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# Prescription patterns of pregabalin and potential misuse in empirical prescription networks



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**Title:** Prescription patterns of pregabalin and potential misuse in empirical prescription networks

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coordination of care, drugs with addictive potential, pregabalin, social network analysis, routine data, ambulatory care

## Abstract

**Objectives** To investigate utilization patterns of the anticonvulsant and anxiolytic drug pregabalin, to identify users potentially misusing pregabalin, and to compare this group of patients to normal pregabalin users concerning their personal characteristics and the coordination among their prescribers. Unintended co-prescription of drugs with addictive potential might occur particularly when care is insufficiently coordinated.

**Design** Secondary data analysis of linked data from three regional sickness funds in Germany (AOK) of the years 2014–2016.

**Setting** Ambulatory and hospital care sector in four German federal states.

**Participants** Patients who received prescriptions of pregabalin and who were classified into normal users and those being dispensed with a higher than medically recommended dose.

**Interventions** None.

**Primary and secondary outcome measures:** Patient characteristics, including personal information about age, sex, morbidities and medications and measures for cooperation among the prescribing physicians, based on social network analysis.

**Results:** Among the 53,049 patients identified as pregabalin users, 1.7% were classified as misusing pregabalin. The majority of this group was male and middle-aged. About 40% of patients misusing pregabalin had a diagnosed history of substance use disorders, and 40% had been prescribed another drug with addictive potential before. The prescribers of those patients misusing pregabalin were more loosely connected within networks compared to prescribers of normal users.

**Conclusion:** This study found that patients could exceed the recommended doses by getting prescriptions from multiple physicians. Specific patients were at higher risk of misusing pregabalin than others, and these patients sought to obtain their prescriptions from physicians who were as loosely connected as possible. Coordination and sharing a relevant number of patients seem to be levers to avoid these problems of unintended co-prescribing.


## Strengths and limitations of this study

- Routine data can serve as an objective measure to depict health service utilization.
- Groups of patients at high risk of abusing pregabalin were identified.
- The results clearly indicate that information exchange among ambulatory physicians is needed to prevent potentially intentional misuse of pregabalin.
- The nature of routine data does not allow drawing conclusions about the reasons for high prescription rates and leads to incomplete information about prescriptions from the hospital sector or prescriptions not filled by the patients.
- The analyzed population is limited to people insured at the included three regional AOK sickness funds and might therefore differ slightly from the general population in Germany.

## INTRODUCTION

The misuse or nonmedical use of prescription drugs may lead to severe substance-related disorders and fatal health effects such as drug addictions, behavioral dependence, or even deaths. The nonmedical use of opioids is one of the leading public health issues in the United States [1] and is characterized as an epidemic. Even though the prevalence is estimated to be lower in European countries, Novak et al.[2] reported past-year prevalence for nonmedical drug use of up to 5% among five EU member states. As many of these misused drugs have great addiction potential, patients may take advantage of coordination problems in health care systems, such as discontinuities or gaps in care.

One possible way for patients to misuse prescription drugs is to consume a higher than medically indicated dose.[3] To this end, patients may seek to obtain prescriptions from multiple health care providers through so-called doctor shopping.[3] Especially in fragmented health care systems, unknown and unintentional double prescribing might occur because patients can choose the physicians they consult without the need for referral and information transfer among health care providers. This requires close cooperation and collaboration among providers when trying to prevent intentional misuse of prescription drugs, particularly when coordination gaps in health care are exploited by patients.

Pregabalin (Lyrica) is one example of such a drug being potentially misused by patients. It was introduced in 2004 and is approved for the treatment of neuropathic pain, general anxiety disorder, and epilepsy in Europe. Pregabalin is a gamma-aminobutyric acid (GABA) that reduces the excitability of neurons in the central nervous system and is structurally related to its predecessor gabapentin.[4] Pregabalin binds to an auxiliary subunit of voltage-dependent calcium channels and thus reduces the release of several neurotransmitters such as glutamate, noradrenaline, and the neuropeptide substance P.[5] This may reduce neuronal excitability and thus seizures and neuropathic pain.[6] Additionally, pregabalin may have a relaxing effect and can produce euphoria, which are both assumed to cause abuse and addictive potential.[5]

Since 2008, concerns have been raised about the abuse and addictive potential of pregabalin, particularly for patients with a history of drug addiction,[4, 7, 8] and warning information was added to the German scientific information in 2011.[9] Nevertheless, the number of pregabalin users has still been increasing in recent years.[10, 11] In Germany, an increase was observed from 2.2 million filled pregabalin prescriptions in 2011 to 3.9 million in 2018.[12, 13] Anecdotal evidence from Germany further suggests that there was also an increase in pregabalin abusers between 2008 and 2015.[14]

Based on prescription data, studies have investigated patient factors that are associated with the risk of being dispensed with pregabalin at a higher than recommended dose.[10, 11, 15] The authors interpreted this high dispensing of the drug as a sign of potential misuse of pregabalin. These studies showed that especially middle-aged men, patients with a history of substance use disorders or drug abuse, and patients with psychological comorbidities are at particularly high risk of misusing pregabalin. Driot et al.[15] found that, at a structural level, misuse of pregabalin was associated with multiple prescribers, which might point to the presence of doctor shopping.

Social network analysis (SNA) methods are commonly applied in the health care sector to identify network structures among health care providers and to investigate the effects of care cooperation among these informal, patient-sharing physician networks on health care provision.[16] For instance, Barnett et al.[17] showed that, if physicians were sharing more

patients in their empirical network, it was more likely that they were cooperating in real life. Making use of this idea, Ong et al.[18] used SNA to analyze networks of physicians prescribing interacting drugs to the same patients. They showed that a patient was more likely to be co-prescribed with interacting drugs if his or her caring physicians shared fewer patients on average. In another study, Ong et al.[19] analyzed multiple providers prescribing benzodiazepines and also showed that two physicians were at a greater risk of prescribing benzodiazepine with overlapping coverage if they shared fewer patients.

The German ambulatory care sector has no formal system to coordinate care among office-based physicians, and information about treatment and medication is not regularly transferred among health care providers. This loose organization might facilitate the intentional misuse of prescription drugs for patients. The present study thus aimed to analyze pregabalin utilization in four German states based on routinely collected health insurance data. It described the characteristics of patients who have been prescribed pregabalin and identifies users potentially misusing this drug. This group was compared to the group of normal users in order to, first, examine the typical characteristics of patients misusing pregabalin and, second, identify the common factors and analyze the connectivity among the physicians prescribing pregabalin to patients who misuse the drug.

## MATERIALS AND METHODS

### Data Source and patient population

Three regionally organized statutory health insurances (AOK), covering four German states, Bavaria, Hesse, Thuringia, and Saxony, provided sickness fund data for this study. The AOK insures about 42% of the population in these regions, and the insured population differs only slightly from the general German population in terms of age and gender.[20] The provided dataset covered about 14% of their insured population from the years 2013 to 2017[1]. It included billed services and diagnoses from the ambulatory and hospital sector as well as prescription data and patient information, such as age and gender.

Patients were included in the analysis if they had received an initial prescription of pregabalin (ATC: N03AX16) between January 2014 and December 2016. To be classified as an initial user, the patient should not been prescribed pregabalin in the year prior to the initial prescription. Patients for whom only incomplete patient information was available, patients younger than 12 years of age, and patients who died during the observation period of one year since their initial prescription were excluded from the analysis. We only considered patients with at least three filled and reimbursed prescriptions for pregabalin during the observation period of one year to identify patients who used pregabalin regularly. Details about the identification of the patient population are depicted in Fig. 1.

### Patient and public involvement

The present study represents a retrospective secondary data analysis, therefore patients and the public were not directly involved.

### Definition of potential misuse

[1] This extended patient population included patients who received at least once one of 34 defined drugs within the observation period (see Supplemental material).

The World Health Organization defines psychoactive substance misuse as "Use of a substance for a purpose not consistent with legal medical guidelines […]".[21] The European public assessment report for pregabalin (Lyrica) recommends a maximum therapeutic dose of 600 mg per day (corresponding to two defined daily doses (DDD)).[22] In order to classify patients with prescriptions for pregabalin into normal users and patients potentially misusing the drug, we therefore compared the prescribed average daily dose during one year to this recommended maximum dose.

The prescription dataset listed all drugs that had been prescribed by any ambulatory physician, dispensed in a pharmacy, and reimbursed by the statutory health insurance. It provided the Anatomical Therapeutic Chemical (ATC) classification, the prescription and dispensing date, and the prescribed dose in terms of the DDD. On this basis, we calculated the sum of dispensed drug per patient during the time span of a maximum of 12 months since initial dispensing, excluding the prescribed dose of the last dispense. We then examined the time span (in days) between first and last dispensing and calculated the average amount of dispensed drug per day. If this average exceeded the maximum dose of 600 mg, we classified the patient as potentially misusing pregabalin with the hazard of behavioral dependence.

**Patient characteristics and medical conditions**

The patient characteristics and medical conditions that we used to describe pregabalin users and compare the two groups included information about a) patient characteristics, b) prevalence of approved indications for pregabalin, c) medical conditions that might increase the risk of misuse, and d) prescriptions of drugs with potential for misuse as follows:

a) The dataset comprised, among others, the age and gender as relevant patient characteristics, as studies have shown that especially younger men seem to be at higher risk of substance abuse in general [23] and also for the misuse of pregabalin.[10, 11, 15] As geographic variation among patients being prescribed with pregabalin exists, for example, in Denmark,[10] we used information about the district of patients' place of residence to differentiate between patients living in urban areas and those living in rural ones.
b) Diagnoses for the approved indications (neuropathic pain, general anxiety disorders, and epilepsy) were identified using information about diagnoses from the hospital and ambulatory sector. To ensure that diagnoses were related to the pregabalin prescription, only diagnoses that had occurred no more than three months prior to the prescription were considered. The patterns of diagnosis codes are presented in the form of the International Classification of Diseases 10th revision (ICD-10) [24] and are summarized in Table 1. The diagnoses were extracted from studies analyzing indications associated with pregabalin prescriptions.[11, 15, 25, 26]
c) Patients with a history of substance use disorders might be at higher risk of misusing pregabalin.[11] Therefore, we examined whether patients had been diagnosed with substance use disorders within two different quarters in hospital ("main diagnosis") or in the ambulatory sector ("confirmed") within one year prior to the initial pregabalin prescription. Additionally, we examined whether patients had been prescribed a drug for the treatment of alcohol, tobacco, or opioid addiction at least once in the year prior to the initial prescription (see Table 1 for ICD-10 and ATC codes).
d) We analyzed whether patients had been prescribed opioids or psychostimulants in the year before initial pregabalin prescription. This is because these drugs have known potential for

abuse and might therefore be more prevalent in the group of users misusing pregabalin (see Table 1 for details).

**Table 1** Patterns of diagnoses (ICD-10) for relevant medical conditions and ATC for relevant prescriptions

| Indications/diagnoses/drugs | ICD-10/ATC codes |
|---|---|
| **Approved indications**[1] | |
| Epilepsy | G40; G41 |
| Generalized anxiety disorders | F41.1 |
| Neuropathic pain-related diagnoses | G35.9; G50.0; G50.1; G51.0; G53.0; G54.4; G54.6; G55.0; G55.1; G56.0; G56.2; G56.4; G56.9; G57.0; G57.1; G57.8; G57.9; G58.0; G58.7; G58.8; G62.9; G63.2; G82.1; G95.0; G95.2; G95.8; G97.9.; I69.1; I69.3; M48.0; M50.1; M53.0; M53.1 M54.1; M54.3; M54.4; M79; M89.0; R52 |
| Additional neuropathic pain-related diagnoses (broad pattern) | B02; G13.0; G52.1; G56; G57; G58; G59; G60; G61; G62; G63; G99.0; M51.1; M54.2; T92.6; T93.6 |
| **Substance use disorders**[2] | F11–F19; T42; T43; Z71.4–5 |
| **Addictive disorder drugs**[3] | |
| Alcohol | N07BB |
| Tobacco | N07BA |
| Opioids | N07BC |
| **Drugs with potential for abuse**[3] | |
| Opioids | N02A |
| Psychostimulants | N06B |
| Benzodiazepines | N05B, N05C |

**Notes**: *[1]Diagnoses during the same quarter as initial prescription; [2]At least one diagnosis in two different quarters during the year before initial prescription; [3]At least one prescription during the year before initial prescription.*

## Prescription networks and structural characteristics

In order to describe and analyze whether and how patterns of utilization differ between the two groups of pregabalin users, we identified a prescription network for each patient. This approach allows an analysis of how strongly the prescribing physicians are connected in networks through shared patients. A large number of shared patients among the prescribers may indicate active cooperation including, e.g., information transfer about dispensed drugs.[17] In contrast, and assuming that doctor shopping is taking place, we expected that the prescribers of patients who potentially misuse pregabalin are less connected to other prescribers. Thus, we hypothesized that prescribers of patients who were identified as misusing pregabalin have fewer network contacts with other prescribers than those prescribers whose patients use pregabalin with the “right” dosage.

The prescription networks were identified per patient for the observation period of one year since initial prescription. They were first built as bipartite networks, in which a patient was connected to his or her prescribing physicians (see the prescription network in Fig. 2a). To analyze cooperation among these prescribing physicians and following the findings of patient-sharing network analyses, we expanded the group of patients in the bipartite networks to all

patients seen by the prescribing physicians during the observation period (see the patient-sharing network in Fig. 2a). The resulting bipartite networks were subsequently summarized to unipartite networks, in which only the physicians were considered and connected through shared patients (see Fig. 2b). The *care density*, as a summary value for cooperation among the physicians, was then calculated as the average number of shared patients between all possible pairs of providers in a patient's prescription network.

In the example in Fig. 2**Error! Reference source not found.**, we identified four physicians filling at least one pregabalin prescription for patient $P_1$. We further identified all patients in the extended patient population who had consulted at least two of these four physicians. Comparing the patient populations of each physician, we examined the number of patients shared between two physicians that led to the unipartite network in Fig. 2b. The physicians in this network shared 1.83 patients on average, which was the care density of this network.

Other structural characteristics of the prescription networks included the number of filled prescriptions, the number of prescribers, the medical specialty of first prescriber per pregabalin user, and the proportion of specialized physicians among the prescribing physicians. Driot et al.[15] showed that the number of prescribers is associated with misuse of pregabalin. The medical specialty of initial prescriber and the specialty mix in the prescription networks may give insights into typical patterns of utilization between the two groups of pregabalin users.

### Statistical methods

We present mean values and standard deviations of the characteristics that were calculated as continuous variables to describe the population of pregabalin users. Characteristics that were collected as categorical variables are presented in terms of numbers and proportions. We conducted univariate statistical tests to compare the group of normal users to the group of patients misusing pregabalin. To this end, we applied the $Chi^2$ test to categorical variables and, if a specification of a binary categorical variable contained fewer than five individuals, we applied Fisher's exact test to that variable instead.[27] Both tests enabled us to analyze whether the group proportions of a categorical variable were equal between the two groups.[27] For continuous variables, we used the nonparametric Wilcoxon–Mann–Whitney U-test to examine whether the values in one group were significantly greater (or smaller) than the values in the other group. This test does not require any assumptions about the distribution of the analyzed variable, and the results can be considered conservative.[27] In order to correct for multiple testing and the related increased risk of a type I error (false positives), we conducted a Bonferroni post-hoc adjustment. This adjustment considers the number of statistical tests conducted to correct the resulting p-values.[28]

## RESULTS

In total, 53,049 patients accounting for less than 1% of the population from the four German states insured with the AOK received an initial pregabalin prescription between January 2014 and December 2016. During the 3 years, the absolute number of new pregabalin users increased from 17,003 patients in 2014 to 18,025 patients in 2016. In the group of initial pregabalin users, 877 patients (1.7%) were prescribed doses that on average exceeded the maximum therapeutic dose of 600 mg per day.

The descriptive statistics of all pregabalin users and the results of the univariate statistical tests are summarized in Table 2. The results indicate that the group of patients classified as normal users had similar characteristics to the total population for all presented values. However, the majority of characteristics for the group of normal users and patients misusing pregabalin differ systematically.

