ORIGINAL ARTICLE

Increase in Opiate Prescription in Germany Between 2000 and 2010

A Study Based on Insurance Data

Ingrid Schubert, Peter Ihle, Rainer Sabatowski

SUMMARY

Background: Insufficient data have been available to date on the prevalence of opioid treatment in Germany, physicians' prescribing habits, and the percentages of cancer patients and non-cancer patients among those receiving opioids for an evaluation of the quality of care and an assessment of possible underuse or misuse.

Methods: The data analyzed in this study were derived from the statutory health insurance sample of the AOK health insurance company in the German state of Hesse / ASHIP Hesse for the years 2000–2010. For the purpose of this study, prevalence was defined as the percentage of insurees who received at least one outpatient prescription of an opioid (ATC N02A, excluding codeine, levomethadone and methadone). In order to control for population aging, the prevalence was standardized to the German population on December 31st of the preceding year and to the age-structure of the population as it was in 1999. Opioid prescribing for cancer was assumed when a cancer diagnosis was documented in the same year in which the opioid prescription was issued.

Results: The percentage of insurees receiving at least one opioid prescription rose over the period of the study from 3.31% in 2000 to 4.53% in 2010, a relative gain of 37%. Opioids were mostly prescribed to patients with non-cancer pain (2010: about 77% of opioid recipients). The percentage of non-cancer patients receiving long-term opioid treatment has also increased over the period of the study.

Conclusion: As opioids are frequently prescribed for non-cancer pain, it cannot be inferred from the observed increase in opioid prescribing that cancer patients are now receiving better opioid treatment than they were before. Further issues of concern are the observed increases in the prescribing of potent immediate release opioids and in the long-term opioid treatment for non-cancer patients, the benefit of which is currently debated.

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Opioids are among the most important substances in the treatment of cancer pain, and since the 1990s they have been increasingly used for the management of chronic non-cancer pain (CNP) (e1). At that time there was a broad consensus that many cancer and CNP patients were undertreated, due largely to very restrictive use of opioids (e2–e5). “Opiophobia” was viewed as the principal barrier to adequate pain therapy (e6–e9). In parallel with the problematization of inadequate prescription of analgesics and particularly opioids to patients with chronic pain, statistics from German statutory health insurance providers and equivalent figures from many other countries show an uninterrupted rise in prescription of opioids since the mid-1990s (1–5). In Germany, the number of dispensed daily doses of opioids first exceeded that of non-opioid analgesics in 2002 (1). The increase in prescription of opioids has been interpreted in various ways. Schwabe reported that in the year 2000, 96% of cancer patients received strong-acting opioids—a calculation based on the assumption that these substances were being prescribed exclusively to patients with cancer (e10). This assumption of practically complete provision was energetically refuted by pain specialists (e11). Regardless of this criticism, the 2011 edition of the annual Drug Prescription Report (*Arzneiverordnungsreport*) for Germany continued to see the increase in prescription of opioids in direct connection with “improved implementation of the WHO’s ladder for cancer pain relief” (1). Data from Norway demonstrate that a considerable proportion of opioids are prescribed to CNP patients (6). Long-term opioid treatment for CNP—the benefit of which is currently debated—is also increasingly being criticized, with demands for close monitoring (7–11).

In Germany, the debate over adequate administration of opioids has become more heated in recent years, partly fueled by the publication of an S3 guideline on long-term opioid treatment of CNP patients (12). The guideline’s conclusion, that there is no sufficient scientific evidence for treatment exceeding 3 months in duration, was controversial, and the discussion did not always remain objective: One group of authors wrote that rampant “opiophobia” was causing “harm” for both patient and physician (e12).

PMV Research Group at the Department of Child and Adolescent Psychiatry and Psychotherapy, University of Cologne: Dr. rer. soc. Schubert, Ihle

University Pain Center, University Hospital Carl Gustav Carus, Dresden: Prof. Dr. med. Sabatowski

Department of Anesthesiology and Intensive Care Medicine, Hannover Medical School: Prof. Dr. med. Sabatowski

