pharmacoepidemiology

MDPI

Article

Opioid Prescribing for Noncancer Patients—Issues of Drug Therapy Safety: Results from a German Study Based on Routine Data

Veronika Lappe [1], Daniel Grandt [2], Ursula Marschall [3] and Ingrid Schubert [1,*]

[1] PMV forschungsgruppe, Faculty of Medicine and University Hospital Cologne, University of Cologne, 50931 Cologne, Germany; veronika.lappe@uk-koeln.de
[2] Internal Medicine 1, Klinikum Saarbrücken gGmbH, 66119 Saarbrücken, Germany; e-mail@danielgrandt.de
[3] Head of Department Medicine/Health Care Research, Barmer, 42285 Wuppertal, Germany; ursula.marschall@barmer.de
* Correspondence: ingrid.schubert@uk-koeln.de

Abstract: Opioids are highly effective drugs but need close monitoring to avoid harm to patients. The aim of this study was to analyze how guideline recommendations are met for (i) the avoidance of the concomitant use of anxiolytics, hypnotics, or sedatives; (ii) the prescribing of laxatives in long-term opioid treatment; (iii) the co-prescribing of drugs to control the emetic effect of opioids; (iv) pretreatment with non-opioids; and (v) screening for depression when initiating opioids. The results are based on a routine data analysis of a large German health insurance fund. Different study populations of noncancer patients (18+ years old) treated with opioids were analyzed: 10.4% of the opioid recipients in 2021 received at least one concomitant prescription with anxiolytics, hypnotics, or sedatives; 69.3% of those with long-term opioid treatment received at least one laxative prescription. Of those with first-time opioid prescriptions, 4.8% received an antiemetic drug; 47.3% of those with a newly initiated opioid therapy received a non-opioid prescription within three months before the start of the opioid therapy; and 22.0% of patients with incident opioid prescription had at least one documentation of a depression diagnosis within three months of the first prescription. There is an urgent need to improve opioid prescribing to avoid risky combinations and adverse effects.

Keywords: opioids; guideline recommendations; quality of prescribing; noncancer patients; drug therapy safety; co-medication; routine data analysis

Citation: Lappe, V.; Grandt, D.; Marschall, U.; Schubert, I. Opioid Prescribing for Noncancer Patients—Issues of Drug Therapy Safety: Results from a German Study Based on Routine Data. *Pharmacoepidemiology* **2024**, *3*, 94–102. https://doi.org/10.3390/pharma3010007

Academic Editor: Matthew Ellis

Received: 16 January 2024
Revised: 10 February 2024
Accepted: 16 February 2024
Published: 22 February 2024

1. Introduction

Opioids are strong painkillers associated with major, avoidable risks and adverse effects such as, e.g., constipation, nausea, pruritus, dizziness and drowsiness, respiratory depression, falls, and addiction if used improperly or inadequately monitored [1,2]. They are prescribed to patients with cancer pain but also to patients with noncancer pain. Internationally, many countries have assessed opioid use in the last ten years due to reports from the United States about the correlation between increased prescribing and emergency admissions to hospitals and deaths between 1990 and 2010 ("the opioid crisis") [3–10]. One influencing factor seemed to be aggressive marketing, which also influenced guidelines for treating noncancer pain [11]. In Germany, experts did not note an opioid crisis, partly due to restrictive regulations for prescribing opioids and access to other non-pharmacological measures and multimodal strategies for pain patients [12]. However, opioid prescribing increased in Germany, as in many other countries—there was a 3.8% increase in defined daily doses from 2012 to 2021 [13]—and special attention is placed on prescribing them for noncancer pain [14–21].

A recent study by Grandt et al. [22] assessed the prevalence of opioid prescribing in about 7.5 million insured persons of a German statutory health insurance fund, and 5.7% of

insured persons without a cancer diagnosis received at least one opioid prescription in 2021 (men: 4.2%, women: 6.8%). Women 80 years old and older showed the highest prevalence (20.3%). Long-term opioid prescribing—defined as treatment with more than 91 daily doses (defined daily dose (DDD)) over a period of more than 91 days [14]—was observed in 1.9% of all insured persons. The highest prevalence for long-term therapy was in those 80 years old and older (total 7.5%; men 4.5%, women 8.7%). Of those with long-term prescriptions in 2021, 62.9% had a yearly opioid prescription for over five years [22]. These findings show that opioids in Germany are prescribed to a relevant extent. Based on the study by Grandt et al. cited above [22], we aim to describe the extent to which selected guideline recommendations on opioid therapy are implemented. Three recommendations will be examined as examples: first, the mortality-increasing combination of prescription opioids with tranquilizers [23]; second, the concomitant prescribing of laxatives to avoid the risk of fecal impaction and intestinal obstruction [24]; and third, the prevalence of the prescription of antiemetics, which is not required in all patients, at the start of therapy with opioids. We further aim to analyze pretreatment with analgesics prior to opioid prescribing and the percentage of opioid recipients with evidence of depression at the onset of opioid prescribing.