The results show that about 60% of initial pregabalin users in the dataset were female. The gender distribution was reversed for the group of patients misusing pregabalin (about 60% male vs. 40% female) and hence differed significantly from the distribution in the group of normal users. Half the patients were 70 years old or older when they received their initial pregabalin prescription, and there were only a few (22) patients who were younger than 18 and older than 11 years old. In contrast, in the group of patients misusing pregabalin, the age structure changed significantly, and most patients were between 30 and 60 years old.

Concerning the place of residence, it can be seen that, of all pregabalin users, approximately 55% of patients lived in rural areas and 45% in urban areas. When focusing on patients misusing pregabalin, these values differed significantly in comparison to normal users: The majority of patients misusing pregabalin lived in urban areas (51%), whereas the distribution of normal users was comparable to that of the total population.

Neuropathic pain was the most frequent indication that pregabalin users were diagnosed within the same quarter as their initial prescription (75% and 79% for the broader definition). General anxiety disorder and epilepsy were prevalent in 5.8% and 3.7% of patients respectively. About 18% of patients had none of these diagnosed indications, and 6% of patients were diagnosed with several indications. In the group of patients misusing pregabalin, the proportion of patients with no medical indication increased to 21%. However, this result was not statistically significant after adjusting for multiple testing. Epilepsy and general anxiety disorder was more prevalent in the group of misusing patients compared to normal users, whereas the proportion of patients with neuropathic pain was slightly smaller. All these differences were found to be significant.

Substance use disorders were prevalent in 12% of patients, and the proportion of patients with this disease increased significantly to 42% among patients misusing pregabalin. Drugs for the treatment of addictive disorders were prescribed to only some patients in both groups, except drugs for the treatment of opioid addiction, which were prescribed to 8.7% of patients misusing pregabalin; this was significantly more than to the normal users (0.3%).

Overall, 18% and 45% of patients had been prescribed benzodiazepines or opioids, respectively, within the year prior to the initial pregabalin prescription. The proportion of patients with a prior prescription of benzodiazepine was significantly higher in the group of patients misusing pregabalin (34%), whereas only 41% of these patients had been prescribed with opioids during the year before.

Most of the patients received their initial pregabalin prescription from a general practitioner (62%), followed by patients receiving their initial prescription from specialists in neuroscience or neurology (about 18%). This characteristic varied only slightly and not significantly between the two groups of patients.

Pregabalin users received on average six prescriptions from two different physicians over one year. In contrast, patients misusing pregabalin got on average about 13 prescriptions from three different physicians. Thus, their prescription networks were significantly larger than those of normal users.

Lastly, physicians prescribing pregabalin to a normal user shared on average 48 patients. This value was significantly smaller (33 patients) among prescribers of patients who misuse pregabalin. The prescription networks of patients who were misusing pregabalin were thus less connected in terms of shared patients. In order to gain further insights into the prescription networks, the maximal geographic distance among the prescribers was calculated and compared between the two groups. It can be seen that, among the patients misusing pregabalin, the maximal distance was about 16 kilometers on average, whereas the prescribers of normal users were less than half that distance away from each other.

**Table 2** Descriptive statistics of the dataset and results of the univariate statistical analyses

| | | All pregabalin users | Groups of users with average doses | | | |
|---|---|---|---|---|---|---|
| | | | ≤600mg/day | >600mg/day | unadjusted | adjusted |
| | | N (%) / M (SD) | N (%) / M (SD) | N (%) / M (SD) | p-values | p-values |
| **Patient characteristics** | | | | | | |
| **Gender** | Male | 21,004 (39.6) | 20,468 (39.2) | 536 (61.1) | <0.001 | <0.001 |
| | Female | 32,045 (60.4) | 31,704 (60.8) | 341 (38.9) | | |
| **Age (years)** | 12–17 | 22 (0.0) | 22 (0.0) | 0 (0.0) | <0.001 | <0.001 |
| | 18–29 | 867 (1.6) | 782 (1.5) | 85 (9.7) | <0.001 | <0.001 |
| | 30–39 | 1,996 (3.8) | 1,808 (3.5) | 188 (21.4) | <0.001 | <0.001 |
| | 40–49 | 4,472 (8.4) | 4,271 (8.2) | 201 (22.9) | <0.001 | <0.001 |
| | 50–59 | 9,434 (17.8) | 9,252 (17.7) | 182 (20.8) | <0.001 | <0.001 |
| | 60–69 | 9,768 (18.4) | 9,677 (18.5) | 91 (10.4) | <0.001 | <0.001 |
| | ≥ 70 | 26,490 (49.9) | 26,360 (50.5) | 130 (14.8) | <0.001 | <0.001 |
| **Place of residence** | Urban area | 23,862 (45.0) | 23,413 (44.9) | 449 (51.2) | <0.001 | 0.006 |
| | Rural area | 29,119 (54.9) | 28,694 (55.0) | 425 (48.5) | <0.001 | 0.006 |
| **Approved indications** | | | | | | |
| Epilepsy | | 1,968 (3.7) | 1,882 (3.6) | 86 (9.8) | <0.001 | <0.001 |
| Generalized anxiety disorder | | 3,068 (5.8) | 2,958 (5.7) | 110 (12.5) | <0.001 | <0.001 |
| Neuropathic pain | | 39,829 (75.1) | 39,249 (75.2) | 580 (66.1) | <0.001 | <0.001 |
| Neuropathic pain (broad definition) | | 42,120 (79.4) | 41,505 (79.6) | 615 (70.1) | <0.001 | <0.001 |
| Multiple | | 3,293 (6.2) | 3,186 (6,1) | 107 (12.2) | <0.001 | <0.001 |
| None | | 9,283 (17.5) | 9,098 (17.4) | 185 (21.1) | 0.005 | 0.184 |
| **Medical pre-conditions with increased risk of abuse** | | | | | | |
| Substance use disorders | | 6,414 (12.1) | 6,049 (11.6) | 365 (41.6) | <0.001 | <0.001 |
| Addictive disorder drug (alcohol) | | 43 (0.1) | 41 (0.1) | 2 (0.2) | 0.345 | 1.000 |
| Addictive disorder drug (tobacco) | | 2 (0.0) | 2 (0.0) | 0 (0.0) | 1.000 | 1.000 |
| Addictive disorder drug (opioids) | | 258 (0.5) | 182 (0.3) | 76 (8.7) | <0.001 | <0.001 |
| **Drugs with potential for abuse** | | | | | | |
| Benzodiazepine | | 9,665 (18.2) | 9,367 (18.0) | 298 (34.0) | <0.001 | <0.001 |
| Opioids | | 23,886 (45.0) | 23,527 (45.1) | 359 (40.9) | 0.015 | 0.526 |
| Psychostimulants | | 288 (0.5) | 263 (0.5) | 25 (2.9) | <0.001 | <0.001 |
| **Prescription networks and structural characteristics** | | | | | | |
| Number of prescriptions | | 6.34 (3.28) | 6.23 (2.91) | 12.70 (10.17) | <0.001 | <0.001 |
| Number of prescribers (physicians) | | 1.79 (1.03) | 1.77 (0.89) | 3.12 (3.91) | <0.001 | <0.001 |
| Number of prescribers (practices) | | 1.59 (0.87) | 1.57 (0.73) | 2.86 (3.61) | <0.001 | <0.001 |
| **Medical specialty of initial prescriber** | | | | | | |
| GP | | 32,911 (62.0) | 32,344 (62.0) | 567 (64.7) | 0.010 | 0.348 |
| Anesthesiology | | 1,935 (3.6) | 1,908 (3.7) | 27 (3.1) | 0.010 | 0.348 |
| Orthopedics | | 1,209 (2.3) | 1,192 (2.3) | 17 (1.9) | 0.010 | 0.348 |
| Neuroscience | | 4,292 (8.1) | 4,223 (8.1) | 69 (7.9) | 0.010 | 0.348 |
| Neurology | | 5,039 (9.5) | 4,984 (9.6) | 55 (6.3) | 0.010 | 0.348 |
| Psychiatry and psychotherapy | | 2,341 (4.4) | 2,289 (4.4) | 52 (5.9) | 0.010 | 0.348 |
| Other | | 5,322 (10.0) | 5,232 (10.0) | 90 (10.3) | 0.010 | 0.348 |
| Proportion of specialists among prescribers | | 0.31 (0.40) | 0.31 (0.40) | 0.31 (0.38) | 0.300 | 1.000 |
| Care density among physicians[1] | | 47.97 (70.61) | 48.29 (70.67) | 33.23 (66.43) | <0.001 | <0.001 |
| Care density among practices[1] | | 17.42 (35.77) | 17.54 (35.84) | 12.90 (32.76) | 0.149 | 1.000 |
| Maximal geographic distance [in kilometers] | | 6.86 (26.63) | 6.71 (26.24) | 15.98 (43.27) | <0.001 | <0.001 |

***Notes:*** *[1]Care density was calculated as the average number of shared patients among all pairs of providers per patient and was calculated for patients with at least two prescribers (physicians/ practices)*

## DISCUSSION

The present study investigated the public health problem of the misuse of prescription drugs through coordination problems in health care systems, such as discontinuities or gaps in care. We presented an extensive list of characteristics for analyzing patients and their utilization patterns of pregabalin. The list comprised both patient and structural characteristics of the prescribing physicians and was applied to patients from four German states. By taking advantage of routine data, all pregabalin prescriptions could be considered, independently of the prescribing physicians. The data were used to identify a group of patients who were receiving a higher than medically recommended dose.

The investigated sample of pregabalin users is comparable to patients presented in studies from other European countries regarding the age and gender structure of the patient population.[10, 11, 26] The most prevalent medical indication in our study was neuropathic pain. This result is consistent with findings from other studies.[11, 15, 29]

The proportion of patients misusing pregabalin amounted to 1.7% in our sample. Compared to the results of studies from Sweden with 8.5%,[11] Denmark with 6.5%,[10] and France with 12.8%,[15] this proportion is clearly smaller. Even though Novak et al.[2] showed that Germany has the lowest rates of drug misuse among the five analyzed European countries, this difference might not only reflect a difference in prevalence but also be explained by slightly different approaches to identifying patients misusing pregabalin, e.g., the German routine data do not include prescriptions filled by hospitals. The presented classification and results could therefore be classified as conservative.

We found evidence that particularly younger men and patients with a history of substance use disorders were overrepresented in the group of patients misusing pregabalin. These results suggest that, among the pregabalin users, there exists a group of patients who are at higher risk of misusing pregabalin and that physicians prescribing pregabalin should pay special attention to pre-existing medical conditions.

An unexpected result of this study is that relatively few patients misusing pregabalin had a prior medication with opioids, as other studies have shown that patients with an opioid addiction might also abuse pregabalin.[4, 30] At the same time, we observed relatively high numbers of patients who had a prior medication with benzodiazepines. Additionally, the proportion of patients with prior medication with drugs for the treatment of opioid addiction in the misusing group was high. One possible interpretation of these results could be that patients with an opioid addiction history might use pregabalin as a substitute, whereas patients with a history of benzodiazepine use are using pregabalin rather as a complement. However, our analysis does not allow for a definite conclusion about this assumption.

Additional to the presented patient characteristics that were associated with misuse of pregabalin, our study sheds light on the network structures of the prescribing ambulatory physicians. The results suggest that patients successfully attempted to get a higher than medically recommended dose of pregabalin. We have shown that these patients not only had a greater number of prescribers (3.12 vs. 1.77 physicians) but also that their prescribing physicians were noticeably more loosely connected to other prescribers than those physicians whose patients were normal users of pregabalin (33 vs. 48 shared patients). Additionally, the locations of the prescribers' practices were further away from each other for patients misusing pregabalin compared to normal users (16 km vs. 7 km). Both these results indicate that the patients are seeking to receive prescriptions from physicians who are as unconnected with

each other and geographically as far from each other as possible. These might be signs of existing doctor shopping when care coordination to control co-prescriptions is not present.

Office-based physicians in Germany can be organized in group practices, and physicians from the same practice usually share a number of patients and might additionally represent each other in terms of filling prescriptions. Therefore, a large number of shared patients between physicians might primarily indicate that they belong to a common practice. In order to control for this issue, we conducted a sensitivity analysis using practices as the unit of prescribers instead of physicians and found comparable results (see Table 2): Normal users received their prescriptions from only 1.59 different practices on average, whereas patients misusing pregabalin had 2.89 different prescribing practices. Also, in terms of care density, the practices in the prescription networks of patients misusing pregabalin shared fewer patients than practices in the prescription networks of normal users (13 vs. 18 shared patients). Even though this difference was not significant, these results support the conclusion that misusing patients seek to obtain prescriptions from loosely connected physicians and physicians who do not coordinate their care.

The application of SNA was used in the present analysis to examine a summary statistic of cooperation in order to compare the prescribers between the two groups of pregabalin users. Future research could additionally visually compare prescription networks and use this methodology to identify clusters with a strikingly high prevalence of drug misuse.[31]

When interpreting our results, one has to take into account some important limitations. First, we only considered prescriptions for pregabalin and not for its predecessor gabapentin, even though the abuse potential of gabapentin is also under discussion.[4] However, as stated in the critical review report from the World Health Organization, the risk of pregabalin abuse might be higher because of its stronger euphoric and relaxing effect.[5] Second, the prescriptions included in the dataset only covered prescriptions from office-based physicians, did not comprise medications that were provided during hospital stays, and might thus have underestimated the amount of pregabalin consumed. Third, the data did not provide information about the compliance of patients, but only about the amount of drug dispensed. We cannot definitely draw a conclusion about the final reason for high dispensed doses of pregabalin. However, with the comparably low number of patients being classified as misusing pregabalin and an average dispensed dose of 905 mg per patient and day within this group, we are confident we have developed a rather conservative measure that primarily discovers patients intentionally misusing pregabalin.

## CONCLUSION

To conclude, this study offers first insights into pregabalin utilization and prescription patterns in Germany. Misuse of pregabalin is one example of patients' intentional exploitation of coordination issues in ambulatory care. It sheds light on the evolving problems when care is not systematically coordinated and information about prescriptions is not exchanged. The study further shows how this problem might be minimized when physicians collaborate more closely, which is represented by a greater number of shared patients. However, absolute prevention of this problem will probably only be possible if information about medications is exchanged between all physicians as a standard and mandatory requirement. Last, the study discovered a group of patients who are potentially misusing this drug and shows that particularly prescribing physicians should be aware of this risk.

## Figure legends

**Fig. 1** Identification of the analyzed patient population in routine data

**Fig. 2** a The bipartite prescription network of patient P1 and the resulting bipartite patient-sharing physician network of P1's prescribers; b Depiction of the resulting unipartite network

***Notes:*** *a The bipartite patient-sharing network of $P_1$ prescribers was calculated based on the extended patient population. b The thickness of tie represents the number of shared patients. The resulting care density is 1.83.*

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**Conflict of Interest**: This paper was written in the context of the WirtMed study, which was granted by the innovation fund program of the German Federal Joint Committee (grant number 01VSF17016).

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- AOK Health Insurance Bavaria (SHI)
- AOK PLUS SHI in Thuringia and Saxony

**Ethic approval:** The present study was a secondary data analysis and therefore did not need an ethics approval.

**Data statement** Due to data protection reasons the data cannot be provided. The data provided were processed exclusively for scientific research purposes within the framework of the Innovation Fund project 'WirtMed study'. The legal basis for the processing is Section 75 of Book X of the German Code of Social Law (§75 SGB X: Transfer of Social Data for Research). An informed consent to participate was therefore not required.
The data transmission from the participating health insurance funds was organized via a trust centre, where the pseudonymized routine data from the three health insurance funds were linked. To prevent re-identification, pseudonymized patient and physician data were pseudonymized again after the linkage and maintained in password-protected, encrypted containers. Inferences to individuals are excluded.