TABLE 1

Treatment prevalence (%) with opioids

Year	Treatment prevalence in% (95% CI)											
	Standardized to the population of Germany on 31 December											
	of the previous year						1999					
	Men		Women		Total		Men		Women		Total	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
2000	2.68	2.61–2.76	3.90	3.82–3.99	3.31	3.25–3.36	2.68	2.61–2.76	3.90	3.82–3.99	3.31	3.25–3.36
2001	2.96	2.88–3.04	4.34	4.25–4.43	3.66	3.60–3.72	2.92	2.84–3.00	4.32	4.23–4.41	3.63	3.57–3.70
2002	2.95	2.87–3.03	4.30	4.21–4.40	3.64	3.58–3.70	2.88	2.80–2.96	4.26	4.16–4.35	3.59	3.52–3.65
2003	3.12	3.04–3.21	4.47	4.37–4.56	3.81	3.75–3.87	3.01	2.93–3.10	4.38	4.29–4.48	3.71	3.65–3.78
2004	3.05	2.97–3.14	4.45	4.36–4.55	3.77	3.70–3.83	2.90	2.82–2.99	4.32	4.23–4.42	3.63	3.57–3.69
2005	3.13	3.04–3.21	4.65	4.56–4.75	3.91	3.84–3.97	2.91	2.83–3.00	4.46	4.37–4.56	3.71	3.64–3.77
2006	3.20	3.11–3.29	4.66	4.56–4.75	3.95	3.88–4.01	2.93	2.85–3.02	4.43	4.33–4.53	3.70	3.64–3.77
2007	3.30	3.21–3.39	4.82	4.72–4.93	4.08	4.01–4.14	2.98	2.89–3.07	4.52	4.42–4.62	3.77	3.70–3.84
2008	3.59	3.49–3.68	5.07	4.96–5.18	4.34	4.27–4.41	3.20	3.11–3.29	4.70	4.60–4.80	3.97	3.90–4.03
2009	3.66	3.57–3.76	5.23	5.12–5.33	4.46	4.39–4.53	3.22	3.13–3.31	4.79	4.69–4.89	4.02	3.95–4.09
2010	3.68	3.58–3.78	5.35	5.24–5.46	4.53	4.46–4.60	3.18	3.09–3.27	4.85	4.75–4.95	4.03	3.96–4.10
Δ 2000 to 2010	+37.3%		+37.1%		+ 37.0%		+ 18.6%		+ 24.3%		+ 22.0%	

The currently available data and opinions cannot be used to demonstrate whether the current situation with regard to the prescription of opioids is satisfactory or whether there is undersupply or otherwise inappropriate provision. The aim of our study was therefore to investigate, over a period of 11 years (2000 to 2010), the prevalence of treatment with different types of opioids and their use in patients with cancer and non-cancer diseases.

Materials and methods

The data source was a sample of persons with health insurance resident in the German state of Hesse, compiled by the Hessian branch of the *Allgemeine Ortskrankenkasse* (AOK; a large general statutory health insurance company) and the Hessian Association of Statutory Health Insurance Physicians (ASHIP Hesse) (*eSupplement*) (e13). Opioids were selected via the Anatomical Therapeutic Chemical (ATC) classification (subgroup N02A excluding codeine, levomethadone, and methadone). The current (2010) defined daily dose (DDD) of each agent was taken as the DDD for the whole study period. The duration of treatment (coverage) was established by counting the number of days of outpatient therapy.

The prevalence (proportion of the sample with at least one prescription of opioids) for each year, as well as the total DDDs and the DDDs per opioid recipient, were standardized to the population of Germany on 31 December of the previous year and additionally, for

delineation of population aging, to the population on 31 December 1999.

An opioid recipient with a new treatment episode was defined as a person who, based on the first opioid prescription in an observation year, had received no opioids in the 365 days preceding that index prescription.

It was assumed that opioids were prescribed for treatment of cancer whenever malignant disease (ICD-10: C00–C97) was coded at least once in the year of prescription. Opioid recipients with no indication of a cancer diagnosis were classified as CNP patients.

Results

Prevalence

The annual proportion of insured persons with at least one prescription of opioids rose from 3.31% (95% confidence interval [CI]: 3.25 to 3.36) in 2000 to 4.53% (95% CI: 4.46 to 4.60) in 2010 (+ 37%) (*Table 1*). Standardized to the population structure in 1999, the increase was 22%; in other words, aging of the population alone led to an increase of 15% in opioid treatment prevalence. Extrapolating to the total population of Germany, the numbers of persons treated with opioids nationwide rose from 2.72 million to 3.71 million.

Figure 1 depicts the changes in three parameters of opioid prescription from 2000 to 2010. It clearly shows that the increase in total daily doses (+ 109%) is accounted for primarily by a higher number of daily doses

per opioid recipient (+ 53.4%) and to a somewhat lesser extent by an increase in the number of patients treated (+ 37%).