2. Materials and Methods

For this study, we analyzed data from one of the largest statutory health insurance funds (BARMER) in Germany, which includes about 9 million people (12%) of the German population insured with statutory health insurance (73 million). (For an explanation of the health insurance system in Germany, see [25]). The data were accessed via the scientific data warehouse, and the location where the data are stored under data protection law. The basic population was adults insured by BARMER (>17 years old) without a diagnosis of malignant neoplasm (ICD-10 code C00-C97). This includes members (compulsorily and voluntarily insured) and co-insured family members. These criteria were fulfilled by n = 6,771,075 people (men n = 2,857,793, women n = 3,913,282) who were continuously insured with BARMER in the observation year or continuously insured for one year before their death. Because there is a subsequent benefit entitlement of one month if certain criteria are met, individuals with an insurance gap of up to 31 days in the observation year were also classified as continuously insured.

We observed prevalent opioid prescriptions in 2021 and incident opioid prescriptions in 2019 and 2018 to 2020, respectively. The study population for 2021 had to be continuously insured with BARMER in 2021 or continuously insured for one year before their death in 2021. In total, 388,095 people had at least one prescription for an opioid in 2021 (121,310 men; 266,785 women). The criteria for long-term opioid prescribing (see Section 1), excluding (dihydro)codeine, were met by 125,315 persons (34,642 men and 90,673 women).

The study population with incident prescribing of opioids, i.e., the first prescription was redeemed in 2019 or 2018 to 2020, respectively, had no opioid prescription documented two years before the first prescription. The incident patients had to be continuously insured during the observation period. In total, 142,598 patients (49,759 men and 92,839 women) started an opioid prescription in 2019, and 407,008 patients received opioids (excluding (dihydro-)codeine) from 2018 to 2020 (143,046 men and 263,962 women).

The topics analyzed have been chosen due to the recommendations and warnings In the guidelines [14,15,17–19,23].

Drugs were assessed by the anatomical therapeutic chemical (ATC) code. Opioids were identified by ATC N02A. (Levo-)methadone (N02AC06/-52) was not included as it is mainly prescribed in substitution therapy. (For other active ingredients, see below). Opioids have to be prescribed by physicians; strong opioids need a narcotic prescription. Some pain medications, such as non-steroidal anti-inflammatory drugs in lower strengths, as well as herbal (M01BP, N02BP) and homeopathic (M01BH, N02BH) medicines, are not reimbursed by the statutory health insurance funds and, therefore, cannot be analyzed with routine prescription data.

The treatment recommendations for opioids include the prescription of laxatives, antiemetics, and sedatives. These drug groups were identified by their respective ATC codes:

- Anxiolytics/hypnotics/sedatives N05B and N05C without herbal ingredients;
- Laxatives (drugs treating constipation) A06A;
- Drugs to control the antiemetic effect of opioids: antiemetic drugs (A04AA, A04AB, A04AD); propulsives (A03FA) and antipsychotics: haloperidol, chlorpromazine and levopromazine (N05AD01, N05AA01/-02), dexamethasone (H02AB02/-BX02), olanzapine (N05AH03/-53), and lorazepam (N05BA06/-56).

There were no electronic prescriptions at the time of this study; these were not introduced until 1 January 2024. For this study, we analyze the drugs dispensed and reimbursed. In order to be as close as possible to the date on which the medication was first taken, the date on which the prescription was filled at the pharmacy was used instead of the date on which the prescription was issued. To analyze the concomitant prescribing of opioids with anxiolytics or laxatives in 2021, we defined the period of drug use by assuming the drug intake of one DDD starting with the date of prescription redemption. Antiemetic drug therapy was assessed for beginners of opioid therapy during a time window of 14 days after the date of the first opioid prescription, and non-opioids had to be prescribed within three months (91 days) before the start of opioid therapy.

Non-opioids were assessed by ATC codes M01A ("non-steroidal anti-inflammatory and anti-rheumatic drugs" and N02B ("other analgesics and antipyretics"). Corresponding analgesic agents with the combination ATC codes M01BA and R05XA were included in the analyses and listed under the ATC codes of the individual substances.

Depression diagnosis was recorded using the ICD-10 codes F32.- and F33.-.