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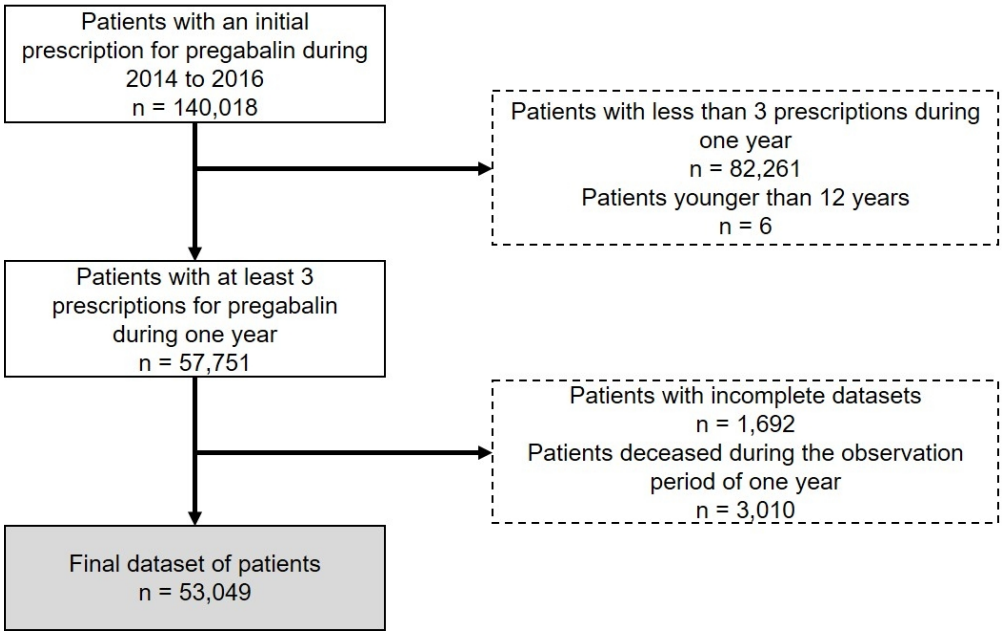
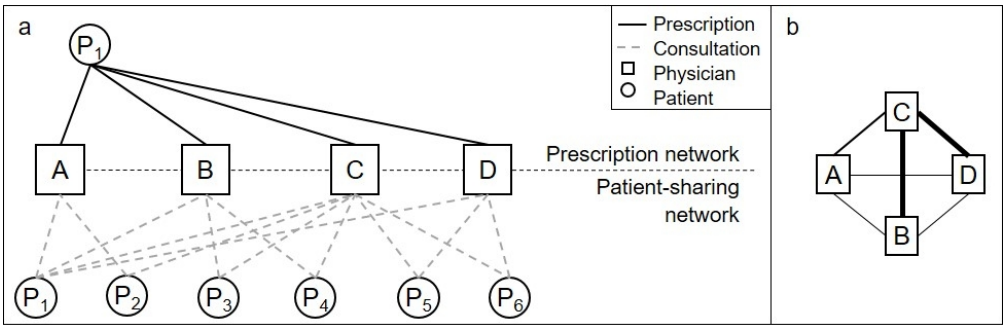



Identification of the analyzed patient population in routine data

177x112mm (150 x 150 DPI)




a The bipartite prescription network of patient P1 and the resulting bipartite patient-sharing physician network of P1's prescribers; b Depiction of the resulting unipartite network

Notes: a The bipartite patient-sharing network of P1 prescribers was calculated based on the extended patient population. b The thickness of tie represents the number of shared patients. The resulting care density is 1.83

164x53mm (150 x 150 DPI)

## Supplemental material

List of drugs for inclusion of patients in the extended population

| ATC | Name |
|---|---|
| N06AX22 | Agomelatin, Valdoxan |
| B01AF02 | Apixaban, Eliquis |
| B01AE07 | Dabigatran, Pradaxa |
| A10BK01 | Dapagliflozin, Forxiga |
| A10BJ05 | Dulaglutid, Trulicity |
| B01AF03 | Edoxaban, Lixiana |
| C03DA04 | Eplerenon, Inspra |
| M04AA03 | Febuxostat, Adenuric |
| C01EB17 | Ivabradin, Procoralan |
| N06BA12 | Lisdexamfetamin, Elvanse |
| N03AX16 | Pregabalin, Lyrica |
| B01AF01 | Rivaroxaban, Xarelto |
| C09DX04 | Sacubitril/Valsartan, Entresto |
| A10BH03 | Saxagliptin, Onglyza |
| A10BH01 | Sitagliptin, Januvia |
| N02AX06 | Tapentadol, Palexia |
| B01AC24 | Ticragelor, Brilique |
| C10BA02 | Ezetimib/Simvastatin, Inegy |
| N02AA55 | Oxycodon/Naloxon, Targin |
| M05BX04 | Denosumab, Prolia |
| N06AX21 | Duloxetin, Cymbalta |
| A10BK02 | Canagliflozin, Invokana |
| A10BK03 | Empagliflozin, Jardiance |
| L04AB01 | Etanercept, Enbrel |
| N06BA09 | Atomoxetin, Strattera |
| N07XX09 | Dimethylfumarat, Tecfidera |
| C01BD07 | Dronedaron, Multaq |
| R03AC18 | Indacaterol/Glycopyrronium, Ultibro Breezhaler |
| A10BJ02 | Liraglutid, Victoza |
| B01AC22 | Prasugrel, Efient |
| A10AE04 | Insulin glargin, Toujeo |
| R03AL06 | Tiotropium/Olodaterol, Spiolto |
| R03AL03 | Umeclidinium/Vilanterol, Anoro |
| G04BD08 | Solifenacin, Vesikur |

***Notes:*** *This list was developed within the WirtMed study and comprises drugs with a high price and/or unsure or unproved medical benefit for patients.*

**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

| | Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|---|---|---|---|---|---|
| **Title and abstract** | | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.<br><br>RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.<br><br>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | p. 2<br><br>p. 2<br><br>p. 2 |
| **Introduction** | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | | | p. 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | | | p. 4 |
| **Methods** | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | | | p. 4 ff. |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | | | p. 4 ff. |

| | | | | | |
|---|---|---|---|---|---|
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | | RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.<br><br>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | p. 4 ff.<br><br>p. 5<br><br>p. 4 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | p. 5-6 |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement).<br>Describe comparability of assessment methods if there is more than one group | | | p. 5-6 |

| | | | | | |
|---|---|---|---|---|---|
| Bias | 9 | Describe any efforts to address potential sources of bias | | | p. 7 |
| Study size | 10 | Explain how the study size was arrived at | | | p. 7 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | | | p. 7 |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | | | p. 7 |
| Data access and cleaning methods | | .. | | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. | p. 4 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | |
| Linkage | | .. | | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | p. 4ff. |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | p. 7-9 |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | | | p. 7-9 |
| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure | | | p. 7-9 |

| | | | | | |
|---|---|---|---|---|---|
| | | category, or summary measures of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | | | p. 7-9 |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | | | |
| **Discussion** | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | | | p. 9-ff. |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | p. 11 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, | | | p. 11 |

| | | | | | |
|---|---|---|---|---|---|
| | | limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | | | p. 9 ff. |
| **Other Information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | | | p. 13 |
| Accessibility of protocol, raw data, and programming code | | .. | | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | p. 13 |

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

# Prescription patterns of pregabalin in four German federal states: Routine data analysis of patient characteristics and empirical prescription networks of patients misusing pregabalin



| | |
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**Title: Prescription patterns of pregabalin in four German federal states: Routine data analysis of patient characteristics and empirical prescription networks of patients misusing pregabalin**

**(Corresponding) Author information:** Ronja Flemming, TU Munich, Chair of health economics, Georg-Brauchle-Ring 60/6, 80992 Munich, Germany, ronja.flemming@tum.de

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**Key Words:**
coordination of care, drugs with addictive potential, pregabalin, social network analysis, routine data, ambulatory care

## Abstract

**Objectives.** The objectives of this study were to investigate utilisation patterns of pregabalin, to identify users misusing pregabalin, and to compare this group of patients to pregabalin users prescribed recommended doses concerning their personal characteristics and the coordination among their prescribers. Unintended co-prescription of drugs with addictive potential might occur when care is insufficiently coordinated.

**Design.** Secondary data analysis of linked data from three regional sickness funds in Germany (AOK) of the years 2014–2016.

**Setting.** Ambulatory and hospital care sector in four German federal states.

**Methods.** On the basis of routine data, I identified patients who received at least three prescriptions of pregabalin and classified them into patients prescribed pregabalin as recommended and those dispensed with a higher than medically recommended dose. I applied social network analysis to identify prescription networks and to analyse cooperation among the prescribers. With descriptive statistics and univariate statistical tests, I examined typical characteristics of the group of patients misusing pregabalin compared to the others.

**Results.** Among the 53,049 pregabalin users, about 2% were classified as potentially misusing pregabalin. The majority of this group was male and between 30 and 60 years old. About 40% of patients misusing pregabalin had a diagnosed history of substance use disorders, and 40% had been prescribed another drug with addictive potential before. The prescribers of those patients misusing pregabalin were more loosely connected within networks compared to prescribers of patients prescribed pregabalin as recommended.

**Conclusion.** This study found that patients could exceed the recommended doses by getting prescriptions from multiple physicians. Specific patients were at higher risk of misusing pregabalin than others, and these patients sought to obtain their prescriptions from physicians who were as loosely connected as possible. Coordination and sharing a relevant number of patients seem to be levers to avoid these problems of unintended co-prescribing.


## Strengths and limitations of this study

- Routine data can serve as an objective measure to depict health service utilisation.
- The applied methodology of social network analysis enables to explore cooperation among health care providers.
- The study includes univariate statistical tests indicating differences between the two analysed groups of pregabalin users and does not provide information about which analysed factors are most predictive.
- The nature of routine data does not allow drawing conclusions about the reasons for high prescription rates and leads to incomplete information about prescriptions from the hospital sector or prescriptions not filled by the patients.
- The analysed population is limited to people insured at the included three regional AOK sickness funds and might therefore differ slightly from the general population in Germany.

## INTRODUCTION

The misuse or nonmedical use of prescription drugs may lead to severe substance-related disorders and fatal health effects such as drug addiction, behavioural dependence, or even death. The nonmedical use of opioids is one of the leading public health issues in the United States [1] and is characterised as an epidemic. Even though the prevalence is estimated to be lower in European countries, Novak et al.[2] reported past-year prevalence for nonmedical drug use of up to 5% among five EU member states. As many of these misused drugs have great addiction potential, patients may take advantage of coordination problems in health care systems, such as discontinuities or gaps in care.

One possible way for patients to misuse prescription drugs is to consume a higher than medically indicated dose.[3] To this end, patients may seek to obtain prescriptions from multiple health care providers through so-called doctor shopping.[3] Especially in fragmented health care systems, unknown and unintentional double prescribing might occur because patients can choose the physicians they consult, without the need for referral and information transfer among health care providers. This requires close cooperation and collaboration among providers when trying to prevent intentional misuse of prescription drugs, particularly when coordination gaps in health care are exploited by patients.

Pregabalin (Lyrica) is one example of such drugs, potentially misused by patients. It was introduced in 2004 and is approved for the treatment of neuropathic pain, general anxiety disorder, and epilepsy in Europe. Pregabalin is a gamma-aminobutyric acid (GABA) that reduces the excitability of neurons in the central nervous system and is structurally related to its predecessor gabapentin.[4] Pregabalin binds to an auxiliary subunit of voltage-dependent calcium channels and thus reduces the release of several neurotransmitters such as glutamate, noradrenaline, and the neuropeptide substance P.[5] This may reduce neuronal excitability and thus seizures and neuropathic pain.[6] Additionally, pregabalin may have a relaxing effect and can produce euphoria, which are both assumed to cause abuse and addictive potential.[5]

Since 2008, concerns have been raised about the abuse and addictive potential of pregabalin, particularly for patients with a history of drug addiction,[4, 7, 8] and warning information was added to the German scientific information in 2011.[9] Nevertheless, the number of pregabalin users has still been growing in recent years.[10, 11] In Germany, an increase was observed from 2.2 million filled pregabalin prescriptions in 2011 to 3.9 million in 2018.[12, 13] Anecdotal evidence from Germany further suggests that there was also a rise in pregabalin abusers between 2008 and 2015.[14] Despite these known issues, there exists no monitoring of prescription quantities of pregabalin in Germany.

Based on prescription data, studies have investigated patient factors that are associated with the risk of being dispensed with pregabalin at a higher than recommended dose.[10, 11, 15] The authors interpreted this high dispensing of the drug as a sign of potential misuse of pregabalin. These studies showed that especially middle-aged men (between 18 and 45 years old), patients with a history of substance use disorders or drug abuse, and patients with psychological comorbidities are at particularly high risk of misusing pregabalin. Driot et al.[15] found that, at a structural level, misuse of pregabalin was associated with multiple prescribers, which might point to the presence of doctor shopping.

Social network analysis (SNA) methods are commonly applied in the health care sector to identify network structures among health care providers and to investigate the effects of care cooperation among these informal, patient-sharing physician networks on health care

provision.[16] For instance, Barnett et al.[17] showed that, if physicians were sharing more patients in their empirical network, it was more likely that they were cooperating in real life. Making use of this idea, Ong et al.[18] used SNA to analyse networks of physicians prescribing interacting drugs to the same patients. They showed that a patient was more likely to be co-prescribed with interacting drugs if his or her caring physicians shared fewer patients on average. In another study, Ong et al.[19] analysed multiple providers prescribing benzodiazepines and also showed that two physicians were at a greater risk of prescribing benzodiazepine with overlapping coverage if they shared fewer patients.

The German ambulatory care sector has no formal system to coordinate care among office-based physicians, and information about treatment and medication is not regularly transferred among health care providers. This loose organisation might facilitate the intentional misuse of prescription drugs for patients. The present study thus aimed to analyse pregabalin utilisation in four German states based on routinely collected health insurance data. It described the characteristics of patients who have been prescribed pregabalin and identified users potentially misusing[1] this drug. This group was compared to the group of patients prescribed pregabalin as recommended in order to, first, examine the typical characteristics of patients misusing pregabalin and, second, identify the common factors and analyse the connectivity among the physicians prescribing pregabalin to patients who misuse the drug.

## MATERIALS AND METHODS

### Data Source and patient population

Three regionally organised statutory health insurances (AOK), covering four German states, Bavaria, Hesse, Thuringia, and Saxony, provided sickness fund data for this study. In Germany, about 90% of the population is insured with a statutory health insurance and the AOK insures about 42% of the population in these regions. The insured population of the AOK differs only slightly from the general German population in terms of age and gender.[20] The provided dataset covered about 14% of their insured population from the years 2013 to 2017[2]. It included billed services and diagnoses from the ambulatory and hospital sector as well as prescription data and patient information, such as age and gender.

Patients were included in the analysis if they had received an initial prescription of pregabalin (ATC: N03AX16) between January 2014 and December 2016, ensuring that both a lead-up and a follow-up year for each patient was included in the dataset. To be classified as an initial user, the patient should not have been prescribed pregabalin in the year prior to the initial prescription. Patients for whom only incomplete patient information was available, patients younger than 12 years of age, and patients who died during the observation period of one year since their initial prescription were excluded from the analysis. I only considered patients with at least three filled prescriptions for pregabalin during the observation period of one year to identify patients who used pregabalin regularly. Details about the identification of the patient population are depicted in Fig. 1.

[1] In this manuscript, the term “misuse” will be used for the group of patients prescribed with a higher than medically recommended dose of pregabalin, which might indicate but not necessarily mean that these patients are misusing pregabalin.

[2] This extended patient population included patients who received at least once one of 34 defined drugs within the observation period (see supplemental material 1).

## Patient and public involvement

The presented study represents a retrospective secondary data analysis, therefore patients and the public were not directly involved.