Table 2 and the eTable show opioid treatment prevalence for the different steps of the WHO ladder for cancer pain relief.

- The prevalence of treatment with immediate release preparations has fallen by almost 25%. This is due to a decrease in immediate release WHO step 2 opioids (–28.8%), particularly, since 2004, the decrease in immediate release tramadol from 2.14% (2000) to 1.29% (2010; –39.6%).
- The prevalence of treatment with extended release WHO step 2 opioids increased (+178.6%), primarily due to growth in prescription of tilidine/naloxone (+468.6%) and tramadol (+102.7%).
- The prevalence of treatment with immediate release morphine rose from 0.04% to 0.12% (+178.2%). Immediate release preparations of hydromorphone, oxycodone, and fentanyl increased distinctly, starting in 2004 and 2007 respectively, but were still at a low level in 2010 (hydromorphone 0.03%, oxycodone 0.01%, fentanyl 0.02%).
- The prevalence of treatment with extended release preparations of WHO step 3 opioids (including plasters) increased almost fourfold between 2000 and 2010. Fentanyl rose from 0.17% to 0.58%, oxycodone from 0.04% to 0.44%, hydromorphone from 0.01% to 0.13%, and buprenorphine from <0.01% to 0.09%.

Prescription target groups: cancer disease/non-cancer pain

The prevalence data in Figure 2 show clearly that opioids are still prescribed primarily to patients with

FIGURE 1

Prescription of opioids, 2000 to 2010*: Rate of change (%) in prevalence, prescribed amount in defined daily doses (DDDs), and DDDs per recipient

* Standardized to the population of Germany on 31 December of the previous year; calculation of change based on the year 2000

CNP: In 2010 this group accounted for 76.7% of all opioid recipients (2000: 80.6%). There was a particularly distinct increase in prescription of WHO step 3 opioids.

Depending on the type of opioid and the duration of action, the distribution of daily doses among opioid recipients with and without indication of a tumor was as follows (Table 3):

TABLE 2

Treatment prevalence (%) by WHO step^{*1} and preparation at the beginning and end of the observation period^{*2}

	2000			2010			Change 2000 to 2010
	Men	Women	Total	Men	Women	Total	
WHO step 2	2.53%	3.71%	3.13%	3.00%	4.23%	3.63%	+ 18.7%
Immediate release	2.14%	3.13%	2.65%	1.55%	2.22%	1.89%	– 28.8%
Extended release	0.60%	0.91%	0.76%	1.76%	2.45%	2.11%	+ 178.6%
WHO step 3	0.32%	0.41%	0.37%	1.00%	1.61%	1.31%	+ 257.8%
Immediate release	0.08%	0.07%	0.08%	0.19%	0.19%	0.19%	+ 146.0%
Extended release/plaster	0.29%	0.38%	0.33%	0.96%	1.56%	1.26%	+ 278.9%
WHO step 2 + 3	2.68%	3.90%	3.31%	3.68%	5.35%	4.53%	+ 37.0%
Immediate release	2.19%	3.18%	2.70%	1.70%	2.36%	2.04%	– 24.4%
Extended release/plaster	0.82%	1.20%	1.02%	2.52%	3.71%	3.13%	+207.9%

Standardized to the population of Germany on 31 December of the previous year

*1 Classification of the opioids included in this study on the WHO pain relief ladder (see eSupplement):

WHO step 2: e.g., tramadol, tilidine/naloxone; WHO step 3: e.g., morphine, hydromorphone, oxycodone, fentanyl, buprenorphine

*2 More than one nomination possible

FIGURE 2

Prevalence: Proportion (%) of opioid recipients by WHO step and presence or absence of cancer disease

- In 2000, 72% of opioid daily doses (146.04/202.55 million) were prescribed to CNP patients (2010: 75%).
- In opioid recipients with indication of a tumor, the relationship between weak and strong opioids remained more or less stable at ca. 50:50. Among CNP patients there was a sharp decrease in the proportion of the total prescribed daily doses accounted for by WHO step 2 opioids over the study period (2000: 84%; 2010: 66%), while long-acting WHO step 3 opioids doubled (2000: 16%; 2010: 33%).

WHO step at beginning of treatment

In 2009, 16% of the incident opioid recipients (those who had previously been prescribed no opioids for at least 365 days) received a WHO step 3 opioid as first prescription (2001: 5.3%). The most frequent WHO step 3 substance, both in 2001 and in 2009, was fentanyl (43% of the incident WHO step 3 opioid recipients in 2009). The WHO step 2 opioid most frequently prescribed to incident opioid recipients in both 2001 and 2009 was tramadol.