3. Results

3.1. Anxiolytics/Hypnotics/Sedatives

The frequency of a parallel prescription of tranquilizers was investigated for insured patients without a tumor diagnosis who were prescribed opioids in 2021. It was found that, on average, one in ten patients with opioid therapy received this risky combination. On average, the amount of DDD prescribed allowed simultaneous use over 55 days.

Although the risk is particularly high in older patients, it was mainly patients over 80 years of age who were treated with opioids in combination with tranquilizers (Figure 1). Up to 15 percent of women and 14 percent of men were affected.

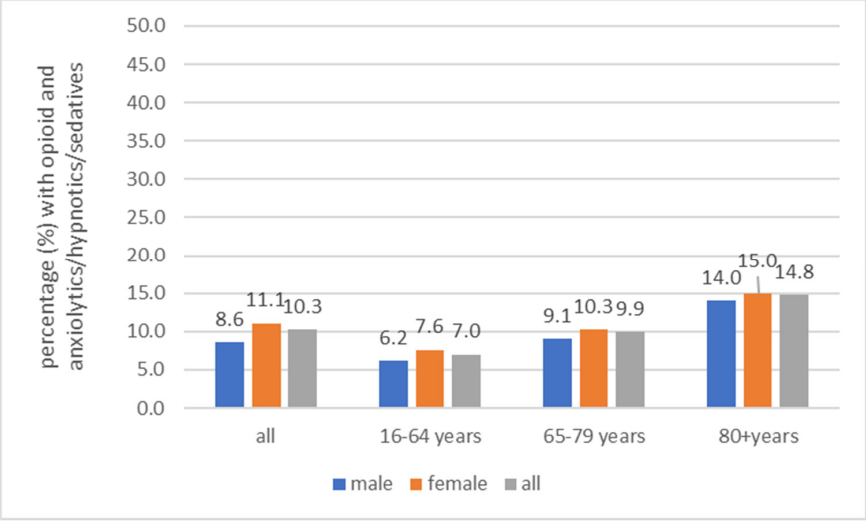

Figure 1. Percentage of opioid recipients with simultaneous prescription of anxiolytics/hypnotics/sedatives in 2021. Source: BARMER data, 2020–2021 [22]. BARMER insured in 2021, without tumor diagnosis, 18 years and older, with opioid prescription in 2021. Total n = 388,095; men n = 121,310, women n = 266,785. Anxiolytics/hypnotics/sedatives N05B and N05C without herbal ingredients.

3.2. Laxatives

The analysis showed that about 70 percent of patients on long-term opioid therapy were prescribed a laxative, meaning that 30 percent did not receive a prescription for a necessary laxative (Figure 2). Age and gender differences were small in this regard.

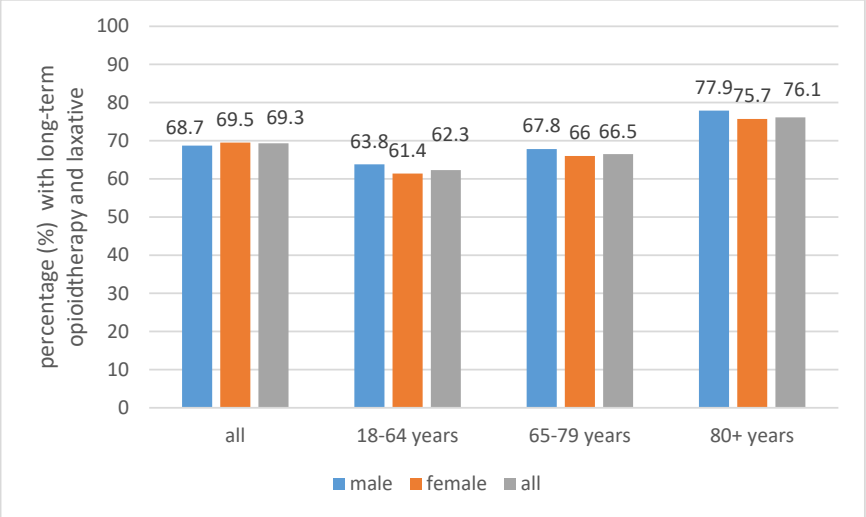

Figure 2. Percentage of long-term opioid recipients with a laxative prescription in 2021 [22]. Source: BARMER data, 2020–2021. BARMER insured in 2021, without cancer diagnosis, 18 years and older with long-term opioid therapy (excluding [dihydro-]codeine) in 2021. Total n = 125,315; men n = 34,642, women n = 90,673.