## Definition of potential misuse

The World Health Organization defines psychoactive substance misuse as "Use of a substance for a purpose not consistent with legal medical guidelines […]".[21] The European public assessment report for pregabalin (Lyrica) recommends a maximum therapeutic dose of 600 mg per day (corresponding to two defined daily doses (DDD)).[22] Therefore, to classify patients with prescriptions for pregabalin as patients prescribed pregabalin as recommended and those potentially misusing the drug, I compared the average daily dose during one year to this recommended maximum dose.[10, 11, 15]

The prescription dataset listed all drugs that had been prescribed by any ambulatory physician and dispensed in a pharmacy. It provided the Anatomical Therapeutic Chemical (ATC) classification, the prescription and dispensing date, and the prescribed dose in terms of the DDD. On this basis, I calculated the sum of dispensed drug per patient during the time span of a maximum of 12 months since initial dispensing, excluding the prescribed dose of the last dispense. I then examined the time span (in days) between first and last dispensing and calculated the average amount of dispensed drug per day. If this average exceeded the maximum dose of 600 mg, I classified the patient as potentially misusing pregabalin with the hazard of behavioural dependence.

## Patient characteristics and medical conditions

The patient characteristics and medical conditions that I used to describe pregabalin users and compare the two groups included information about a) patient characteristics, b) prevalence of approved indications for pregabalin, c) medical conditions that might increase the risk of misuse, and d) prescriptions of drugs with potential for misuse as follows:

a) The dataset comprised, among others, the age and gender as relevant patient characteristics, as studies have shown that especially men between 18 and 45 years old seem to be at higher risk of misusing pregabalin.[10, 11, 15] As geographic variation among patients prescribed with pregabalin exists, for example, in Denmark,[10] I used information about the district of patients' place of residence to differentiate between patients living in urban areas and those living in rural ones.[23]
b) Diagnoses for the approved indications (neuropathic pain, general anxiety disorders, and epilepsy) were identified using information about diagnoses from the hospital and ambulatory sector. To ensure that diagnoses were related to the pregabalin prescription, only diagnoses that had occurred no more than three months prior to the prescription were considered. The patterns of diagnosis codes are presented in the form of the International Classification of Diseases 10th revision (ICD-10) [24] and are summarised in Table 1. The diagnoses were extracted from studies analysing indications associated with pregabalin prescriptions.[11, 15, 25, 26]
c) Patients with a history of substance use disorders might be at higher risk of misusing pregabalin.[11] Therefore, I examined whether patients had been diagnosed with substance use disorders within two different quarters in hospital ("main diagnosis") or in the ambulatory sector ("confirmed") within one year prior to the initial pregabalin prescription. Additionally, I examined whether patients had been prescribed a drug for the treatment of alcohol,

tobacco, or opioid addiction at least once in the year prior to the initial prescription (see Table 1 for ICD-10 and ATC codes).

d) I analysed whether patients had been prescribed opioids or psychostimulants (ATC N06B including centrally acting sympathomimetics, xanthine derivatives and other psychostimulants and nootropics such as meclofenoxate or pyritinol) [27] in the year before the initial pregabalin prescription, because these drugs have a known potential for abuse and might therefore be more prevalent in the group of users potentially misusing pregabalin. Since gabapentin as the predecessor of pregabalin is also under discussion because of its potential of abuse, I also controlled for gabapentin prescriptions during the observation period (see Table 1 for details).

**Table 1** Patterns of diagnoses (ICD-10) for relevant medical conditions and ATC for relevant prescriptions

| Indications/diagnoses/drugs | ICD-10/ATC codes |
|---|---|
| **Approved indications[1]** | |
| Epilepsy | G40; G41 |
| Generalised anxiety disorders | F41.1 |
| Neuropathic pain-related diagnoses | G35.9; G50.0; G50.1; G51.0; G53.0; G54.4; G54.6; G55.0; G55.1; G56.0; G56.2; G56.4; G56.9; G57.0; G57.1; G57.8; G57.9; G58.0; G58.7; G58.8; G62.9; G63.2; G82.1; G95.0; G95.2; G95.8; G97.9.; I69.1; I69.3; M48.0; M50.1; M53.0; M53.1 M54.1; M54.3; M54.4; M79; M89.0; R52 |
| Additional neuropathic pain-related diagnoses (broad pattern) | B02; G13.0; G52.1; G56; G57; G58; G59; G60; G61; G62; G63; G99.0; M51.1; M54.2; T92.6; T93.6 |
| **Substance use disorders[2]** | F11–F19; T42; T43; Z71.4–5 |
| **Addictive disorder drugs[3]** | |
| Alcohol | N07BB |
| Tobacco | N07BA |
| Opioids | N07BC |
| **Drugs with potential for abuse[3]** | |
| Opioids | N02A |
| Psychostimulants | N06B |
| Benzodiazepines | N05B, N05C |
| Contemporaneous prescription of gabapentin[4] | N03AX12 |

**Notes**: *[1]Diagnoses during the same quarter as the initial prescription; [2]At least one diagnosis in two different quarters during the year before the initial prescription; [3]At least one prescription during the year before the initial prescription; [4]At least one prescription during the observation period of one year.*

### Prescription networks and structural characteristics

To describe and analyse if and how patterns of utilisation differ between the two groups of pregabalin users, I identified a prescription network for each patient. This approach allows an analysis of how strongly the prescribing physicians are connected in networks through shared patients. A large number of shared patients among the prescribers may indicate active cooperation including, e.g., information transfer about dispensed drugs.[17] In contrast, and

assuming that doctor shopping is taking place, I expected that the prescribers of patients who potentially misuse pregabalin are less connected to other prescribers. Thus, I hypothesised that prescribers of patients who were identified as misusing pregabalin have fewer network contacts with other prescribers than those prescribers whose patients were prescribed with dosages as recommended.

The prescription networks were identified per patient for the observation period of one year since the initial prescription. They were first built as bipartite networks, in which a patient was connected to his or her prescribing physicians (see the prescription network in Fig. 2a). To analyse cooperation among these prescribing physicians and following the findings of patient-sharing network analyses, I expanded the group of patients in the bipartite networks to all patients seen by the prescribing physicians during the observation period (see the patient-sharing network in Fig. 2a). The resulting bipartite networks were subsequently summarised to unipartite networks, in which only the physicians were considered and connected through shared patients (see Fig. 2b). The *care density*, as a summary value for cooperation among the physicians, was then calculated as the average number of shared patients between all possible pairs of providers in a patient's prescription network.

In the example in Fig. 2**Error! Reference source not found.**, I identified four physicians filling at least one pregabalin prescription for patient $P_1$. I further identified all patients in the extended patient population who had consulted at least two of these four physicians. Comparing the patient populations of each physician, I examined the number of patients shared between two physicians that led to the unipartite network in Fig. 2b. The physicians in this network shared 1.83 patients on average, which was the care density of this network.

Other structural characteristics of the prescription networks included the number of filled prescriptions, the number of prescribers, the medical specialty of first prescriber per pregabalin user, and the proportion of specialised physicians among the prescribing physicians. Driot et al.[15] showed that the number of prescribers is associated with misuse of pregabalin. The medical specialty of initial prescriber and the specialty mix in the prescription networks may give insights into typical patterns of utilisation between the two groups of pregabalin users.

### Statistical methods

I present mean values and standard deviations of the characteristics that were calculated as continuous variables to describe the population of pregabalin users. Characteristics that were collected as categorical variables are presented in terms of numbers and proportions. I conducted univariate statistical tests to compare the group of patients prescribed pregabalin as recommended to the group of patients misusing pregabalin. To this end, I applied the $Chi^2$ test to categorical variables and, if a specification of a binary categorical variable contained fewer than five individuals, I applied Fisher's exact test to that variable instead.[28] Both tests enabled me to analyse whether the group proportions of a categorical variable were equal between the two groups.[28] For continuous variables, I used the nonparametric Wilcoxon–Mann–Whitney U-test to examine whether the values in one group were significantly greater (or smaller) than the values in the other group. This test does not require any assumptions about the distribution of the analysed variable, and the results can be considered conservative.[28] In order to correct for multiple testing and the related increased risk of a type I error (false positives), I conducted a Bonferroni post-hoc adjustment. This adjustment considers the number of statistical tests conducted to correct the resulting p-values.[29]

## RESULTS

In total, 53,049 patients accounting for less than 1% of the population from the four German states insured with the AOK received an initial pregabalin prescription between January 2014 and December 2016. During the 3 years, the absolute number of new pregabalin users increased from 17,003 patients in 2014 to 18,025 patients in 2016. In the group of initial pregabalin users with three or more prescriptions of pregabalin, 877 patients (1.7%) were prescribed doses that on average exceeded the maximum therapeutic dose of 600 mg per day.

The descriptive statistics of all pregabalin users and the results of the univariate statistical tests are summarised in Table 2. The results indicate that the group of patients classified as patients prescribed pregabalin as recommended had similar characteristics to the total population for all presented values. However, the majority of characteristics differ systematically between the two groups built based on the amount of described pregabalin.

The results show that about 60% of initial pregabalin users in the dataset were female. The gender distribution was reversed for the group of patients misusing pregabalin (about 60% male vs. 40% female) and hence differed significantly from the distribution in the group of patients prescribed pregabalin as recommended. Half the patients were 70 years old or older when they received their initial pregabalin prescription, and there were only a few (22) patients who were between 11 and 18 years old. In contrast, in the group of patients misusing pregabalin, the age structure changed significantly, and most patients were between 30 and 60 years old.

Concerning the place of residence, it can be seen that, of all pregabalin users, approximately 55% of patients lived in rural areas and 45% in urban areas. When focusing on patients misusing pregabalin, these values differed significantly in comparison to the other group of patients prescribed with less pregabalin: The majority of patients with high dosages of pregabalin lived in urban areas (51%), whereas the distribution of patients prescribed pregabalin as recommended was comparable to that of the total population.

Neuropathic pain was the most frequent indication that pregabalin users were diagnosed within the same quarter as their initial prescription (75% and 79% for the broader definition). General anxiety disorder and epilepsy were prevalent in about 6% and 4% of patients respectively. About 18% of patients had none of these diagnosed indications, and 6% of patients were diagnosed with several indications. In the group of patients potentially misusing pregabalin, the proportion of patients with no medical indication increased to 21%. However, this result was not statistically significant after adjusting for multiple testing. Epilepsy and general anxiety disorder was more prevalent in the group of patients potentially misusing pregabalin compared to the other group, whereas the proportion of patients with neuropathic pain was slightly smaller. All these differences were found to be significant.

About 12% of patients had a history of substance use disorders, and the proportion of patients increased significantly to 42% among patients potentially misusing pregabalin. Drugs for the treatment of addictive disorders were prescribed to only some patients in both groups, except drugs for the treatment of opioid addiction, which were prescribed to about 9% of patients with high dosages of pregabalin; this was significantly more than to the group of patients prescribed pregabalin as recommended (0.3%).

Overall, 18% and 45% of patients had been prescribed benzodiazepines or opioids, respectively, within the year prior to the initial pregabalin prescription. The proportion of

patients with a prior prescription of benzodiazepine was significantly higher in the group of patients potentially misusing pregabalin (34%), whereas 41% of these patients had been prescribed with opioids during the year before.

Gabapentin was prescribed to about 6% of all pregabalin users and to about 10% of patients with high dosages of prescribed pregabalin.

Most of the patients received their initial pregabalin prescription from a general practitioner (62%), followed by patients receiving their initial prescription from specialists in neuroscience or neurology (about 18%). This characteristic varied only slightly and not significantly between the two groups of patients.

Pregabalin users received on average six prescriptions from two different physicians over one year. In contrast, patients misusing pregabalin got on average about 13 prescriptions from three different physicians. Thus, their prescription networks were significantly larger than those of patients with recommended prescription doses were.

Lastly, physicians prescribing pregabalin to a patient with recommended dosages shared on average 48 patients. This value was significantly smaller (33 patients) among prescribers of patients who misuse pregabalin. The prescription networks of patients who were misusing pregabalin were thus less connected in terms of shared patients. In order to gain further insights into the prescription networks, the maximal geographic distance among the prescribers was calculated and compared between the two groups. It can be seen that, among the patients misusing pregabalin, the maximal distance was about 16 kilometres on average, whereas the prescribers of the other group were less than half that distance away from each other.

**Table 2** Descriptive statistics of the dataset and results of the univariate statistical analyses

| | | | Groups of users with average doses | | | |
|---|---|---|---|---|---|---|
| | | **All pregabalin users** | **≤600mg/day** | **>600mg/day** | unadjusted | Bonferroni adjusted |
| | | N (%) / M (SD) | N (%) / M (SD) | N (%) / M (SD) | p-values | p-values |
| **Patient characteristics** | | | | | | |
| **Gender** | Male | 21,004 (39.6) | 20,468 (39.2) | 536 (61.1) | <0.001 | <0.001 |
| | Female | 32,045 (60.4) | 31,704 (60.8) | 341 (38.9) | | |
| **Age (years)** | 12–17 | 22 (0.0) | 22 (0.0) | 0 (0.0) | | |
| | 18–29 | 867 (1.6) | 782 (1.5) | 85 (9.7) | | |
| | 30–39 | 1,996 (3.8) | 1,808 (3.5) | 188 (21.4) | | |
| | 40–49 | 4,472 (8.4) | 4,271 (8.2) | 201 (22.9) | <0.001 | <0.001 |
| | 50–59 | 9,434 (17.8) | 9,252 (17.7) | 182 (20.8) | | |
| | 60–69 | 9,768 (18.4) | 9,677 (18.5) | 91 (10.4) | | |
| | ≥ 70 | 26,490 (49.9) | 26,360 (50.5) | 130 (14.8) | | |
| **Place of residence** | Urban area | 23,862 (45.0) | 23,413 (44.9) | 449 (51.2) | <0.001 | 0.004 |
| | Rural area | 29,119 (54.9) | 28,694 (55.0) | 425 (48.5) | | |
| **Approved indications** | | | | | | |
| Epilepsy | | 1,968 (3.7) | 1,882 (3.6) | 86 (9.8) | <0.001 | <0.001 |
| Generalised anxiety disorder | | 3,068 (5.8) | 2,958 (5.7) | 110 (12.5) | <0.001 | <0.001 |
| Neuropathic pain | | 39,829 (75.1) | 39,249 (75.2) | 580 (66.1) | <0.001 | <0.001 |
| Neuropathic pain (broad definition) | | 42,120 (79.4) | 41,505 (79.6) | 615 (70.1) | <0.001 | <0.001 |
| Multiple | | 3,293 (6.2) | 3,186 (6,1) | 107 (12.2) | <0.001 | <0.001 |
| None of the indications recorded in the records | | 9,283 (17.5) | 9,098 (17.4) | 185 (21.1) | 0.005 | 0.135 |
| **Medical pre-conditions with increased risk of abuse** | | | | | | |
| Substance use disorders | | 6,414 (12.1) | 6,049 (11.6) | 365 (41.6) | <0.001 | <0.001 |
| Addictive disorder drug (alcohol) | | 43 (0.1) | 41 (0.1) | 2 (0.2) | 0.345 | 1.000 |
| Addictive disorder drug (tobacco) | | 2 (0.0) | 2 (0.0) | 0 (0.0) | 1.000 | 1.000 |
| Addictive disorder drug (opioids) | | 258 (0.5) | 182 (0.3) | 76 (8.7) | <0.001 | <0.001 |
| **Drugs with potential for abuse** | | | | | | |
| Benzodiazepine | | 9,665 (18.2) | 9,367 (18.0) | 298 (34.0) | <0.001 | <0.001 |
| Opioids | | 23,886 (45.0) | 23,527 (45.1) | 359 (40.9) | 0.015 | 0.386 |
| Psychostimulants | | 288 (0.5) | 263 (0.5) | 25 (2.9) | <0.001 | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| **Contemporaneous prescription of gabapentin** | 2,973 (5.6) | 2,890 (5.5) | 83 (9.5) | <0.001 | <0.001 |
| **Prescription networks and structural characteristics** | | | | | |
| Number of prescriptions | 6.34 (3.28) | 6.23 (2.91) | 12.70 (10.17) | <0.001 | <0.001 |
| Number of prescribers (physicians) | 1.79 (1.03) | 1.77 (0.89) | 3.12 (3.91) | <0.001 | <0.001 |
| Number of prescribers (practices) | 1.59 (0.87) | 1.57 (0.73) | 2.86 (3.61) | <0.001 | <0.001 |
| **Medical specialty of initial prescriber** | | | | | |
| GP | 32,911 (62.0) | 32,344 (62.0) | 567 (64.7) | | |
| Anaesthesiology | 1,935 (3.6) | 1,908 (3.7) | 27 (3.1) | | |
| Orthopaedics | 1,209 (2.3) | 1,192 (2.3) | 17 (1.9) | | |
| Neuroscience | 4,292 (8.1) | 4,223 (8.1) | 69 (7.9) | 0.010 | 0.256 |
| Neurology | 5,039 (9.5) | 4,984 (9.6) | 55 (6.3) | | |
| Psychiatry and psychotherapy | 2,341 (4.4) | 2,289 (4.4) | 52 (5.9) | | |
| Other | 5,322 (10.0) | 5,232 (10.0) | 90 (10.3) | | |
| Proportion of specialists among prescribers | 0.31 (0.40) | 0.31 (0.40) | 0.31 (0.38) | 0.300 | 1.000 |
| Care density among physicians[1] | 47.97 (70.61) | 48.29 (70.67) | 33.23 (66.43) | <0.001 | <0.001 |
| Care density among practices[1] | 17.42 (35.77) | 17.54 (35.84) | 12.90 (32.76) | 0.149 | 1.000 |
| Maximal geographic distance [in kilometres] | 6.86 (26.63) | 6.71 (26.24) | 15.98 (43.27) | <0.001 | <0.001 |

***Notes:*** *[1]Care density was calculated as the average number of shared patients among all pairs of providers per patient and was calculated for patients with at least two prescribers (physicians/ practices)*

## DISCUSSION

The presented study investigated the public health problem of the misuse of prescription drugs through coordination problems in health care systems, such as discontinuities or gaps in care. I presented an extensive list of characteristics for analysing patients and their utilisation patterns of pregabalin. The list comprised both patient and structural characteristics of the prescribing physicians and was applied to patients from four German states. By taking advantage of routine data, all pregabalin prescriptions could be considered, independently of the prescribing physicians. The data were used to identify a group of patients who were receiving a higher than medically recommended dose.