Treatment duration in CNP opioid recipients without opioid prescription in previous year

The proportion of opioid recipients with a single prescription of opioids sank from 59.1% in 2001 to 52.7% in 2009. The proportion of longer-term treatment rose accordingly. Opioids were prescribed at least once in every quarter-year for 8.8% of opioid recipients in 2001 and for 12.8% in 2009. Long-term treatment (defined as >90 days with intervals between prescriptions not exceeding 30 days) was found in 4.3% of cases in 2001 and 7.5% in 2009.

Discussion

Prevalence and drug choice

Based on a prevalence of 4.53% (2010), and assuming that the regional data used in our study can be extrapolated nationwide, around 3.71 million inhabitants of Germany received at least one prescription of opioids in 2010. Figures on opioid consumption by persons insured by the statutory health insurance provider Barmer in 2006 to 2009 showed a higher prevalence: 5.7% at the beginning and 5.9% at the end of the study period (13). The comparability of these data is limited, however, as the Barmer study included codeine, which was prescribed almost as often as tramadol. Higher prevalence than in our study is thus to be expected.

Changes in opioid consumption have also been investigated in other countries (4, 5, 14–16, e14). Worldwide, opioid use has almost tripled since 1991 (e15). A moderate increase of 47% in the number of DDDs/1000 inhabitants/day was described for five WHO step 3 opioids (morphine, oxycodone, pethidine, methadone, and fentanyl) over the period 2000 to 2008 in Israel (5). This increase was due largely to a fourfold increase in the consumption of fentanyl, while the number of daily doses of morphine halved (5). In Spain a 14-fold increase in opioid daily doses was recorded between 1992 and 2006, mainly attributable to increased prescription of fentanyl and tramadol (14). Consumption of morphine in Spain decreased slightly following the introduction of fentanyl in 1998 (14). Studies in northern Europe and data from the International Narcotic Control Board show distinct variation among countries with regard to the development of opioid consumption (4, e15). Although these statistics enable limited international comparisons, they do not permit any conclusions regarding treatment prevalences (15).

Fredheim et al. conducted a study comparable to ours, but based on person-related pharmacological data from Norway (6). They found an increase of approximately 10% in the number of opioid recipients between 2004 and 2007, resulting in a treatment prevalence of 9.37% and 9.94%, respectively. These figures are much higher than ours (2007: 4.08%), but the difference is principally due to Fredheim et al.'s inclusion of codeine.

The low volume of morphine prescription in relation to other WHO step 3 opioids has led some authors to speak of “morphine phobia” (14, e14). Our data also show a clear increase in treatment prevalence for other

TABLE 3

Prescription volume in DDDs by group (cancer/non-cancer) and preparation at the beginning and end of the observation period*

	2000			2010		
	Defined daily doses (DDDs) in millions* (%)					
	Cancer	Non-cancer	Total	Cancer	Non-cancer	Total
WHO step 2	27.71 (49.0%)	121.95 (83.5%)	149.66 (73.9%)	52.64 (50.4%)	211.86 (66.3%)	264.50 (62.4%)
Immediate release	20.81 (36.8%)	89.40 (61.2%)	110.21 (54.4%)	18.98 (18.2%)	78.24 (24.5%)	97.22 (23.0%)
Extended release	6.90 (12.2%)	32.55 (22.3%)	39.45 (19.5%)	33.66 (32.2%)	133.62 (41.8%)	167.28 (39.5%)
WHO step 3	28.80 (51.0%)	24.09 (16.5%)	52.89 (26.1%)	51.78 (49.6%)	107.60 (33.7%)	159.38 (37.6%)
Immediate release	2.86 (5.1%)	1.44 (1.0%)	4.30 (2.1%)	3.69 (3.5%)	3.74 (1.2%)	7.43 (1.7%)
Extended release/ plaster	25.94 (45.9%)	22.65 (15.5%)	48.59 (24.0%)	48.10 (46.1%)	103.86 (32.5%)	151.96 (35.8%)
WHO step 2 + 3	56.51 (100%)	146.04 (100%)	202.55 (100%)	104.42 (100%)	319.46 (100%)	423.88 (100%)
Immediate release	23.67 (41.9%)	90.84 (62.2%)	114.51 (56.5%)	22.67 (21.7%)	81.98 (25.7%)	104.65 (24.7%)
Extended release/ plaster	32.84 (58.1%)	55.20 (37.8%)	88.04 (43.5%)	81.76 (78.3%)	237.48 (74.3%)	319.24 (75.3%)