3.3. Antiemetic Drugs

The frequency of prescribing antiemetics (ATC; see Section 2) at the start of opioid therapy, i.e., at intervals of up to two weeks from the date of the first opioid prescription, was investigated. It was found that, in all age and sex groups, only about one in twenty patients was prescribed an antiemetic, and women slightly more often than men (Table 1).

Table 1. Percentage of first-time opioid recipients being prescribed an antiemetic drug within the first 14 days after the start of opioid therapy in 2018–2020.

Sex	Percentage of First-Time Opioid Recipients with Antiemetic Drugs			
	Percent			
	Total	18–64 years	65–79 years	80+ years
Male	4.2	4.0	4.2	5.4
Female	5.2	4.6	5.0	6.4
Total	4.8	4.4	4.8	6.2

Source: BARMER data, 2016–2021 [22]. Redemption of a prescription for antiemetic drugs up to two weeks after redemption of the incident opioid prescription (excluding [dihydro]codeine). BARMER insured, without tumor diagnosis, aged 18 years and older with opioid prescription in 2018–2021. Total n = 407,008; men n = 143,046, women n = 263,962.

3.4. Pretreatment with Non-Opioids

According to the guidelines, nonmedical activation treatments (physiotherapy, psychotherapy) and non-opioid prescribing should be optimized before initiating an opioid prescription [15].

According to our data, less than half (47.3 percent) of those with newly initiated opioid therapy received a non-opioid prescription within the three months (91 days) before the start of the opioid therapy, with a mean of 17 DDD (see Table 2).

Table 2. Percentage of first-time opioid recipients being given a non-opioid prescription three months before the initiation of opioids.

		First-Time Opioid Recipients with a Non-Opioid Prescription Three Months before the Initiation of Opioids	
Age	**Sex**	**Percent**	**Mean DDD ***
18–64	Male	40.4	14
	Female	44.5	16
	All	42.8	15
65–79	Male	47.6	18
	Female	53.2	20
	All	51.5	19
80+	Male	50.7	17
	Female	58.3	20
	All	56.9	19
Total	Male	42.9	15
	Female	49.6	18
	All	47.3	17

* DDD: defined daily dose; Source: BARMER data, 2017–2021. BARMER insured, 18+, without cancer diagnosis, with incident opioid prescribing in 2019, continuously insured 2017–2021. Total: n = 142,598; men: n = 49,759, women: n = 92,839.

3.5. Depression

The data analysis showed that, for patients with an incident prescription of opioids, 22.0 percent had at least one documentation of a depression diagnosis (ICD-10 code F32, F33) in the same quarter as the first prescription. When looking back four quarters (including the quarter of incidence), 26.6 percent had a depression diagnosis (Figure 3).

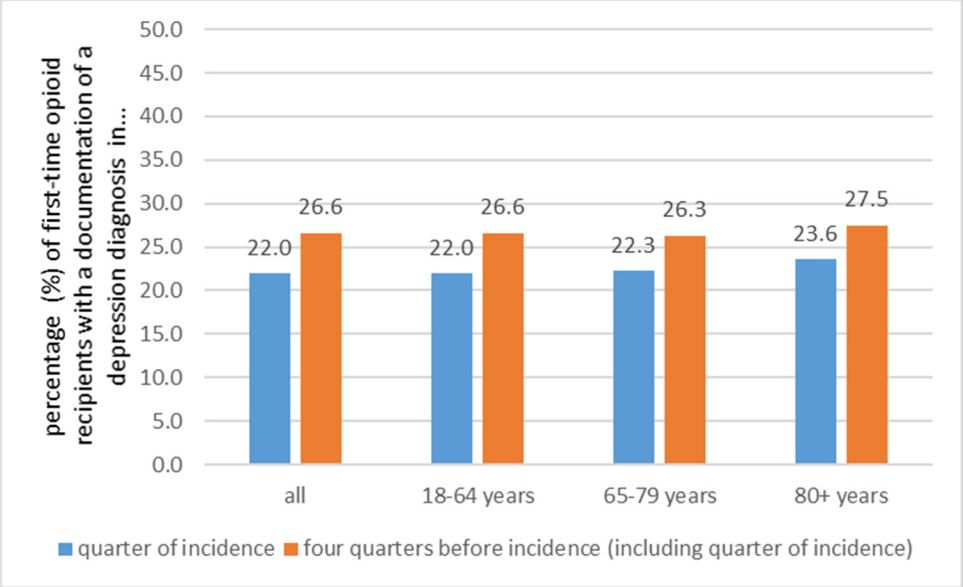

Figure 3. Percentage of first-time opioid recipients with documentation of a depression diagnosis at the time of the incident prescription and in the three quarters before. Source: BARMER data, 2017–2021. BARMER insured, 18+, without cancer diagnosis, with an incident opioid prescription in 2019, continuously insured 2017-2021. Total: n = 142,598; men: n = 49,759, women: n = 92,839.