The investigated sample of pregabalin users is comparable to patients presented in studies from other European countries regarding the age and gender structure of the patient population.[10, 11, 26] The most prevalent medical indication in our study was neuropathic pain. This result is consistent with findings from other studies.[11, 15, 30]

The proportion of patients with high prescription volumes of pregabalin amounted to slightly under 2% in our sample. Compared to the results of studies from Sweden with about 9%,[11] Denmark with about 7%,[10] and France with almost 13%,[15] this proportion is clearly smaller. Even though Novak et al.[2] showed that Germany has the lowest rates of drug misuse among the five analysed European countries, this difference might not only reflect a difference in prevalence but also be explained by slightly different approaches to identifying patients misusing pregabalin, e.g., the German routine data do not include prescriptions filled by hospitals, or the fact that I only considered patients with at least 3 prescriptions during one year.

I found evidence that particularly men aged 30 – 60 years and patients with a history of substance use disorders were overrepresented in the group of patients misusing pregabalin. These results suggest that, among the pregabalin users, there exists a group of patients who are at higher risk of misusing pregabalin and that physicians prescribing pregabalin should pay special attention to pre-existing medical conditions.

Compared to other studies, an unexpected result of this analysis is that compared to all pregabalin users only relatively few patients potentially misusing pregabalin had a prior

medication with opioids, as this was the case in other studies.[4, 31] At the same time, I observed relatively high numbers of patients who had a prior medication with benzodiazepines. Additionally, the proportion of patients with prior medication with drugs for the treatment of opioid addiction in the misusing group was high. One possible explanation for these results could be that pregabalin is sometimes used to relieve withdrawal symptoms from opioids or benzodiazepines, even though the drug is not approved for this application and the efficacy lacks evidence.[32] Additionally, patients with neuropathic pain are also often treated with opioids or benzodiazepines and thus a consecutive prescription with pregabalin might be part of the treatment plan. However, this does not conclusively explain why there are significantly more patients with high amounts of pregabalin and a prior medication with benzodiazepines compared to patients prescribed pregabalin as recommended.

Additional to the presented patient characteristics that were associated with misuse of pregabalin, my study sheds light on the network structures of the prescribing ambulatory physicians. The results suggest that patients successfully attempted to get a higher than medically recommended dose of pregabalin. I have shown that these patients not only had a greater number of prescribers (3.12 vs. 1.77 physicians) but also that their prescribing physicians were noticeably more loosely connected to other prescribers than those physicians whose patients were prescribed pregabalin in recommended doses (33 vs. 48 shared patients). Additionally, the locations of the prescribers' practices were further away from each other for patients misusing pregabalin compared to the other patients (16 km vs. 7 km). Both these results indicate that the patients are potentially seeking to receive prescriptions from physicians who are as unconnected with each other and geographically as far from each other as possible. Even though I cannot conclude about the reasons for the high prescription volumes in this group, these might be signs of existing doctor shopping when care coordination to control co-prescriptions is not present.

To further analyse the group of patients potentially misusing pregabalin, I added a sensitivity analysis (see supplementary material 2) in which I differentiated the group of patients between those receiving pregabalin from only one prescriber (practice) and those who were prescribed by multiple practices. The results indicate that, for example, the age structure of patients prescribed by only one provider shifted to higher ages (most of the patients were older than 50 years). Concerning the approved indications, it can be seen that there were more patients (24%) in the group with only one prescriber who did not have any of the indications recorded in the dataset compared to the group with multiple prescribers (19%). At the same time, patients with only one prescriber were less likely to have received medications for addictive disorders or to have been prescribed other medications with addiction potential in the previous year. These results might indicate that being prescribed with a higher than recommended dose of pregabalin might not necessarily indicate doctor shopping or the lack of communication between health care providers but could also be medically explainable or caused by the data structure and a false classification (see also limitations).

Office-based physicians in Germany can be organised in group practices, and physicians from the same practice usually share a number of patients and might additionally represent each other in terms of filling prescriptions. Therefore, a large number of shared patients between physicians might primarily indicate that they belong to a common practice. In order to control for this issue, I conducted a sensitivity analysis using practices as the unit of prescribers instead of physicians and found comparable results (see Table 2): Patients prescribed pregabalin as recommended received their prescriptions from only 1.59 different practices on average, whereas patients misusing pregabalin had 2.89 different prescribing practices. In

addition, in terms of care density, the practices in the prescription networks of patients potentially misusing pregabalin shared fewer patients than practices in the prescription networks of normal users (13 vs. 18 shared patients). Even though this difference was not significant, these results support the conclusion that patients potentially misusing pregabalin seek to obtain prescriptions from loosely connected physicians and physicians who do not coordinate their care.

The application of SNA was used in the present analysis to examine a summary statistic of cooperation in order to compare the prescribers between the two groups of pregabalin users. Future research could additionally visually compare prescription networks and use this methodology to identify clusters with a strikingly high prevalence of drug misuse.[33]

When interpreting our results, one has to take into account some important limitations. First, I only analysed prescriptions for pregabalin and not for gabapentin, even though the abuse potential of gabapentin is also under discussion.[4] However, as stated in the critical review report from the World Health Organization, the risk of pregabalin misuse might be higher because of its stronger euphoric and relaxing effect.[5] Second, the prescriptions included in the dataset only covered prescriptions from office-based physicians, did not comprise medications that were provided during hospital stays, and might thus have underestimated the amount of pregabalin consumed. Third, I only considered one possible way of misusing pregabalin, i.e., consuming a higher than recommended dosage and did not consider other possibilities of misusing pregabalin, e.g., the intake of drug combinations (e.g., pregabalin and opioids). Fourth, the assumption that the patients with high prescription volumes of pregabalin are misusing the drug cannot conclusively be justified by the analysed data. For example, the data did not provide information about the compliance of patients, but only about the amount of drug dispensed. Thus, I cannot definitely draw a conclusion about the final reason for high dispensed doses of pregabalin. Additionally, the sensitivity analysis differentiating the group of misusers into those with prescriptions from one or multiple providers point to the fact that this group might include some patients being falsely classified as “misusers” and that there might exist other reasons for the high prescribed dosages. With the comparably low number of patients being classified as misusing pregabalin and an average dispensed dose of 905 mg per patient and day within this group, I am confident I have developed a rather conservative measure that primarily discovers patients intentionally misusing pregabalin. However, a conclusive confirmation of this assumption can only be made by clinical studies that include patients and all their physicians.

## CONCLUSION

To conclude, this study offers first insights into pregabalin utilisation and prescription patterns in Germany. Misuse of pregabalin is one example of patients’ intentional exploitation of coordination issues in ambulatory care. It sheds light on the evolving problems when care is not systematically coordinated and information about prescriptions is not exchanged. The study further shows how this problem might be minimised when physicians collaborate more closely, which is represented by a greater number of shared patients. However, absolute prevention of this problem will probably only be possible if information about medications is exchanged between all physicians as a standard and mandatory requirement. Last, the study discovered a group of patients who are potentially misusing this drug and shows that particularly prescribing physicians should be aware of this risk.

## Figure legends

**Fig. 1** Identification of the analysed patient population in routine data

**Fig. 2** a The bipartite prescription network of patient P1 and the resulting bipartite patient-sharing physician network of P1's prescribers; b Depiction of the resulting unipartite network

***Notes:*** *a The bipartite patient-sharing network of $P_1$ prescribers was calculated based on the extended patient population. b The thickness of tie represents the number of shared patients. The resulting care density is 1.83.*

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**Conflict of Interest**: I declare no competing interests.

**Contributors:** RF designed and conducted the analysis, provided the results and wrote the manuscript.

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- Department of General Medicine, Preventive and Rehabilitation Medicine, University of Marburg
- AOK Health Insurance Hesse (SHI)
- AOK Health Insurance Bavaria (SHI)
- AOK PLUS SHI in Thuringia and Saxony

**Ethic approval:** The present study was a secondary data analysis and therefore did not need an ethics approval.

**Data statement** Due to data protection reasons the data cannot be provided. The data provided were processed exclusively for scientific research purposes within the framework of the Innovation Fund project 'WirtMed study'. The legal basis for the processing is Section 75 of Book X of the German Code of Social Law (§75 SGB X: Transfer of Social Data for Research). An informed consent to participate was therefore not required.
The data transmission from the participating health insurance funds was organised via a trust centre, where the pseudonymised routine data from the three health insurance funds were linked. To prevent re-identification, pseudonymised patient and physician data were pseudonymised again after the linkage and maintained in password-protected, encrypted containers. Inferences to individuals are excluded.

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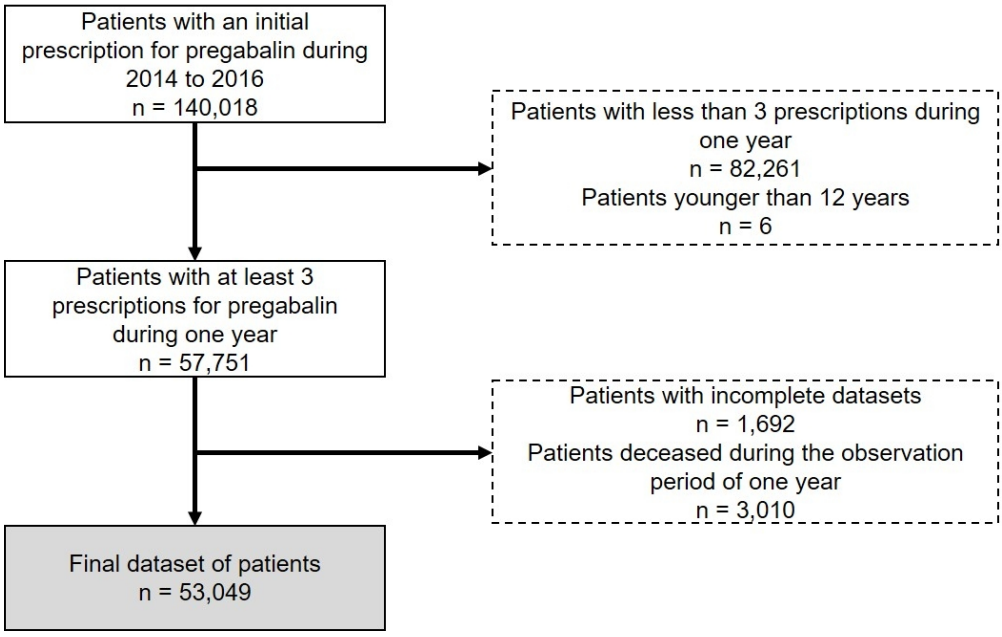
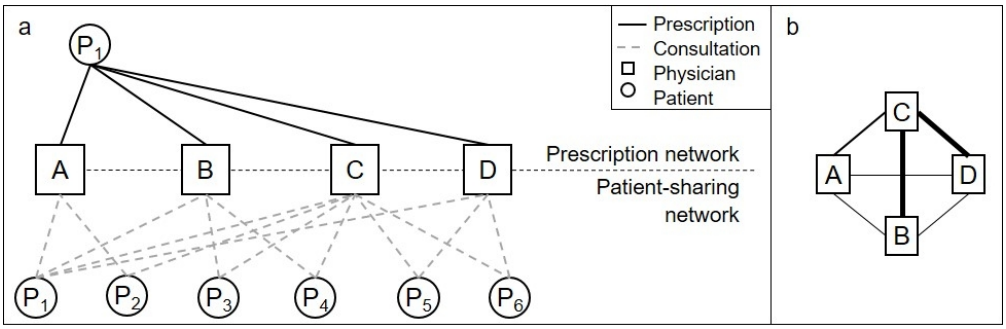



Identification of the analyzed patient population in routine data

177x112mm (150 x 150 DPI)




a The bipartite prescription network of patient P1 and the resulting bipartite patient-sharing physician network of P1's prescribers; b Depiction of the resulting unipartite network
Notes: a The bipartite patient-sharing network of P1 prescribers was calculated based on the extended patient population. b The thickness of tie represents the number of shared patients. The resulting care density is 1.83

164x53mm (150 x 150 DPI)

## Supplemental material

List of drugs for inclusion of patients in the extended population

| ATC | Name |
|---|---|
| N06AX22 | Agomelatin, Valdoxan |
| B01AF02 | Apixaban, Eliquis |
| B01AE07 | Dabigatran, Pradaxa |
| A10BK01 | Dapagliflozin, Forxiga |
| A10BJ05 | Dulaglutid, Trulicity |
| B01AF03 | Edoxaban, Lixiana |
| C03DA04 | Eplerenon, Inspra |
| M04AA03 | Febuxostat, Adenuric |
| C01EB17 | Ivabradin, Procoralan |
| N06BA12 | Lisdexamfetamin, Elvanse |
| N03AX16 | Pregabalin, Lyrica |
| B01AF01 | Rivaroxaban, Xarelto |
| C09DX04 | Sacubitril/Valsartan, Entresto |
| A10BH03 | Saxagliptin, Onglyza |
| A10BH01 | Sitagliptin, Januvia |
| N02AX06 | Tapentadol, Palexia |
| B01AC24 | Ticragelor, Brilique |
| C10BA02 | Ezetimib/Simvastatin, Inegy |
| N02AA55 | Oxycodon/Naloxon, Targin |
| M05BX04 | Denosumab, Prolia |
| N06AX21 | Duloxetin, Cymbalta |
| A10BK02 | Canagliflozin, Invokana |
| A10BK03 | Empagliflozin, Jardiance |
| L04AB01 | Etanercept, Enbrel |
| N06BA09 | Atomoxetin, Strattera |
| N07XX09 | Dimethylfumarat, Tecfidera |
| C01BD07 | Dronedaron, Multaq |
| R03AC18 | Indacaterol/Glycopyrronium, Ultibro Breezhaler |
| A10BJ02 | Liraglutid, Victoza |
| B01AC22 | Prasugrel, Efient |
| A10AE04 | Insulin glargin, Toujeo |
| R03AL06 | Tiotropium/Olodaterol, Spiolto |
| R03AL03 | Umeclidinium/Vilanterol, Anoro |
| G04BD08 | Solifenacin, Vesikur |