* Standardized to the population of Germany on 31 December of the previous year

WHO step 3 opioids compared with morphine. We too observed the sharp rise in the prescription volume of oxycodone that has been described and critically debated in other countries (4, 14, 17). Because there is no clinically relevant difference between morphine and oxycodone or hydromorphone in terms of efficacy and toxicity, the most likely explanation for the increased consumption of the latter substances is intensive marketing (4, 14, 17, e16). There are indications that the increase in consumption of opioids (including oxycodone) may be directly connected with a large number of deaths (18–20, e17). Recent statistics from the USA show more deaths from prescribed opioids than from consumption of illegal drugs (21, 22). Authors in various countries have particularly linked a significant rise in opioid-related deaths with no sign of suicidal intent to the introduction of extended release oxycodone (18, 23–26). The risk of opioid overdose increased with the prescribed daily dose of opioid (20, 27). Oxycodone has also been discussed in connection with abuse in the German speaking countries, although no robust data have been provided on the mortality risk in the context of pain treatment (e18). Moreover, there are signs that the problem of opioid-associated deaths is not related to a specific property of oxycodone. Rather, the use of other highly potent opioids also seems to be attended by an increased risk of death from overdose (28). In contrast, the authors of a study published in 2000 perceived no connection between increasing medical consumption of opioids and abuse (29).

Independently of the discussion of opioid-associated deaths, elderly patients in particular are at greater danger of fractures while taking opioids. The fracture risk seems to differ among the various opioids; it appears to be greatest at the beginning of the treatment period, at higher doses, and with immediate release opioids (30–32).

The sharp rise we observed in the prescription volume of extended release preparations—especially of fentanyl—has also been described in other countries (5, 14, e14). Various publications have drawn attention to the failure to follow guidelines for the prescription of fentanyl (17, 33, e19). According to the current recommendation of the Drug Commission of the German Medical Association, against the backdrop of a recently published study, prescription of transdermal fentanyl as the first opioid should be avoided if at all possible (33, 34). This study recorded a far higher proportion of opioid-naïve patients among the first-time users of fentanyl than we found in our analysis. The main reason for this difference, however, was the inclusion of recipients of WHO step 2 opioids in the opioid-naïve group (33, 35).

The developments in prescription of immediate release preparations have to be viewed critically. Pharmaceuticals characterized by rapid pharmacokinetics and swift delivery to the CNS have increased addictive potential (36). In the USA 30% of immediate release opioids are prescribed for pain of the musculoskeletal system and connective tissue. Because of their

suspected negative effects, opioids in general are subject to a risk minimization program initiated by the FDA (37). It currently remains unclear whether the introduction of additional products into the market leads to an increase in prescription volume or whether new active substances or forms of application displace existing preparations. The short period of observation following the market entry of new preparations of fentanyl has shown a steep rise in prescription of fentanyl since 2008 while prescription of immediate release morphine has remained stable. Looking at international trends, particularly with regard to the increasing use of so-called rapid-onset opioids (principally various preparations of fentanyl), undesirable developments can be discerned. Our own data—showing doubling of the treatment prevalence of immediate release WHO step 3 opioids in opioid recipients with CNP (*eTable*)—go some way towards demonstrating this trend in Germany. In 2010, one third of those who received immediate release WHO step 3 opioids were CNP patients (*eTable*). The use of immediate release fentanyl for indications other than cancer pain is especially controversial (38, 39, e20–e22). Furthermore, there are already early signs that the use of these substances can lead to symptoms of addiction, not only in cancer patients—i.e., the indication for which they were originally licensed—but also in controlled studies (40, e23).

Limitations

The patients whose data we analyzed were all from the same region of Germany and all had the same form of health insurance. Differences in age structure and sex ratio between our sample and the German general population were taken into account. Nevertheless, regional variations in morbidity and treatment have to be assumed, so the findings cannot simply be extrapolated to the whole country—particularly in view of the fact that 10% of the population are not insured with statutory providers. We believe our data are robust, however, because the AOK insures approximately one quarter of the population of Hesse and because global parameters such as the change in total prescribed daily doses are comparable with the data in the Drug Prescription Report, which covers all types of health insurance provider (*eSupplement*). The database contains no information on hospital treatment, private prescriptions, or the reason for prescription. We cannot exclude the possibility that opioid recipients with a diagnosis of cancer may have been prescribed opioids for relief of non-cancer-related pain. In dividing the patients between the two groups (cancer disease and CNP) we adopted a conservative approach to the assessment of prescription for non-cancer pain, so we may have overestimated the number of prescriptions for cancer pain.

