.5)	24,220 (38.1)	4,642 (34.8)	< 0.001
Subacute	5,468 (7.1)	4,446 (7.0)	1,022 (7.7)	
Chronic	42,638 (55.4)	34,976 (55.0)	7,662 (57.5)	
Recommended medications				
Laxative drugs	40,937 (53.2)	31,994 (50.3)	8,943 (67.1)	< 0.001
Antiemetic drugs	45,595 (59.2)	34,544 (54.3)	11,051 (82.9)	< 0.001
Propulsive drugs	29,998 (39.0)	21,417 (33.7)	8,581 (64.4)	< 0.001
Antispasmolytic drugs	477 (0.6)	406 (0.6)	71 (0.5)	0.2
Not recommended medications				
Benzodiazepines	27,654 (35.9)	21,548 (33.9)	6,106 (45.8)	< 0.001
Stimulants	555 (0.7)	404 (0.6)	151 (1.1)	< 0.001
Medications for mood disorders				
Antidepressants	27,681 (36.0)	23,175 (36.4)	4,506 (33.8)	< 0.001
Antipsychotic drugs	11,913 (15.5)	9,729 (15.3)	2,184 (16.4)	0.002
Drugs for bipolar disorders	217 (0.3)	194 (0.3)	23 (0.2)	0.007

The Kruskal–Wallis test was used for the comparison of continuous variables, and the chi-square test was used for categorical variables.

Discussion

The major finding of this study was that in 80% of strong opioids prescriptions, the indication was noncancer pain. Patients with recurrent strong opioid claims for noncancer pain were less likely to use laxative, antiemetic, and propulsive drugs compared with cancer patients. Benzodiazepines were coprescribed in one-third of patients with noncancer pain, and in almost every second cancer episode. Overall, one-third of patients with recurrent opioid use received antidepressants, and one-sixth received antipsychotic medications indicating a mood disorder.

Results in Light of the Literature

Worldwide, the use of opioids increased over the last 20 years. In North America, liberal opioid prescription practices and policies promoting opioids for appropriate pain management resulted in an opioid epidemic (31). Although studies also showed an increased use of strong opioids in Europe (16,17,32,33), the consequences were less clear, and a study in the United Kingdom found no increase in opioid dependence despite an increased use in opioids (34). Many studies were based on consumer data (32,33) that did not reflect the use in clinical practice driving a debate among clinicians about the implications in Europe (35,36). Although in Switzerland, studies based on consumer data indicate the highest use internationally (37), however, analyses of insurance claims data indicate a much smaller increase in the use of strong opioids (18). The difference is mainly because consumer data also include opioids used within addiction substitution programs that are covered by compulsory insurance since the 1990s. However, a recently published study in the primary care setting in the United Kingdom found long-term opioid use to be associated with serious adverse events such as major trauma, addiction, and overdose (34).

Although the American Society of Interventional Pain Physicians issued guidance for clinicians on the responsible, safe, and effective prescription of opioids for chronic noncancer pain (8), the European Pain Federation position paper focuses more on the access to opioids and misconceptions that may be barriers to the appropriate opioid use (12). Effective and safe pain management remain a challenge. The main goal is to alleviate pain with as little side effects as possible. Both guidelines recommend treating potential side effects (e.g., constipation and nausea) and to avoid the coprescribing of benzodiazepines. Opioid-related constipation may not be identified by clinicians and is a major concern and burden to patients. An international survey