4. Discussion

4.1. Comparison with Other Studies

For this study, we analyzed a population of noncancer patients with opioid prescriptions with regard to drug therapy safety issues. The issues addressed refer to basic recommendations for opioid prescribing: concomitant use with sedatives/hypnotics, the

avoidance and treatment of obstipation in long-term use, and the treatment of nausea in incident users. For these issues, as well as for recommendations on pretreatment and screening for mental disorders before the start of opioid prescribing, evidence-based recommendations are available.

Sedatives/hypnotics: Based on several studies showing that concomitant treatment with opioids and sedative medications, such as benzodiazepines or Z-substances, often results in severe side effects, the need for hospitalization, and an increased number of deaths [5,26,27]. The German evidence-based guideline "Long-term use of opioids for chronic non-tumor-related pain (LONTS)" [14] strongly recommends not combining the prescription of tranquilizers with opioids.

In our study, 10.3% of opioid recipients received at least one prescription with an anxiolytic, hypnotic, or sedative. In the elderly (80+ years old), the proportion was 14.8%. In a Norwegian study in 2004, the authors reported that 21% of noncancer opioid users also received benzodiazepines or benzodiazepine-related hypnotics in a one-year period. Of those with persistent opioid use, the percentage increased to 60% [28]. Jani et al. [29] reported the co-prescribing of benzodiazepine in first-time opioid users in several countries. There is regional variation, e.g., in Canada: Quebec, 20.0%, vs. Alberta, 4.1%; as well as Boston, Massachusetts (USA), 7.2%, the UK, 7.0%, and Taiwan, 18.2%. The data from all the studies underline the necessity of informing prescribers, patients, and caregivers of the need to avoid this concurrent drug use.

Obstipation: It is well known that opioids induce obstipation in 40 to 60 percent of treated patients [30], even in patients without tumors [31]. Both strong and weak opioids can cause this side effect [32]. Constipation can occur rapidly or develop slowly, but, most importantly, it is a symptom that persists throughout the duration of therapy [30]. Prophylactic prescription of laxatives concomitant with the initiation of therapy is indicated according to expert consensus and guidelines [24]. According to our data, 30% of patients on long-term opioid therapy did not receive a prescription for a necessary laxative. Other studies showed that prescribed laxatives have not been taken as recommended. Patients seem not to be well informed [33]. Again, there are hints of undertreatment and the need for further education of patients and healthcare professionals, as untreated constipation can lead to intestinal obstruction, which poses a great risk.

Nausea: A further side effect of opioid treatment is nausea and vomiting, especially at the beginning of treatment with opioids [34]. In contrast to constipation, the symptoms usually subside quickly. According to data from a Canadian guideline [18], the incidence of nausea for opioid users is 15% (3% for non-opioid users). The guideline recommends minimizing this side effect by slowly increasing the dose of the drug. If necessary, antinausea drugs and bowel stimulants can be prescribed. The German guideline LONTS [14] gives no strong recommendation for antiemetic drug prescribing; only 4.8% of the first-time opioid users in our study received an antiemetic drug. Patients should be encouraged to inform their prescribers about nausea, as the success of the therapy may be impaired.

Pretreatment: Guidelines for opioid prescribing strongly recommend multimodal strategies [14,15]. Monotherapy with opioids should be strictly avoided. This means that the patient should receive non-pharmacological treatment and pretreatment with non-opioid analgesics. In our study, less than half of the first opioid users (47.3%) had a non-opioid prescription within the three months before the initial prescription. Non-prescription (over-the-counter) analgesic drugs are not included; therefore, the percentage with pretreatment might be underestimated. The results should, therefore, be interpreted with caution. Furthermore, we have no information about the individual pain situation. The Australian study by Lalic et al. [3] found an even lower proportion of about one-third who had been treated with non-opioids within three months before the initiation of opioid prescribing.

Mental disorders: Patients in whom chronic pain is a symptom of mental disorders should not receive opioids [15]. This also applies to depression. Guidelines recommend screening for mental disorders. We found documentation of depression in 22.0% of the

study population in the same quarter as the first opioid prescription. The data do not allow us to differentiate the severity of the disease, however. Several studies show the proportion of opioid users with depression. Lalic et al. [3] reported a comparable percentage of 19.5% of persons with a documentation of a depression diagnosis within the 365 days prior to opioid initiation. Scherrer et al. showed an increased risk for long-term opioid users of developing depression with frequent or daily use of an opioid, and so recommended repeated screening for depression during the therapy [35].