***Notes:*** *This list was developed within the WirtMed study and comprises drugs with a high price and/or unsure or unproved medical benefit for patients.*

| | | All pregabalin users N (%) / M (SD) | Groups of users with average doses ≤600mg/day N (%) / M (SD) | >600mg/day N (%) / M (SD) | Users with >600mg/day One provider (practice) N (%) / M (SD) | Multiple providers (practices) N (%) / M (SD) |
|---|---|---|---|---|---|---|
| **Number of patients per group** | | **53,049** | **52,172** | **877** | **295** | **582** |
| **Patient characteristics** | | | | | | |
| **Gender** | Male | 21,004 (39.6) | 20,468 (39.2) | 536 (61.1) | 190 (64.4) | 346 (59.5) |
| | Female | 32,045 (60.4) | 31,704 (60.8) | 341 (38.9) | 105 (35.6) | 236 (40.5) |
| **Age (years)** | 12–17 | 22 (0.0) | 22 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 18–29 | 867 (1.6) | 782 (1.5) | 85 (9.7) | 26 (8.8) | 59 (10.1) |
| | 30–39 | 1,996 (3.8) | 1,808 (3.5) | 188 (21.4) | 40 (13.6) | 148 (25.4) |
| | 40–49 | 4,472 (8.4) | 4,271 (8.2) | 201 (22.9) | 56 (19.0) | 145 (24.9) |
| | 50–59 | 9,434 (17.8) | 9,252 (17.7) | 182 (20.8) | 71 (24.1) | 111 (19.1) |
| | 60–69 | 9,768 (18.4) | 9,677 (18.5) | 91 (10.4) | 47 (15.9) | 44 (7.6) |
| | ≥ 70 | 26,490 (49.9) | 26,360 (50.5) | 130 (14.8) | 55 (18.6) | 75 (12.9) |
| **Place of residence** | Urban area | 23,862 (45.0) | 23,413 (44.9) | 449 (51.2) | 137 (46.4) | 312 (53.6) |
| | Rural area | 29,119 (54.9) | 28,694 (55.0) | 425 (48.5) | 157 (53.2) | 268 (46.0) |
| **Approved indications** | | | | | | |
| Epilepsy | | 1,968 (3.7) | 1,882 (3.6) | 86 (9.8) | 18 (6.1) | 68 (11.7) |
| Generalised anxiety disorder | | 3,068 (5.8) | 2,958 (5.7) | 110 (12.5) | 25 (8.5) | 85 (14.6) |
| Neuropathic pain | | 39,829 (75.1) | 39,249 (75.2) | 580 (66.1) | 184 (62.4) | 396 (68.0) |
| Neuropathic pain (broad definition) | | 42,120 (79.4) | 41,505 (79.6) | 615 (70.1) | 203 (68.8) | 412 (70.8) |
| Multiple | | 3,293 (6.2) | 3,186 (6,1) | 107 (12.2) | 21 (7.1) | 86 (14.8) |
| None of the indications recorded in the records | | 9,283 (17.5) | 9,098 (17.4) | 185 (21.1) | 71 (24.1) | 114 (19.6) |
| **Medical pre-conditions with increased risk of abuse** | | | | | | |
| Substance use disorders | | 6,414 (12.1) | 6,049 (11.6) | 365 (41.6) | 104 (35.3) | 261 (44.8) |
| Addictive disorder drug (alcohol) | | 43 (0.1) | 41 (0.1) | 2 (0.2) | 0 (0.0) | 2 (0.3) |
| Addictive disorder drug (tobacco) | | 2 (0.0) | 2 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Addictive disorder drug (opioids) | | 258 (0.5) | 182 (0.3) | 76 (8.7) | 16 (5.4) | 60 (10.3) |
| **Drugs with potential for abuse** | | | | | | |
| Benzodiazepine | | 9,665 (18.2) | 9,367 (18.0) | 298 (34.0) | 69 (23.4) | 229 (39.3) |
| Opioids | | 23,886 (45.0) | 23,527 (45.1) | 359 (40.9) | 108 (36.6) | 251 (43.1) |
| Psychostimulants | | 288 (0.5) | 263 (0.5) | 25 (2.9) | 9 (3.1) | 16 (2.7) |
| **Contemporaneous prescription of gabapentin** | | 2,973 (5.6) | 2,890 (5.5) | 83 (9.5) | 25 (8.5) | 58 (10.0) |
| **Prescription networks and structural characteristics** | | | | | | |
| Number of prescriptions | | 6.34 (3.28) | 6.23 (2.91) | 12.70 (10.17) | 8.76 (5.46) | 14.69 (11.35) |
| Number of prescribers (physicians) | | 1.79 (1.03) | 1.77 (0.89) | 3.12 (3.91) | - | - |
| Number of prescribers (practices) | | 1.59 (0.87) | 1.57 (0.73) | 2.86 (3.61) | - | - |
| **Medical specialty of initial prescriber** | | | | | | |
| GP | | 32,911 (62.0) | 32,344 (62.0) | 567 (64.7) | 204 (69.2) | 363 (62.4) |
| Anaesthesiology | | 1,935 (3.6) | 1,908 (3.7) | 27 (3.1) | 11 (3.7) | 16 (2.7) |
| Orthopaedics | | 1,209 (2.3) | 1,192 (2.3) | 17 (1.9) | 2 (0.7) | 15 (2.6) |
| Neuroscience | | 4,292 (8.1) | 4,223 (8.1) | 69 (7.9) | 20 (6.8) | 49 (8.4) |
| Neurology | | 5,039 (9.5) | 4,984 (9.6) | 55 (6.3) | 26 (8.8) | 29 (5.0) |
| Psychiatry and psychotherapy | | 2,341 (4.4) | 2,289 (4.4) | 52 (5.9) | 18 (6.1) | 34 (5.8) |
| Other | | 5,322 (10.0) | 5,232 (10.0) | 90 (10.3) | 14 (4.7) | 76 (13.1) |
| Proportion of specialists among prescribers | | 0.31 (0.40) | 0.31 (0.40) | 0.31 (0.38) | 0.30 (0.46) | 0.31 (0.34) |
| Care density among physicians[1] | | 47.97 (70.61) | 48.29 (70.67) | 33.23 (66.43) | - | - |
| Care density among practices[1] | | 17.42 (35.77) | 17.54 (35.84) | 12.90 (32.76) | - | - |
| Maximal geographic distance [in kilometres] | | 6.86 (26.63) | 6.71 (26.24) | 15.98 (43.27) | - | - |

**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

| | Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|---|---|---|---|---|---|
| **Title and abstract** | | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.<br><br>RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.<br><br>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | p. 2<br><br>p. 2<br><br>p. 2 |
| **Introduction** | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | | | p. 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | | | p. 4 |
| **Methods** | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | | | p. 4 ff. |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | | | p. 4 ff. |

| | | | | | |
|---|---|---|---|---|---|
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | | RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.<br><br>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | p. 4 ff.<br><br>p. 5<br><br>p. 4 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | p. 5-6 |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement).<br>Describe comparability of assessment methods if there is more than one group | | | p. 5-6 |

| | | | | | |
|---|---|---|---|---|---|
| Bias | 9 | Describe any efforts to address potential sources of bias | | | p. 7 |
| Study size | 10 | Explain how the study size was arrived at | | | p. 7 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | | | p. 7 |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | | | p. 7 |
| Data access and cleaning methods | | .. | | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. | p. 4 |

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|---|---|---|---|---|---|
| | | | | RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | |
| Linkage | | .. | | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | p. 4ff. |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | p. 7-9 |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | | | p. 7-9 |
| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure | | | p. 7-9 |

| | | | | | |
|---|---|---|---|---|---|
| | | category, or summary measures of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | | | p. 7-9 |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | | | |
| **Discussion** | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | | | p. 9-ff. |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | p. 11 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, | | | p. 11 |

| | | | | | |
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| | | limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | | | p. 9 ff. |
| **Other Information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | | | p. 13 |
| Accessibility of protocol, raw data, and programming code | | .. | | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | p. 13 |

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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# Patterns of pregabalin prescribing in four German federal states: analysis of routine data to investigate potential misuse of pregabalin

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**Patterns of pregabalin prescribing in four German federal states: analysis of routine data to investigate potential misuse of pregabalin**

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## Abstract

**Objectives:** The objectives of this study were to investigate utilisation patterns of pregabalin, to identify users potentially misusing pregabalin, and to compare this group of patients to patients prescribed recommended doses pregabalin concerning their personal characteristics and the coordination among their prescribers. Unintended co-prescription of drugs with addictive potential might occur when care is insufficiently coordinated.

**Design:** Secondary data analysis of linked data from three regional sickness funds in Germany (AOK) for the years 2014–2016.

**Setting:** Ambulatory and hospital care sector in four German federal states.

**Methods:** On the basis of routine data, patients who received at least three prescriptions of pregabalin were identified and classified into patients prescribed pregabalin as recommended and those dispensed with a higher than recommended dose (>600mg/day). Social network analysis was applied to identify prescription networks and to analyse cooperation among the prescribers. With descriptive statistics and univariate statistical tests, typical characteristics of the group of patients potentially misusing pregabalin were compared to the others.

**Results:** Among the 53,049 patients prescribed pregabalin, about 2% (877) were classified as potentially misusing pregabalin. The majority of this group was male and aged between 30 and 60 years. Of the patients misusing pregabalin, 365 (42%) had a diagnosed history of substance use disorders and 359 (41%) had been prescribed another drug with addictive potential (opioids) before. The prescribers of those patients potentially misusing pregabalin were more loosely connected within networks compared to prescribers of patients prescribed pregabalin as recommended.

**Conclusion:** This study found that patients could exceed recommended doses of pregabalin by getting prescriptions from multiple physicians. Specific patients were at increased risk of potentially misusing pregabalins, and these patients sought to obtain their prescriptions from physicians who were as loosely connected as possible. Coordination and sharing a relevant number of patients seem to be levers to avoid these problems of unintended co-prescribing.


## Strengths and limitations of this study

- Routine data can serve as an objective measure to depict health service utilisation.
- The applied methodology of social network analysis enables the exploration of cooperation among health care providers.
- The study includes univariate statistical tests indicating differences between the two analysed groups of patients prescribed pregabalin but does not provide information about which analysed factors are most predictive.
- The nature of routine data does not allow drawing conclusions about the reasons for high prescription rates and leads to incomplete information about prescriptions from the hospital sector or prescriptions not filled by the patients.
- The analysed population is limited to people insured at the included three regional AOK sickness funds and might therefore differ slightly from the general population in Germany.

## INTRODUCTION

The misuse or nonmedical use of prescription drugs may lead to severe substance-related disorders and fatal health effects such as drug addiction, behavioural dependence, or even death. The nonmedical use of opioids is one of the leading public health issues in the United States [1] and is characterised as an epidemic. Even though the prevalence is estimated to be lower in European countries, Novak et al.[2] reported past-year prevalence for nonmedical drug use of up to 5% among five EU member states. As many of these misused drugs have great addiction potential, patients may take advantage of coordination problems in health care systems, such as discontinuities or gaps in care.

One possible way for patients to misuse prescription drugs is to consume a higher than medically indicated dose.[3] To this end, patients may seek to obtain prescriptions from multiple health care providers through so-called doctor shopping.[3] Especially in fragmented health care systems, unknown and unintentional double prescribing might occur because patients can choose the physicians they consult, without the need for referral and information transfer among health care providers. This requires close cooperation and collaboration among providers when trying to prevent intentional misuse of prescription drugs, particularly when coordination gaps in health care are exploited by patients.

Pregabalin (Lyrica) is one example of such drugs, potentially misused by patients. It was introduced in 2004 and is approved for the treatment of neuropathic pain, general anxiety disorder, and epilepsy in Europe. Pregabalin is a gamma-aminobutyric acid (GABA) that reduces the excitability of neurons in the central nervous system and is structurally related to its predecessor gabapentin.[4] Pregabalin binds to an auxiliary subunit of voltage-dependent calcium channels and thus reduces the release of several neurotransmitters such as glutamate, noradrenaline, and the neuropeptide substance P.[5] This may reduce neuronal excitability and thus seizures and neuropathic pain.[6] Additionally, pregabalin may have a relaxing effect and can produce euphoria, which are both assumed to cause abuse and addictive potential.[5]

Since 2008, concerns have been raised about the abuse and addictive potential of pregabalin, particularly for patients with a history of drug addiction,[4, 7, 8] and warning information was added to the German scientific information in 2011.[9] Nevertheless, the number of patients prescribed pregabalin has still been growing in recent years.[10, 11] In Germany, an increase was observed from 2.2 million filled pregabalin prescriptions in 2011 to 3.9 million in 2018.[12, 13] Anecdotal evidence from Germany further suggests that there was also a rise in pregabalin abusers between 2008 and 2015.[14] Despite these known issues, there exists no monitoring of prescription quantities of pregabalin in Germany.

Based on prescription data, studies have investigated patient factors that are associated with the risk of being dispensed with pregabalin at a higher than recommended dose.[10, 11, 15] This high dispensing of the drug could be a sign of potential misuse of pregabalin. These studies showed that especially middle-aged men (between 18 and 45 years old), patients with a history of substance use disorders or drug abuse, and patients with psychological comorbidities are at particularly high risk of misusing pregabalin. Driot et al.[15] found that, at a structural level, misuse of pregabalin was associated with multiple prescribers, which might point to the presence of doctor shopping.

Social network analysis (SNA) methods are commonly applied in the health care sector to identify network structures among health care providers and to investigate the effects of care cooperation among these informal, patient-sharing physician networks on health care

provision.[16] For instance, Barnett et al.[17] showed that, if physicians were sharing more patients in their empirical network, it was more likely that they were cooperating in real life. Making use of this idea, Ong et al.[18] used SNA to analyse networks of physicians prescribing interacting drugs to the same patients. They showed that a patient was more likely to be co-prescribed with interacting drugs if his or her caring physicians shared fewer patients on average. In another study, Ong et al.[19] analysed multiple providers prescribing benzodiazepines and also showed that two physicians were at a greater risk of prescribing benzodiazepine with overlapping coverage if they shared fewer patients.

The German ambulatory care sector has no formal system to coordinate care among office-based physicians, and information about treatment and medication is not regularly transferred among health care providers. This loose organisation might facilitate the intentional misuse of prescription drugs for patients. The present study thus aimed to analyse pregabalin utilisation in four German states based on routinely collected health insurance data. It described the characteristics of patients who have been prescribed pregabalin and identified users potentially misusing[1] this drug. This group was compared to the group of patients prescribed pregabalin as recommended in order to, first, examine the typical characteristics of patients misusing pregabalin and, second, identify the common factors and analyse the connectivity among the physicians prescribing pregabalin to patients who misuse the drug.

## METHODS

### Data source and patient population

Three regionally organised statutory health insurances (AOK), covering four German states, Bavaria, Hesse, Thuringia, and Saxony, provided sickness fund data for this study. In Germany, about 90% of the population is insured with a statutory health insurance and the AOK insures about 42% of the population in these regions (about 9.3 million persons). The insured population of the AOK differs only slightly from the general German population in terms of age and gender.[20] The provided dataset covered about 14% (about 1.25 million persons) of their insured population from the years 2013 to 2017[2]. It included billed services and diagnoses from the ambulatory and hospital sector as well as prescription data and patient information, such as age and gender.

Patients were included in the analysis if they had received an initial prescription of pregabalin (ATC: N03AX16) between January 2014 and December 2016, ensuring that both a lead-up and a follow-up year for each patient was included in the dataset. To be classified as an initial user, the patient should not have been prescribed pregabalin in the year prior to the initial prescription. Patients for whom only incomplete patient information was available, patients younger than 12 years of age, and patients who died during the observation period of one year since their initial prescription were excluded from the analysis. Further, only patients with at least three filled prescriptions for pregabalin during the observation period of one year were

[1] In this manuscript, the term “misuse” will be used for the group of patients prescribed with a higher than medically recommended dose of pregabalin, which might indicate but not necessarily mean that these patients are misusing pregabalin.