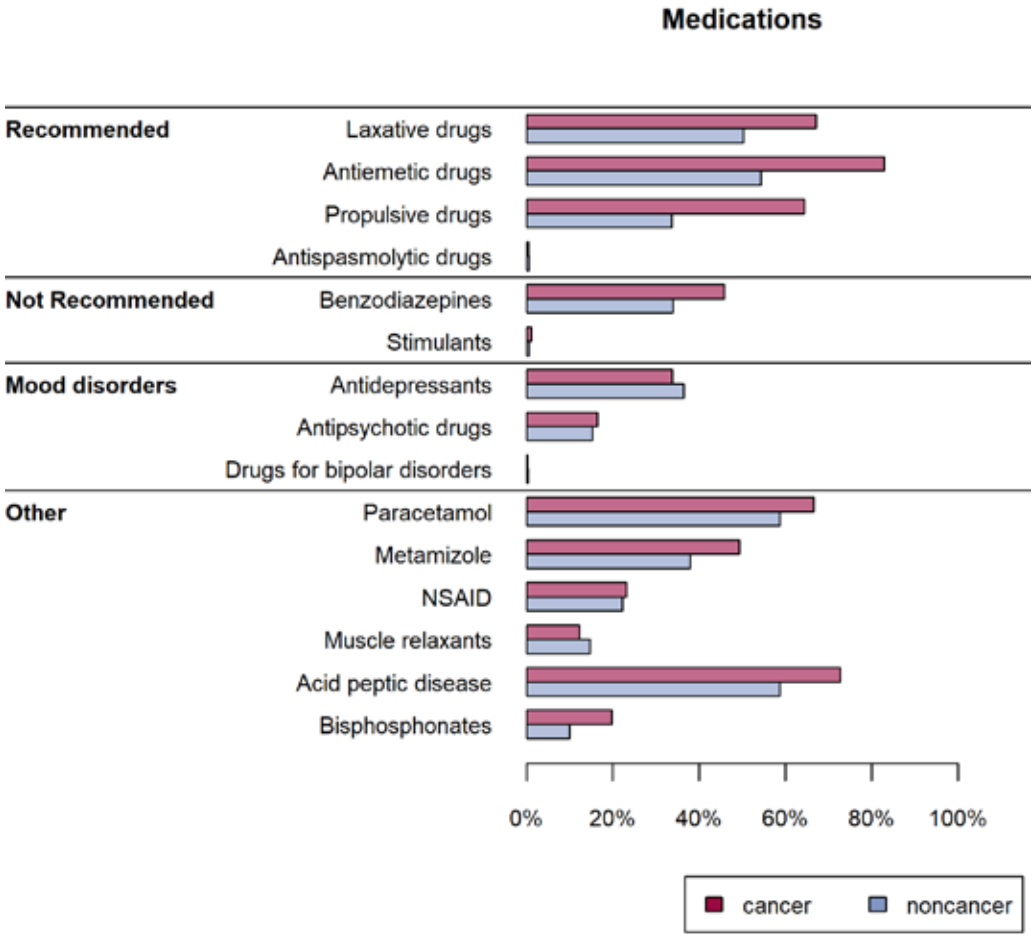

Fig. 1. *Coprescription of medications in recurrent strong opioid episodes.*

found in patients using opioids for chronic noncancer pain, almost 60% had straining bowl movements that affected their quality of life (38). In a cohort study of chronic opioid users, 82% reported gastrointestinal symptoms equally severe in intensity as their pain (21). One-third of the patients who had seen their health care provider during the past month reported that they had not spoken about constipation and were not asked if they had constipation in the past month. Health care providers and patients did not agree on the presence of constipation at baseline in 40% (21). The study also found differences across countries on how health care providers discussed gastrointestinal side effects (in 46% in the United Kingdom, 52% in Canada, 64% in the United States, and 76% in Germany) (21). In the current study, every second patient with recurrent strong opioid use was never prescribed a laxative, indicating that the uptake of the guideline recommendations remains particularly low in patients with noncancer pain.

Therefore, education of physicians treating pain may be necessary to improve the management of opioid use in clinical practice. This is particularly relevant because long-term opioid use has been found to increase the all-cause mortality (39), and the concomitant use of benzodiazepines increased the risk for opioid overdose (19). According to our study, one-third of patients with recurrent opioid claims may be at an increased risk for an opioid overdose due to concomitant benzodiazepine use.

Strengths and Limitations

The major strength of this study was the large number of opioid claims analyzed. The health insur-

ance database covers approximately one-sixth of the Swiss population covering all parts of the country, and therefore it is a quasirepresentative sample. In contrast to consumer data, insurances claims data allow to analyze prescription patterns and their association with patient characteristics and geographic variation. This is a unique way of knowing more about how opioids are used (40).

The major limitation is that we were not able to analyze the relationship between clinical information (e.g., clinical diagnosis, disease severity, and symptoms) and opioid prescription patterns of physicians. We used ATC and TarMed codes to identify cancer treatments related to the opioid prescription. Although this approach has been used as an approximation in many studies (26-29), we were not able to identify persons who received opioids for cancer-related pain but did not undergo specific treatments. To investigate the appropriateness of opioid use, further studies are needed. Further, we may have missed some medication use because patients did not send their invoices or because their annual expenses did not exceed their annual deductible. Internal analyses of Helsana showed that ≤ 2% of costs were missing because persons did not send in their invoices. However, due to increased use of electronic invoicing, this effect is of decreasing importance. The database therefore provides an approximately complete picture of opioid prescriptions.

Finally, we did not have information on the use of hydrocodone (ATC code R05DA03), which is not covered by the basic insurance in Switzerland. However, hydrocodone is in rare cases prescribed by physicians, and a prescription for narcotic substances is required with the same regulations that apply for other strong opioids.

Implication for Research

Our study showed that the main increase is not related to cancer treatment. Future studies should assess whether the use of strong opioids results, as this was the case in the United States, in an increased risk of overdose and deaths. Further, studies should aim to analyze the differences in physician practices in Europe that may explain wide geographic variations. In addition, future studies should quantify the amount of opioids in noncancer patients prescribed in end-of-life situations. These prescriptions are likely to be appropriate and should therefore be distinguished from the treatment of pain in nonpalliative situations.

Implication for Clinical Practice

Chronic pain is a major health care problem. Studies indicate that musculoskeletal pain are among the top 10 diseases resulting in pain-related disability. In musculoskeletal pain, several studies show that opioids are no more effective than nonopioid pain medications. Therefore, the prescription of pain medications should be based on the patient's preferences, individual contraindications, and adverse effects of medications. In acute pain, clinicians should weight the benefit and harm of each pain medication individually (12). Opioids should be used as short as necessary when treatment goals are achieved. In chronic pain, prescribing opioids should include the definition of treatment goals that are monitored (10,12). In case goals are not reached or opioids seem to be ineffective, the pain and other adverse effects may improve after opioids are stopped (41). Opioid-related constipation may not be identified by clinicians (21) and is a major concern and burden to patients (38). Our study showed that patients receiving strong opioids for noncancer pain were less likely to receive laxatives, antiemetic drugs, and propulsive drugs. Further, clinicians should be aware of an increased risk for opioid overdose with the concomitant use of benzodiazepines, which was found in our study in one-third of the patients.

Conclusions

In this study, we showed that opioids were primarily used outside the context of cancer treatment. In noncancer-related opioid use, we found a substantial proportion without recommended antiemetic and laxative medications. Coprescription of benzodiazepines may increase the risk for opioid overdose and was present in one-third of the noncancer episodes and in almost every second cancer episode.

Acknowledgments

Author contributions: M.W., U.H., J.B., E.B., and J.S. designed the study and interpreted the study results. A.S. and U.H. conducted the analysis and interpreted the study results. M.W. drafted the manuscript. All authors discussed the results and commented on the manuscript.

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Appendix Table 1

Appendix Table 2

Appendix Table 3

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