4.2. Strengths and Limitations

This study has strengths and limitations. The strengths are those involved in routine data analyses: a large dataset, no selection bias, and no interviewer or recall bias. The data are from one large statutory health insurance fund; therefore, we have to be careful to extrapolate the results to the total population. But, as we are analyzing medical practices, we feel confident that the results also apply to other health insurance funds.

As we used prescription data, we only analyzed drugs reimbursed by the statutory health insurance. Therefore, we might underestimate the use of over-the-counter drugs in self-medication, such as some non-opioids (mainly NSAR) or laxatives. Moreover, we did not include private prescriptions, e.g., for tranquilizers. Further, we must point out that an issued and filled prescription does not guarantee ingestion of the drug, which cannot be verified from routine data. Therefore, with routine data, we can only monitor the probability of concomitant drug use. Whether antiemetics were prescribed prophylactically or the treatment of existing nausea and vomiting cannot be distinguished in routine data.

4.3. Implications for Policy, Practice, and Research

In order to improve the safety of opioid use, the prescribing physician needs to take a complete medical and medication history and make an actual medication plan to avoid risky combinations. Up to now, the existence of a medication plan as a prerequisite for drug safety has not always been guaranteed for German patients [36]. There is hope that this situation will improve in the coming years with the introduction of electronic prescriptions and electronic patient files. Further research could focus on patients and situations where there is an increased risk of unforeseen events during opioid use. It is imperative that, in addition to doctors, other healthcare professionals, such as pharmacists and nurses, as well as patients and their families, are informed about the benefits and risks of opioid therapy. Guidelines and multiple interventions with prescribing feedback to physicians seem to be helpful tools [37], but we still need to learn more about their successful implementation.

Author Contributions: Conceptualization, D.G., V.L., I.S. and U.M.; methodology, V.L. and I.S.; formal analysis, V.L.; writing—original draft preparation, I.S.; writing—review and editing, V.L.; supervision, D.G. and U.M.; project administration, I.S.; funding acquisition, I.S. and V.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Statutory Health Insurance Fund BARMER.

Institutional Review Board Statement: Ethical review and approval were waived for this study due to routine data analysis based on anonymized data.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets generated during and/or analyzed during the current study are not publicly available due to data protection regulations for data of statutory health insurance but are available upon justified request in agreement with BARMER and upon successful application to the competent supervisory authority.

Conflicts of Interest: V.L., I.S. and D.G. received funding from BARMER. U.M. is employed by BARMER.