The strengths of the database are that it permits observation of long-term developments and that the data are complete. There is no selection, no drop-out, and no recall or interviewer bias. We were able to improve the interpretability of the findings by differ-

KEY MESSAGES

- The prevalence of treatment with opioids and the number of daily doses per recipient both increased between 2000 and 2010.
- There is a pronounced trend towards prescription of WHO step 3 opioids, particularly in non-cancer patients.
- The prescription of immediate release preparations of highly potent opioids (WHO step 3) is also increasing.
- Opioids are prescribed predominantly for non-cancer patients.
- The frequency of long-term treatment of non-cancer diseases with opioids is growing, despite controversy surrounding its benefit.

entiating between prescriptions for cancer and non-cancer disease, thus satisfying an oft-stated demand (15).

Opioids form an important element of medicinal pain treatment. Underuse of opioids can result in inadequate pain relief. Uncritical prescription may be hazardous, however, possibly even leading to abuse and addiction. Our analysis shows that opioids are being used principally for treatment of non-cancer pain. An increase in total prescribed daily doses of opioids thus by no means permits the conclusion that cancer patients are being adequately supplied with opioids (1). Furthermore, the findings we present (intensification of opioid treatment in CNP patients, increasing long-term treatment, high proportion of immediate release opioids in CNP patients) point to possible shortcomings in the care of patients with CNP. Particularly in light of the potential risks involved, a close eye needs to be kept on the developments in opioid treatment.

Conflict of interest statement

Dr. Schubert has received third-party funding for the PMV Research Group from health insurance providers (Federal Association of the AOK, AOK Hesse, AOK Baden-Württemberg), government ministries (Federal Ministry of Health, Federal Ministry of Education and Research, Hessian Ministry of Social Affairs), the Hessian Association of Statutory Health Insurance Physicians, and the companies Bayer, Schering, Novo Nordisk, Sanofi, and Abbott.

Prof. Sabatowski has acted as consultant for Cephalon and Janssen-Cilag. He has received fees for the preparation of specialist training courses from MSD and Grünenthal. The University Pain Center Dresden has received payments from Grünenthal, Astellas, and Allergan for conducting commissioned clinical studies.

Mr. Ihle declares that no conflict of interest exists.

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Corresponding author

Dr. rer. soc. Ingrid Schubert
PMV forschungsgruppe an der Klinik und Poliklinik für Psychiatrie und Psychotherapie des Kindes- und Jugendalters der Universität zu Köln
50931 Köln, Germany
Ingrid.Schubert@uk-koeln.de

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ORIGINAL ARTICLE

Increase in Opiate Prescription in Germany Between 2000 and 2010

A Study Based on Insurance Data

Ingrid Schubert, Peter Ihle, Rainer Sabatowski

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eSUPPLEMENT

Increase in Opiate Prescription in Germany Between 2000 and 2010

A Study Based on Insurance Data

Ingrid Schubert, Peter Ihle, Rainer Sabatowski

Detailed description of methods

The aim of the study was to investigate the prevalence of treatment with different types of opioids and their prescription for cancer and non-cancer diseases over a period of 11 years (2000 to 2010). The database, the variables, and the methods are described below.

Database and sampling procedure

The database for the study is the AOK Hesse/ASHIP Hesse Sample (*Versichertenstichprobe AOK-Hessen/KV-Hessen*; VSH). The following bodies participate in the VSH project:

- The Hessian branch of the AOK (Bad Homburg)
- The Hessian Association of Statutory Health Insurance Physicians (ASHIP) (Frankfurt)
- The Hessian Ministry of Social Affairs
- The PMV Research Group (University of Cologne).

The aim of the project was to create a complete, long-term database containing information on health-care services provided to the insured persons (e25). The VSH sample has been surveyed annually since 1998; so far, data for the years 1998 to 2010 are available.

The population of the VSH sample has decreased while the average age rises. In 2000 the sample comprised 326 554 persons, 51% of them women. By 2010 this had gone down to 265 213 (51.8% women). The mean age rose from 43.9 years (SD 23.8) in 2000 to 46.3 years (SD 24.4) in 2010. Mortality was 1.5% in 2000, 1.6% in 2010.