[2] This extended patient population included patients who received at least once one of 34 defined drugs within the observation period (see supplemental material 1).

considered to identify patients who used pregabalin regularly. Details about the identification of the patient population are depicted in Fig. 1.

**Definition of potential misuse**

The World Health Organization defines psychoactive substance misuse as "Use of a substance for a purpose not consistent with legal medical guidelines […]".[21] The European public assessment report for pregabalin (Lyrica) recommends a maximum therapeutic dose of 600 mg per day (corresponding to two defined daily doses (DDD)).[22] Therefore, to classify patients with prescriptions for pregabalin as patients prescribed pregabalin as recommended and those potentially misusing the drug, the average daily dose during one year was compared to this recommended maximum dose.[10, 11, 15]

The prescription dataset listed all drugs that had been prescribed by any ambulatory physician and dispensed in a pharmacy. It provided the Anatomical Therapeutic Chemical (ATC) classification, the prescription and dispensing date, and the prescribed dose in terms of the DDD. On this basis, the sum of dispensed drug per patient during the time span of a maximum of 12 months since initial dispensing was calculated, excluding the prescribed dose of the last dispense. Subsequently, the time span (in days) between first and last dispensing was examined and the average amount of dispensed drug per day was calculated. If this average exceeded the maximum dose of 600 mg, the patient was classified as potentially misusing pregabalin with the hazard of behavioural dependence.

**Patient characteristics and medical conditions**

The patient characteristics and medical conditions that were used to describe the patient population and to compare the two groups included information about a) patient characteristics, b) prevalence of approved indications for pregabalin, c) medical conditions that might increase the risk of misuse, and d) prescriptions of drugs with potential for misuse as follows:

a) The dataset comprised, among others, the age and gender as relevant patient characteristics, as studies have shown that especially men between 18 and 45 years old seem to be at higher risk of misusing pregabalin.[10, 11, 15] As geographic variation among patients prescribed with pregabalin exists, for example, in Denmark,[10] information about the district of patients' place of residence was used to differentiate between patients living in urban areas and those living in rural ones.[23]
b) Diagnoses for the approved indications (neuropathic pain, general anxiety disorders, and epilepsy) were identified using information about diagnoses from the hospital and ambulatory sector. To ensure that diagnoses were related to the pregabalin prescription, only diagnoses that had occurred no more than three months prior to the prescription were considered. The patterns of diagnosis codes are presented in the form of the International Classification of Diseases 10th revision (ICD-10) [24] and are summarised in Table 1. The diagnoses were extracted from studies analysing indications associated with pregabalin prescriptions.[11, 15, 25, 26]
c) Patients with a history of substance use disorders might be at higher risk of misusing pregabalin.[11] Therefore, it was examined whether patients had been diagnosed with substance use disorders within two different quarters in hospital ("main diagnosis") or in the ambulatory sector ("confirmed") within one year prior to the initial pregabalin prescription.

Additionally, it was examined whether patients had been prescribed a drug for the treatment of alcohol, tobacco, or opioid addiction at least once in the year prior to the initial prescription (see Table 1 for ICD-10 and ATC codes).

d) It was analysed whether patients had been prescribed opioids or psychostimulants (ATC N06B including centrally acting sympathomimetics, xanthine derivatives and other psychostimulants and nootropics such as meclofenoxate or pyritinol) [27] in the year before the initial pregabalin prescription, because these drugs have a known potential for abuse and might therefore be more prevalent in the group of users potentially misusing pregabalin. Since gabapentin as the predecessor of pregabalin is also under discussion because of its potential of abuse, it was also controlled for gabapentin prescriptions during the observation period (see Table 1 for details).

**Table 1. Patterns of diagnoses (ICD-10) for relevant medical conditions and ATC for relevant prescriptions**

| Indications/diagnoses/drugs | ICD-10/ATC codes |
|---|---|
| **Approved indications[1]** | |
| Epilepsy | G40; G41 |
| Generalised anxiety disorders | F41.1 |
| Neuropathic pain-related diagnoses | G35.9; G50.0; G50.1; G51.0; G53.0; G54.4; G54.6; G55.0; G55.1; G56.0; G56.2; G56.4; G56.9; G57.0; G57.1; G57.8; G57.9; G58.0; G58.7; G58.8; G62.9; G63.2; G82.1; G95.0; G95.2; G95.8; G97.9.; I69.1; I69.3; M48.0; M50.1; M53.0; M53.1 M54.1; M54.3; M54.4; M79; M89.0; R52 |
| Additional neuropathic pain-related diagnoses (broad pattern) | B02; G13.0; G52.1; G56; G57; G58; G59; G60; G61; G62; G63; G99.0; M51.1; M54.2; T92.6; T93.6 |
| **Substance use disorders[2]** | F11–F19; T42; T43; Z71.4–5 |
| **Addictive disorder drugs[3]** | |
| Alcohol | N07BB |
| Tobacco | N07BA |
| Opioids | N07BC |
| **Drugs with potential for abuse[3]** | |
| Opioids | N02A |
| Psychostimulants | N06B |
| Benzodiazepines | N05B, N05C |
| Contemporaneous prescription of gabapentin[4] | N03AX12 |

*[1]Diagnoses during the same quarter as the initial prescription; [2]At least one diagnosis in two different quarters during the year before the initial prescription; [3]At least one prescription during the year before the initial prescription; [4]At least one prescription during the observation period of one year.*

### Prescription networks and structural characteristics

To describe and analyse if and how patterns of utilisation differ between the two groups of patients prescribed pregabalin, a prescription network for each patient was identified. This approach allows an analysis of how strongly the prescribing physicians are connected in networks through shared patients. A large number of shared patients among the prescribers

may indicate active cooperation including, e.g., information transfer about dispensed drugs.[17] In contrast, and assuming that doctor shopping is taking place, it was expected that the prescribers of patients who potentially misuse pregabalin are less connected to other prescribers. Thus, the hypothesis was that prescribers of patients who were identified as misusing pregabalin have fewer network contacts with other prescribers than those prescribers whose patients were prescribed with dosages as recommended.

The prescription networks were identified per patient for the observation period of one year since the initial prescription. They were first built as bipartite networks, in which a patient was connected to his or her prescribing physicians (see the prescription network in Fig. 2a). To analyse cooperation among these prescribing physicians and following the findings of patient-sharing network analyses, the group of patients in the bipartite networks was expanded to all patients seen by the prescribing physicians during the observation period (see the patient-sharing network in Fig. 2a). The resulting bipartite networks were subsequently summarised to unipartite networks, in which only the physicians were considered and connected through shared patients (see Fig. 2b). The *care density*, as a surrogate measure of care coordination among the physicians, was then calculated as the average number of shared patients between all possible pairs of providers in a patient's prescription network.[18, 28]

In the example in Fig. 2**Error! Reference source not found.**, four physicians filling at least one pregabalin prescription for patient $P_1$ and the patients of the extended patient population who had consulted at least two of these four physicians are depicted. Comparing the patient populations of each physician, the number of patients shared between two physicians was examined and led to the unipartite network in Fig. 2b. The physicians in this network shared 1.83 patients on average, which was the care density of this network.

Other structural characteristics of the prescription networks included the number of filled prescriptions, the number of prescribers, the medical specialty of first prescriber per patient, and the proportion of specialised physicians among the prescribing physicians. Driot et al.[15] showed that the number of prescribers is associated with misuse of pregabalin. The medical specialty of initial prescriber and the specialty mix in the prescription networks may give insights into typical patterns of utilisation between the two groups of patients prescribed pregabalin.

### Statistical methods

Mean values and standard deviations of the characteristics that were calculated as continuous variables are presented to describe the population of patients prescribed pregabalin. Characteristics that were collected as categorical variables are presented in terms of numbers and proportions. Univariate statistical tests were conducted to compare the group of patients prescribed pregabalin as recommended to the group of patients misusing pregabalin. To this end, the $Chi^2$ test was applied to categorical variables and, if a specification of a binary categorical variable contained fewer than five individuals, Fisher's exact test was applied instead to that variable.[29] Both tests were used to analyse whether the group proportions of a categorical variable were equal between the two groups.[29] For continuous variables, the nonparametric Wilcoxon–Mann–Whitney U-test was used to examine whether the values in one group were significantly greater (or smaller) than the values in the other group. This test does not require any assumptions about the distribution of the analysed variable, and the results can be considered conservative.[29] In order to correct for multiple testing and the related increased risk of a type I error (false positives), a Bonferroni post-hoc adjustment was

conducted. This adjustment considers the number of statistical tests conducted to correct the resulting p-values.[30]

### Patient and public involvement

None.

## RESULTS

In total, 53,049 patients (i.e. about 0.2% of the locality population insured with the AOK) received an initial pregabalin prescription between January 2014 and December 2016. During the three years, the absolute number of patients who were initially prescribed pregabalin and who received three or more prescriptions during one year increased from 17,003 patients in 2014 to 18,025 patients in 2016. In this group of patients, 877 patients (1.7%) were prescribed doses that on average exceeded the maximum therapeutic dose of 600 mg per day.

The descriptive statistics of all patients prescribed pregabalin and the results of the univariate statistical tests are summarised in Table 2. The results indicate that the group of patients classified as patients prescribed pregabalin as recommended had similar characteristics to the total population for all presented values. However, the majority of characteristics differ systematically between the two groups built based on the amount of described pregabalin.

The results show that 32,045 (60%) patients prescribed pregabalin in the dataset were female. The gender distribution was reversed for the group of patients misusing pregabalin: 536 patients (61%) were male and 341 (39%) female. Hence, the gender distribution differed significantly between the two groups of patients. Half the patients were 70 years old or older when they received their initial pregabalin prescription, and there were only a few (22) patients who were between 11 and 18 years old. In contrast, in the group of patients misusing pregabalin, the age structure changed significantly, and most patients were between 30 and 60 years old.

Concerning the place of residence, it can be seen that, of all patients prescribed pregabalin, approximately 55% of patients (29,119) lived in rural areas and 45% (23,862) in urban areas. When focusing on patients misusing pregabalin, these values differed significantly in comparison to the other group of patients prescribed with less pregabalin: The majority of patients with high dosages of pregabalin lived in urban areas (51%; 449 patients), whereas the distribution of patients prescribed pregabalin as recommended was comparable to that of the total population.

Neuropathic pain was the most frequent indication that patients prescribed pregabalin were diagnosed within the same quarter as their initial prescription (39,829 patients (75%) and 42,120 patients (79%) for the broader definition). General anxiety disorder and epilepsy were prevalent in 3,068 and 1,968 patients respectively. About 18% of patients (9,283) had none of these diagnosed indications, and 6% of patients (3,293) were diagnosed with several indications. In the group of patients potentially misusing pregabalin, the proportion of patients with no medical indication increased to 21% (185 patients). However, this result was not statistically significant after adjusting for multiple testing. Epilepsy and general anxiety disorder was more prevalent in the group of patients potentially misusing pregabalin compared to the other group, whereas the proportion of patients with neuropathic pain was slightly smaller. All these differences were found to be significant.

About 12% of patients (6,414) had a history of substance use disorders, and the proportion of patients increased significantly to 42% (365) among patients potentially misusing pregabalin. Drugs for the treatment of addictive disorders were prescribed to only some patients in both groups, except drugs for the treatment of opioid addiction, which were prescribed to 76 patients (9%) with high dosages of pregabalin; this was significantly more than to the group of patients prescribed pregabalin as recommended (0.3%; 182 patients).

Overall, 9,665 (18%) and 23,886 (45%) patients had been prescribed benzodiazepines or opioids, respectively, within the year prior to the initial pregabalin prescription. The proportion of patients with a prior prescription of benzodiazepine was significantly higher in the group of patients potentially misusing pregabalin (34%; 298), whereas 41% of these patients (359) had been prescribed with opioids during the year before.

Gabapentin was prescribed to 2,973 (6%) of all patients prescribed pregabalin and to 83 (10%) of patients with high dosages of prescribed pregabalin.

Most of the patients received their initial pregabalin prescription from a general practitioner, followed by patients receiving their initial prescription from specialists in neuroscience or neurology. This characteristic varied only slightly and not significantly between the two groups of patients.

Patients prescribed pregabalin received on average six prescriptions from two different physicians over one year. In contrast, patients misusing pregabalin got on average about 13 prescriptions from three different physicians. Thus, their prescription networks were significantly larger than those of patients with recommended prescription doses were.

Lastly, physicians prescribing pregabalin to a patient with recommended dosages shared on average 48 patients. This value was significantly smaller (33 patients) among prescribers of patients who misuse pregabalin. The prescription networks of patients who were misusing pregabalin were thus less connected in terms of shared patients. In order to gain further insights into the prescription networks, the maximal geographic distance among the prescribers was calculated and compared between the two groups. It can be seen that, among the patients misusing pregabalin, the maximal distance was about 16 kilometres on average, whereas the prescribers of the other group were less than half that distance away from each other.

**Table 2. Descriptive statistics of the dataset and results of the univariate statistical analyses**

| | | All patients prescribed pregabalin | Groups of patients with average doses | | | |
|---|---|---|---|---|---|---|
| | | | ≤600mg/day | >600mg/day | unadjusted | Bonferroni adjusted |
| | | N (%) / M (SD) | N (%) / M (SD) | N (%) / M (SD) | p-values | p-values |
| **Patient characteristics** | | | | | | |
| **Gender** | Male | 21,004 (39.6) | 20,468 (39.2) | 536 (61.1) | <0.001 | <0.001 |
| | Female | 32,045 (60.4) | 31,704 (60.8) | 341 (38.9) | | |
| **Age (years)** | 12–17 | 22 (0.0) | 22 (0.0) | 0 (0.0) | | |
| | 18–29 | 867 (1.6) | 782 (1.5) | 85 (9.7) | | |
| | 30–39 | 1,996 (3.8) | 1,808 (3.5) | 188 (21.4) | | |
| | 40–49 | 4,472 (8.4) | 4,271 (8.2) | 201 (22.9) | <0.001 | <0.001 |
| | 50–59 | 9,434 (17.8) | 9,252 (17.7) | 182 (20.8) | | |
| | 60–69 | 9,768 (18.4) | 9,677 (18.5) | 91 (10.4) | | |
| | ≥ 70 | 26,490 (49.9) | 26,360 (50.5) | 130 (14.8) | | |
| **Place of residence** | Urban area | 23,862 (45.0) | 23,413 (44.9) | 449 (51.2) | <0.001 | 0.004 |
| | Rural area | 29,119 (54.9) | 28,694 (55.0) | 425 (48.5) | | |
| **Approved indications** | | | | | | |
| Epilepsy | | 1,968 (3.7) | 1,882 (3.6) | 86 (9.8) | <0.001 | <0.001 |
| Generalised anxiety disorder | | 3,068 (5.8) | 2,958 (5.7) | 110 (12.5) | <0.001 | <0.001 |
| Neuropathic pain | | 39,829 (75.1) | 39,249 (75.2) | 580 (66.1) | <0.001 | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| Neuropathic pain (broad definition) | 42,120 (79.4) | 41,505 (79.6) | 615 (70.1) | <0.001 | <0.001 |
| Multiple | 3,293 (6.2) | 3,186 (6,1) | 107 (12.2) | <0.001 | <0.001 |
| None of the indications recorded in the records | 9,283 (17.5) | 9,098 (17.4) | 185 (21.1) | 0.005 | 0.135 |
| **Medical pre-conditions with increased risk of abuse** | | | | | |
| Substance use disorders | 6,414 (12.1) | 6,049 (11.6) | 365 (41.6) | <0.001 | <0.001 |
| Addictive disorder drug (alcohol) | 43 (0.1) | 41 (0.1) | 2 (0.2) | 0.345 | 1.000 |
| Addictive disorder drug (tobacco) | 2 (0.0) | 2 (0.0) | 0 (0.0) | 1.000 | 1.000 |
| Addictive disorder drug (opioids) | 258 (0.5) | 182 (0.3) | 76 (8.7) | <0.001 | <0.001 |
| **Drugs with potential for abuse** | | | | | |
| Benzodiazepine | 9,665 (18.2) | 9,367 (18.0) | 298 (34.0) | <0.001 | <0.001 |
| Opioids | 23,886 (45.0) | 23,527 (45.1) | 359 (40.9) | 0.015 | 0.386 |
| Psychostimulants | 288 (0.5) | 263 (0.5) | 25 (2.9) | <0.001 | <0.001 |
| **Contemporaneous prescription of gabapentin** | 2,973 (5.6) | 2,890 (5.5) | 83 (9.5) | <0.001 | <0.001 |
| **Prescription networks and structural characteristics** | | | | | |
| Number of prescriptions | 6.34 (3.28) | 6.23 (2.91) | 12.70 (10.17) | <0.001 | <0.001 |
| Number of prescribers (physicians) | 1.79 (1.03) | 1.77 (0.89) | 3.12 (3.91) | <0.001 | <0.001 |
| Number of prescribers (practices) | 1.59 (0.87) | 1.57 (0.73) | 2.86 (3.61) | <0.001 | <0.001 |
| **Medical specialty of initial prescriber** | | | | | |
| GP | 32,911 (62.0) | 32,344 (62.0) | 567 (64.7) | | |
| Anaesthesiology | 1,935 (3.6) | 1,908 (3.7) | 27 (3.1) | | |
| Orthopaedics | 1,209 (2.3) | 1,192 (2.3) | 17 (1.9) | | |
| Neuroscience | 4,292 (8.1) | 4,223 (8.1) | 69 (7.9) | 0.010 | 0.256 |
| Neurology | 5,039 (9.5) | 4,984 (9.6) | 55 (6.3) | | |
| Psychiatry and psychotherapy | 2,341 (4.4) | 2,289 (4.4) | 52 (5.9) | | |
| Other | 5,322 (10.0) | 5,232 (10.0) | 90 (10.3) | | |
| Proportion of specialists among prescribers | 0.31 (0.40) | 0.31 (0.40) | 0.31 (0.38) | 0.300 | 1.000 |
| Care density among physicians[1] | 47.97 (70.61) | 48.29 (70.67) | 33.23 (66.43) | <0.001 | <0.001 |
| Care density among practices[1] | 17.42 (35.77) | 17.54 (35.84) | 12.90 (32.76) | 0.149 | 1.000 |
| Maximal geographic distance [in kilometres] | 6.86 (26.63) | 6.71 (26.24) | 15.98 (43.27) | <0.001 | <0.001 |