References

1. Gustafsson, M.; Matos, C.; Joaquim, J.; Scholl, J.; van Hunsel, F. Adverse Drug Reactions to Opioids: A Study in a National Pharmacovigilance Database. *Drug Saf.* **2023**, *46*, 1133–1148. [CrossRef]
2. Bedson, J.; Chen, Y.; Ashworth, J.; Hayward, R.A.; Dunn, K.M.; Jordan, K.P. Risk of adverse events in patients prescribed long-term opioids: A cohort study in the UK Clinical Practice Research Datalink. *Eur. J. Pain* **2019**, *23*, 908–922. [CrossRef]
3. Lalic, S.; Ilomäki, J.; Bell, J.S.; Korhonen, M.J.; Gisev, N. Prevalence and incidence of prescription opioid analgesic use in Australia. *Br. J. Clin. Pharmacol.* **2019**, *85*, 202–215. [CrossRef]
4. Hamina, A.; Muller, A.E.; Clausen, T.; Skurtveit, S.; Hesse, M.; Tjagvad, C.; Thylstrup, B.; Odsbu, I.; Zoega, H.; Jónsdóttir, H.L.; et al. Prescription opioids among older adults: Ten years of data across five countries. *BMC Geriatr.* **2022**, *22*, 429. [CrossRef] [PubMed]
5. Dasgupta, N.; Funk, M.J.; Proescholdbell, S.; Hirsch, A.; Ribisl, K.M.; Marshall, S. Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. *Pain Med.* **2016**, *17*, 85–98. [CrossRef] [PubMed]
6. García-Sempere, A.; Hurtado, I.; Robles, C.; Llopis-Cardona, F.; Sánchez-Saez, F.; Rodriguez-Bernal, C.; Peiró-Moreno, S.; Sanfélix-Gimeno, G. Initial opioid prescription characteristics and risk of opioid misuse, poisoning and dependence: Retrospective cohort study. *BMJ Qual. Saf.* **2024**, *33*, 13–23. [CrossRef] [PubMed]
7. Keto, J.; Heiskanen, T.; Hamunen, K.; Kalliomäki, M.L.; Linna, M. Opioid trends in Finland: A register-based nationwide follow-up study. *Sci. Rep.* **2022**, *12*, 7261. [CrossRef]
8. Muller, A.E.; Clausen, T.; Sjøgren, P.; Odsbu, I.; Skurtveit, S. Prescribed opioid analgesic use developments in three Nordic countries, 2006–2017. *Scand. J. Pain* **2019**, *19*, 345–353. [CrossRef] [PubMed]
9. Rosner, B.; Neicun, J.; Yang, J.C.; Roman-Urrestarazu, A. Opioid prescription patterns in Germany and the global opioid epidemic: Systematic review of available evidence. *PLoS ONE* **2019**, *14*, e0221153. [CrossRef]
10. Fischer, B.; Robinson, T. The marked oscillatory pattern in prescription opioid utilization in Canada since 2000: Selected observations and questions for outcomes and policy. *Pharmacoepidemiol. Drug Saf.* **2024**, *33*, e5748. [CrossRef]
11. Spithoff, S.; Leece, P.; Sullivan, F.; Persaud, N.; Belesiotis, P.; Steiner, L. Drivers of the opioid crisis: An appraisal of financial conflicts of interest in clinical practice guideline panels at the peak of opioid prescribing. *PLoS ONE* **2020**, *15*, e0227045. [CrossRef] [PubMed]
12. Häuser, W.; Petzke, F.; Radbruch, L.; Tölle, T.R. The opioid epidemic and the long-term opioid therapy for chronic noncancer pain revisited: A transatlantic perspective. *Pain Manag.* **2016**, *6*, 249–263. [CrossRef] [PubMed]
13. Böger, R. Symptomatische Behandlung von Schmerz, Fieber und Entzündung. In *Arzneiverordnungs-Report*; Ludwig, W.D., Mühlbauer, B., Seifert, R., Eds.; Springer: Berlin, Germany, 2022; pp. 387–412.
14. Häuser, W.; Bock, F.; Hüppe, M.; Nothacker, M.; Norda, H.; Radbruch, L.; Schiltenwolf, M.; Schuler, M.; Tölle, T.; Viniol, A.; et al. Empfehlungen der zweiten Aktualisierung der Leitlinie LONTS. *Der Schmerz* **2020**, *34*, 204–244. [CrossRef] [PubMed]
15. Busse, J.W.; Craigie, S.; Juurlink, D.N.; Buckley, D.N.; Wang, L.; Couban, R.J.; Agoritsas, T.; Akl, E.A.; Carrasco-Labra, A.; Cooper, L.; et al. Guideline for opioid therapy and chronic noncancer pain. *CMAJ* **2017**, *189*, E659–E666. [CrossRef] [PubMed]
16. Eccleston, C.; Fisher, E.; Thomas, K.H.; Hearn, L.; Derry, S.; Stannard, C.; Knaggs, R.; Moore, R.A. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. *Cochrane Database Syst. Rev.* **2017**, *11*, Cd010323. [CrossRef] [PubMed]
17. Furlan, A.D.; Reardon, R.; Weppler, C. Opioids for chronic noncancer pain: A new Canadian practice guideline. *CMAJ* **2010**, *182*, 923–930. [CrossRef] [PubMed]
18. Kahan, M.; Mailis-Gagnon, A.; Wilson, L.; Srivastava, A. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: Clinical summary for family physicians. Part 1: General population. *Can. Fam. Physician Med. Fam. Can.* **2011**, *57*, 1257–1266, e1407-1218.
19. Kim, E.D.; Lee, J.Y.; Son, J.S.; Byeon, G.J.; Yeo, J.S.; Kim, D.W.; Yoo, S.H.; Hong, J.H.; Park, H.J. Guidelines for prescribing opioids for chronic non-cancer pain in Korea. *Korean J. Pain* **2017**, *30*, 18–33. [CrossRef]
20. Manchikanti, L.; Kaye, A.M.; Knezevic, N.N.; McAnally, H.; Slavin, K.; Trescot, A.M.; Blank, S.; Pampati, V.; Abdi, S.; Grider, J.S.; et al. Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain Physician* **2017**, *20*, S3–S92. [CrossRef]
21. Espnes, K.A.; Nøst, T.H.; Handal, M.; Skurtveit, S.O.; Langaas, H.C. Can academic detailing reduce opioid prescriptions in chronic non-cancer pain? *BMC Prim. Care* **2023**, *24*, 84. [CrossRef]
22. Grandt, D.; Lappe, V.; Schubert, I. *Arzneimittelreport 2023: Medikamentöse Schmerztherapie Nicht-Onkologischer Ambulanter Patientinnen und Patienten*; BARMER: Berlin, Germany, 2023.
23. Manchikanti, L.; Abdi, S.; Atluri, S.; Balog, C.C.; Benyamin, R.M.; Boswell, M.V.; Brown, K.R.; Bruel, B.M.; Bryce, D.A.; Burks, P.A.; et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2—Guidance. *Pain Physician* **2012**, *15*, S67–S116.
24. Crockett, S.; Greer, K.B.; Sultan, S. Opioid-Induced Constipation (OIC) Guideline. *Gastroenterology* **2019**, *156*, 228. [CrossRef]
25. Busse, R.; Blümel, M.; Knieps, F.; Bärnighausen, T. Statutory health insurance in Germany: A health system shaped by 135 years of solidarity, self-governance, and competition. *Lancet* **2017**, *390*, 882–897. [CrossRef]
26. Sun, E.C.; Dixit, A.; Humphreys, K.; Darnall, B.D.; Baker, L.C.; Mackey, S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: Retrospective analysis. *BMJ* **2017**, *356*, j760. [CrossRef] [PubMed]