The members of the sample were chosen at random from the set of all persons insured by the Hessian AOK. The proportion selected remained constant at 18.75% over the observation period. This proportion results from the generation of a random number on the basis of the health insurance number (e26, e27). Approximately 1.5 million people were insured by the Hessian AOK in 2010. The constant selection rate ensures that the sample follows the natural fluctuation of the population insured by the AOK. New memberships of the AOK (births, transfers, etc.) were taken account of, as were resignations from the AOK and deaths (see [e25] for an exhaustive description of the VSH [in German]).

The data sectors are listed below with some examples of the items contained. The basic pseudo-

onymized person-related data are available as an SQL database:

- Master data: sex, year of birth, nationality, residential postal code
- Membership: beginning and end, category of insurance, death
- Non-hospital medical diagnoses (by quarter-year, ICD-10 coded), medical service codes (with day of service provision), and details of billing physician (physician group)
- Prescription data: product identification code (information on drug name, package size, strength, etc.), prescription/dispensing date, information on prescribing physician (group)
- Data on hospital treatment and rehabilitation (beginning, end, diagnoses, referring physician group, treating departments, services provided)
- Periods of work incapacity: beginning, end, diagnosis
- Services from non-medical service providers, e.g., remedies and appliances, with date of prescription, information on prescribing specialist (group), travel costs
- Care insurance services (German Social Code XI): type of nursing care, care level, beginning, end

Data protection

The sampling process adhered to the stipulations of §75, Social Code X and was approved by the competent supervisory authority (Hessian Ministry of Social Affairs). Data acquisition, pseudonymization, and data transfer procedures were checked by the data protection officer of the state of Hesse and carried out in coordination with the data protection officers of the Hessian AOK and the Hessian ASHIP (e28, e29). Pseudonymization of the data was a multistage process with the involvement of an independent monitor. De-pseudonymization of the study number by the evaluators is impossible on technical grounds, and re-identification of the insured person is not permissible.

Performance of the opioid study on the basis of the VSH data was approved by the VSH advisory committee. Ethics committee approval was not necessary because the data were derived exclusively from statutory health insurance records (e30).

Data for the opioid study

In addition to the master data including age, sex, and period of insurance cover, the following data were used for the opioid study:

- Non-hospital and hospital diagnoses for division of the opioid recipients into cancer and non-cancer patients
- Drug prescriptions
- Hospital stays.

The data from the various sectors (inpatient, non-hospital, drug prescription) were brought together by means of the pseudonymized patient identification number.

In the non-hospital sector, the diagnoses coded according to ICD-10 (e31) are supplied quarterly to the ASHIP and health insurance providers. The diagnoses are therefore not linked directly with the reason for treatment on a given day or with a prescription. From the inpatient sector we derived the discharge diagnosis (with discharge date) for definition of cancer patients.

The PMV Research Group receives the prescription data in electronic form. For every prescription, the raw data contain the product identification code. By means of a dedicated project database the product identification code is used to obtain information on the prescribed proprietary drug, aid/appliance, or bandage. The active substances are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System, and the prescribed amounts are measured in defined daily doses (DDDs) (e32, e33).

For the opioid study the opioids were selected via subgroup N02A of the ATC system. Codeine and codeine combinations, which are used primarily for short-term treatment and mostly in younger patients, were not included (e34). Methadone and levomethadone were also excluded, because in the year 2000 it could not be determined using the ATC system whether they were being prescribed for pain treatment or for substitution purposes.

Since the DDD of some opioids (particularly fentanyl) has changed during the observation period, the most recent available DDD of each drug (in most cases from December 2010) was taken as the DDD for prescriptions throughout the study period.

The opioids were classified into weak (WHO step 2) and strong (WHO step 3) agents. The weak-acting opioids include, for example, dihydrocodeine, pethidine, dextropropoxyphene, tapentadol, tilidine, and tramadol, as well as codeine combinations (not included in the study). Strong-acting opioids include morphine, hydromorphone, oxycodone, ketobemidone, piritramide, nalbuphine, fentanyl, pentazocine, buprenorphine, and others.

Definitions

For the purposes of the study an opioid prescription was assumed to be for treatment of cancer disease whenever there was at least one cancer diagnosis (ICD-10: C00–C97) in the year of prescription. Opioid recipients for whom there was no indication of a cancer

diagnosis were classified as patients with chronic non-cancer pain (CNP).

For the assessment of treatment prevalence, we counted all persons who had received at least one prescription in the year concerned.