27. Häuser, W.; Schubert, T.; Scherbaum, N.; Tölle, T. Long-term opioid therapy of non-cancer pain: Prevalence and predictors of hospitalization in the event of possible misuse. *Schmerz* **2018**, *32*, 419–426. [CrossRef] [PubMed]
28. Mellbye, A.; Svendsen, K.; Borchgrevink, P.C.; Skurtveit, S.; Fredheim, O.M. Concomitant medication among persistent opioid users with chronic non-malignant pain. *Acta Anaesthesiol. Scand.* **2012**, *56*, 1267–1276. [CrossRef]
29. Jani, M.; Girard, N.; Bates, D.W.; Buckeridge, D.L.; Sheppard, T.; Li, J.; Iqbal, U.; Vik, S.; Weaver, C.; Seidel, J.; et al. Opioid prescribing among new users for non-cancer pain in the USA, Canada, UK, and Taiwan: A population-based cohort study. *PLoS Med.* **2021**, *18*, e1003829. [CrossRef] [PubMed]
30. Sizar, O.; Genova, R.; Gupta, M. *Opioid-Induced Constipation*; StatPearls Publishing: Treasure Island, FL, USA, 2023. Available online: https://www.ncbi.nlm.nih.gov/books/NBK493184/?report=reader (accessed on 16 January 2024).
31. Sonohata, M.; Wada, S.; Koretaka, Y.; Morioka, Y.; Mishima, H.; Mawatari, M. A Survey of the Incidence of Constipation in Patients with Chronic Non-cancer Pain Using Opioid Analgesics in Japan. *Pain Ther.* **2022**, *11*, 845–859. [CrossRef]
32. Andresen, V.; Banerji, V.; Hall, G.; Lass, A.; Emmanuel, A.V. The patient burden of opioid-induced constipation: New insights from a large, multinational survey in five European countries. *United Eur. Gastroenterol. J.* **2018**, *6*, 1254–1266. [CrossRef] [PubMed]
33. Varrassi, G.; Banerji, V.; Gianni, W.; Marinangeli, F.; Pinto, C. Impact and Consequences of Opioid-Induced Constipation: A Survey of Patients. *Pain Ther.* **2021**, *10*, 1139–1153. [CrossRef]
34. Smith, H.S.; Laufer, A. Opioid induced nausea and vomiting. *Eur. J. Pharmacol.* **2014**, *722*, 67–78. [CrossRef] [PubMed]
35. Scherrer, J.F.; Salas, J.; Miller-Matero, L.R.; Sullivan, M.D.; Ballantyne, J.C.; Debar, L.; Grucza, R.A.; Lustman, P.J.; Ahmedani, B. Long-term prescription opioid users' risk for new-onset depression increases with frequency of use. *Pain* **2022**, *163*, 1581–1589. [CrossRef] [PubMed]
36. Grandt, D.; Lappe, V.; Schubert, I. *Arzneimittelreport 2020: Sektorenübergreifende Arzneimitteltherapie*; BARMER: Berlin, Germany, 2020.
37. Phinn, K.; Liu, S.; Patanwala, A.E.; Penm, J. Effectiveness of organizational interventions on appropriate opioid prescribing for noncancer pain upon hospital discharge: A systematic review. *Br. J. Clin. Pharmacol.* **2023**, *89*, 982–1002. [CrossRef] [PubMed]