To determine whether the duration of treatment of new cases changed between 2000 and 2010, persons commencing a course of treatment had to be identified and the treatment duration operationalized:

- Opioid recipients with a new treatment episode were defined as those persons who had received no opioids in the 365-day period before the first opioid prescription in a given year (index prescription). Because interest is focused on the type of prescription in new treatment episodes over the study period, it is accepted that the treatment beginners defined in this way may later receive further prescriptions after an opioid-free period of at least 365 days and therefore be included in two or more cross-sectional investigations (by calendar year). This is the case for ca. 5% to 10% of opioid recipients. Only opioids on the same WHO step need not to have been prescribed in the preceding 365-day period for the patient to count as a new recipient. The first observation year for patients with a new prescription is 2001 (with the prescription-free interval beginning in 2000). The last observation year for patients with a new prescription is 2009, to allow for 365 days' observation after the index prescription.
- The duration of treatment (coverage) in days was counted from the dispensing date and determined by the number of daily doses dispensed, assuming consumption of one DDD per day. In calculating the length of the "first" treatment period, gaps of up to 30 days between prescriptions are permitted. In addition, sensitivity analyses were carried out to determine the coverage: Any treatment gaps (60 days/90 days) were closed under the assumption that the prescribed daily doses actually suffice for a longer time and thus less than 1 DDD was taken per day.

Representativeness

The choice of sampling procedure and the high sampling rate of 18.75% ensure that the sample is representative of the population of Hesse. However, the following characteristics of the sample must be considered with regard to extrapolation of the results to the overall population of persons with statutory health insurance or the population of Germany as a whole. The sample was drawn from one type of health insurance provider (AOK) and one federal state (Hesse). Therefore, it cannot be assumed that the VSH sample is representative of the population of Germany as a whole. Comparison of the age structure and sex ratio in these two populations shows that older people are overrepresented in the Hessian AOK. This can be compensated by age and sex standardization. It has to be assumed that the sample population (and thus the AOK population)

differs from the general population, or from those with health insurance from other providers, in further ways (socioeconomic factors, lifestyle) (e35, e36). The data required for standardization are either completely absent (lifestyle, clinical parameters) or present for only some age groups or insured persons (e.g., income, education, occupation, nationality).

For the opioid study we standardized the prevalence data (proportion of insured persons with a least one opioid prescription) as well as the total daily doses and the daily doses per recipient in a given year. This standardization was based on the population of Germany at the end of the previous year and on the population in 1999 to allow for the influence of demographic change (aging of the population).

To check to what extent the developments described in the VSH sample can be generalized to Germany as a whole, the opioid study used the rate of change in total prescribed daily doses. Comparison of changes in con-

sumption of opioids (excluding codeine and substances used for substitution) between our data and the nationwide statistics in the Drug Prescription Report (DPR) (e37, e38), which covers all types of health insurance providers, reveals similar figures for the increase in total DDDs from 2000 to 2010 (VSH:109%; DPR: 104%).

Statistics

The study data are contained in a database (MS-SQL Server 2008 running under Windows Server 2008 R2) and are analyzed with SQL and the statistical software package SAS for Windows release 9.2 (SAS Institute, Inc., Cary, NC, USA). Estimations of frequency were expressed in% with 95% confidence intervals.

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eTABLE

Treatment prevalence (%) by WHO step and preparation at the beginning and end of the observation period by group (cancer/non-cancer)*

	Proportion (%) with opioids						Change 2000 to 2010
	2000			2010			
	Cancer	Non-cancer	Total	Cancer	Non-cancer	Total	Total
WHO step 2	0.56	2.58	3.13	0.75	2.88	3.63	+ 18.7%
Immediate release	0.47	2.18	2.65	0.39	1.50	1.89	– 28.8%
Extended release	0.15	0.61	0.76	0.44	1.67	2.11	+ 178.6%
WHO step 3	0.19	0.18	0.37	0.45	0.86	1.31	+ 257.8%
Immediate release	0.04	0.03	0.08	0.11	0.07	0.19	+ 146.0%
Extended release/plaster	0.17	0.16	0.33	0.44	0.83	1.26	+ 278.9%
WHO step 2 + 3	0.64	5.33	3.31	1.06	6.95	4.53	+ 37.0%
Immediate release	0.50	2.20	2.70	0.48	1.56	2.04	– 24.4%
Extended release/plaster	0.29	0.73	1.02	0.79	2.34	3.13	+207.9%

Standardized to the population of Germany on 31 December of the previous year

* More than one nomination possible