*[1]Care density was calculated as the average number of shared patients among all pairs of providers per patient and was calculated for patients with at least two prescribers (physicians/ practices)*

## DISCUSSION

The presented study investigated the public health problem of the misuse of prescription drugs through coordination problems in health care systems, such as discontinuities or gaps in care. It included an extensive list of characteristics for analysing patients and their utilisation patterns of pregabalin. The list comprised both patient and structural characteristics of the prescribing physicians and was applied to patients from four German states. By taking advantage of routine data, all pregabalin prescriptions could be considered, independently of the prescribing physicians. The data were used to identify a group of patients who were receiving a higher than medically recommended dose.

The investigated sample of patients prescribed pregabalin is comparable to patients presented in studies from other European countries regarding the age and gender structure of the patient population.[10, 11, 26] The most prevalent medical indication in our study was neuropathic pain. This result is consistent with findings from other studies.[11, 15, 31]

The proportion of patients with high prescription volumes of pregabalin amounted to 877 patients in our sample (1.7%). Compared to the results of studies from Sweden with about 9%,[11] Denmark with about 7%,[10] and France with almost 13%,[15] this proportion is clearly smaller. Even though Novak et al.[2] showed that Germany has the lowest rates of drug misuse among the five analysed European countries, this difference might not only reflect a difference in prevalence but also be explained by slightly different approaches to identifying patients misusing pregabalin, e.g., the German routine data do not include prescriptions filled by hospitals, or the fact that only patients with at least three prescriptions during one year were considered.

Evidence was found that particularly men aged 30 – 60 years and patients with a history of substance use disorders were overrepresented in the group of patients misusing pregabalin. These results suggest that, among the patients prescribed pregabalin, there exists a group of patients who are at higher risk of misusing pregabalin and that physicians prescribing pregabalin should pay special attention to pre-existing medical conditions.

Compared to other studies, an unexpected result of this analysis is that compared to all patients prescribed pregabalin only relatively few patients potentially misusing pregabalin had a prior medication with opioids, as this was the case in other studies.[4, 32] At the same time, relatively high numbers of patients who had a prior medication with benzodiazepines were observed. Additionally, the proportion of patients with prior medication with drugs for the treatment of opioid addiction in the misusing group was high. One possible explanation for these results could be that pregabalin is sometimes used to relieve withdrawal symptoms from opioids or benzodiazepines, even though the drug is not approved for this application and the efficacy lacks evidence.[33] Additionally, patients with neuropathic pain are also often treated with opioids or benzodiazepines and thus a consecutive prescription with pregabalin might be part of the treatment plan. However, this does not conclusively explain why there are significantly more patients with high amounts of pregabalin and a prior medication with benzodiazepines compared to patients prescribed pregabalin as recommended.

Additional to the presented patient characteristics that were associated with misuse of pregabalin, the study sheds light on the network structures of the prescribing ambulatory physicians. The results suggest that patients successfully attempted to get a higher than medically recommended dose of pregabalin. It has been shown that these patients not only had a greater number of prescribers (3.12 vs. 1.77 physicians) but also that their prescribing physicians were noticeably more loosely connected to other prescribers than those physicians whose patients were prescribed pregabalin in recommended doses (33 vs. 48 shared patients). Additionally, the locations of the prescribers' practices were further away from each other for patients misusing pregabalin compared to the other patients (16 km vs. 7 km). Both these results indicate that the patients are potentially seeking to receive prescriptions from physicians who are as unconnected with each other and geographically as far from each other as possible. Even though the reasons for the high prescription volumes in this group cannot be determined, these might be signs of existing doctor shopping when care coordination to control co-prescriptions is not present.

To further analyse the group of patients potentially misusing pregabalin, a sensitivity analysis was conducted (see supplemental material 2) in which the group of patients were differentiated between those receiving pregabalin from only one prescriber (practice) and those who were prescribed by multiple practices. The results indicate that, for example, the age structure of patients prescribed by only one provider shifted to higher ages (most of the patients were older than 50 years). Concerning the approved indications, it can be seen that there were more patients (24%; 71) in the group with only one prescriber who did not have any of the indications recorded in the dataset compared to the group with multiple prescribers (20%; 114). At the same time, patients with only one prescriber were less likely to have received medications for addictive disorders or to have been prescribed other medications with addiction potential in the previous year. These results might indicate that being prescribed with a higher than recommended dose of pregabalin might not necessarily indicate doctor shopping or the lack of communication between health care providers but could also be medically explainable or caused by the data structure and a false classification (see also limitations).

Office-based physicians in Germany can be organised in group practices, and physicians from the same practice usually share a number of patients and might additionally represent each other in terms of filling prescriptions. Therefore, a large number of shared patients between physicians might primarily indicate that they belong to a common practice. In order to control for this issue, another sensitivity analysis was conducted using practices as the unit of prescribers instead of physicians and found comparable results (see Table 2): Patients prescribed pregabalin as recommended received their prescriptions from only 1.57 different practices on average, whereas patients misusing pregabalin had 2.86 different prescribing practices. In addition, in terms of care density, the practices in the prescription networks of patients potentially misusing pregabalin shared fewer patients than practices in the prescription networks of patients with medically recommended prescription doses (13 vs. 18 shared patients). Even though this difference was not significant, these results support the conclusion that patients potentially misusing pregabalin seek to obtain prescriptions from loosely connected physicians and physicians who do not coordinate their care.

The application of SNA was used in the present analysis to examine a summary statistic of cooperation in order to compare the prescribers between the two groups of patients prescribed pregabalin. Future research could additionally visually compare prescription networks and use this methodology to identify clusters with a strikingly high prevalence of drug misuse.[34]

When interpreting the results, one has to take into account some important limitations. First, only pregabalin prescriptions and not gabapentin prescriptions were analysed, even though the abuse potential of gabapentin is also under discussion.[4] However, as stated in the critical review report from the World Health Organization, the risk of pregabalin misuse might be higher because of its stronger euphoric and relaxing effect.[5] Second, the prescriptions included in the dataset only covered prescriptions from office-based physicians, did not comprise medications that were provided during hospital stays, and might thus have underestimated the amount of pregabalin consumed. Third, only one possible way of misusing pregabalin was considered in the study, i.e., consuming a higher than recommended dosage and did not consider other possibilities of misusing pregabalin, e.g., the intake of drug combinations (e.g., pregabalin and opioids). Fourth, the assumption that the patients with high prescription volumes of pregabalin are misusing the drug cannot conclusively be justified by the analysed data. For example, the data did not provide information about the compliance of patients, but only about the amount of drug dispensed. Thus, a conclusion about the final reason for high dispensed doses of pregabalin cannot definitely be drawn. Additionally, the sensitivity analysis differentiating the group of misusers into those with prescriptions from one or multiple providers point to the fact that this group might include some patients being falsely classified as “misusers” and that there might exist other reasons for the high prescribed dosages. With the comparably low number of patients being classified as misusing pregabalin and an average dispensed dose of 905 mg per patient and day within this group, the developed measure can be assumed as rather conservative that primarily discovers patients intentionally misusing pregabalin. However, a conclusive confirmation of this assumption can only be made by clinical studies that include patients and all their physicians.

## CONCLUSION

To conclude, this study offers first insights into pregabalin utilisation and prescription patterns in Germany. Misuse of pregabalin is one example of patients’ intentional exploitation of

coordination issues in ambulatory care. It sheds light on the evolving problems when care is not systematically coordinated and information about prescriptions is not exchanged. The study further shows how this problem might be minimised when physicians collaborate more closely, which is represented by a greater number of shared patients. However, absolute prevention of this problem will probably only be possible if information about medications is exchanged between all physicians as a standard and mandatory requirement. Last, the study discovered a group of patients who are potentially misusing this drug and shows that particularly prescribing physicians should be aware of this risk.

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**Competing interests:** I declare no competing interests.

**Contributors:** RF designed and conducted the analysis, provided the results and wrote the manuscript.

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- Department of General Medicine, Preventive and Rehabilitation Medicine, University of Marburg
- AOK Health Insurance Hesse (SHI)
- AOK Health Insurance Bavaria (SHI)
- AOK PLUS SHI in Thuringia and Saxony

**Ethics approval:** The present study was a secondary data analysis and therefore did not need an ethics approval. The data transmission from the participating statutory health insurances was organised via a trust centre, where the pseudonymised routine data were linked. To prevent re-identification, pseudonymised patient and physician data were pseudonymised again after the linkage and maintained in password-protected, encrypted containers. The following Ministries in their role as supervisory authorities of the statutory health insurances approved the utilisation of the data: Bavarian State Ministry for Health and Care, Hessian Ministry for Social Affairs and Integration and Saxon State Ministry for Social Affairs and Consumer Protection. The legal basis for the processing was given by the section 75 of Book X of the German Code of Social Law. By contract, inferences to individual patients are excluded and only aggregated results are presented.

**Data availability statement:** The data processed in this study were provided by the three statutory health insurances (AOK PLUS, AOK Bavaria and AOK Hesse). However, restrictions apply to the availability of these data, which were used under license for the current study (Innovation Fund project 'WirtMed study'), and are not publicly available. Data are available from the corresponding author upon reasonable request and with permission of the statutory health insurances and their supervisory authorities.

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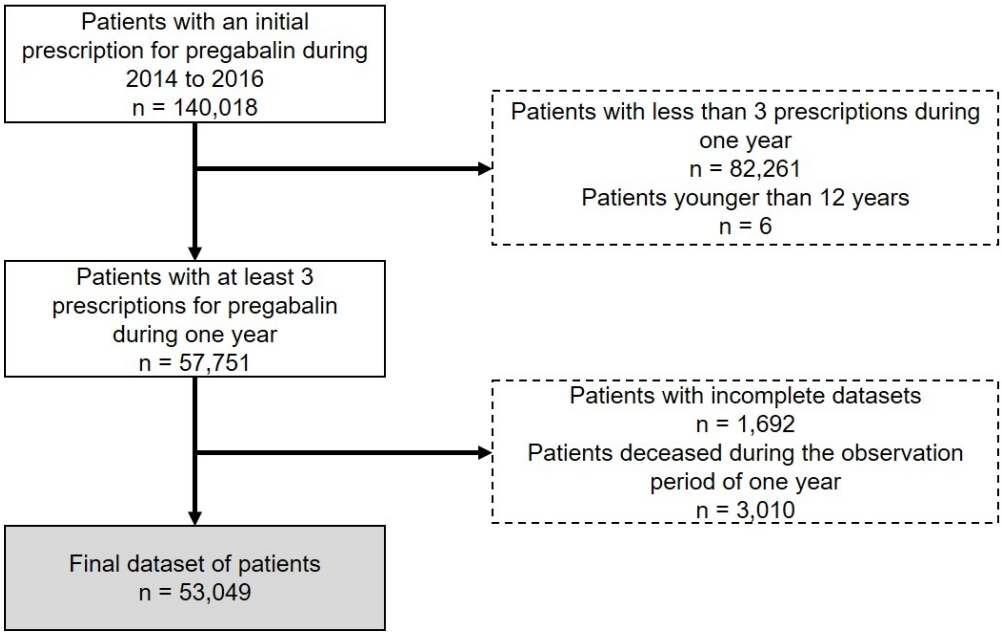
## Figure titles/legends

**Figure 1. Identification of the analysed patient population in routine data**

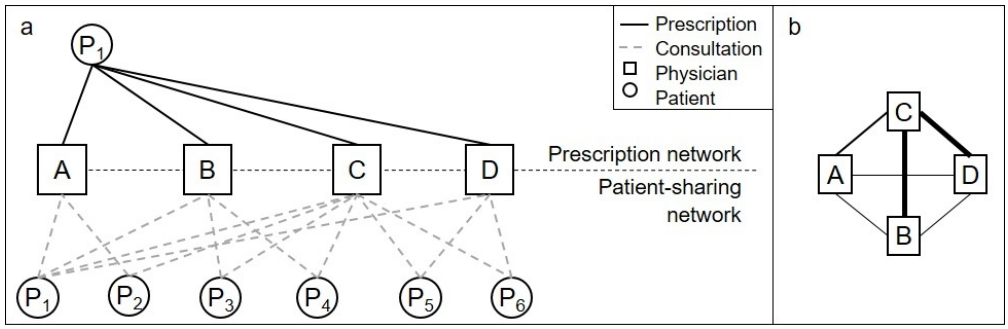
**Figure 2. The bipartite prescription network of patient P1 and the resulting bipartite patient-sharing physician network of P1's prescribers (a) and depiction of the resulting unipartite network (b)**

*(a) The bipartite patient-sharing network of $P_1$ prescribers was calculated based on the extended patient population. (b) The thickness of tie represents the number of shared patients. The resulting care density is 1.83.*




Identification of the analyzed patient population in routine data

177x112mm (150 x 150 DPI)




a The bipartite prescription network of patient P1 and the resulting bipartite patient-sharing physician network of P1's prescribers; b Depiction of the resulting unipartite network

Notes: a The bipartite patient-sharing network of P1 prescribers was calculated based on the extended patient population. b The thickness of tie represents the number of shared patients. The resulting care density is 1.83

164x53mm (150 x 150 DPI)

## Supplemental material 1

List of drugs for inclusion of patients in the extended population

| ATC | Name |
|---|---|
| N06AX22 | Agomelatin, Valdoxan |
| B01AF02 | Apixaban, Eliquis |
| B01AE07 | Dabigatran, Pradaxa |
| A10BK01 | Dapagliflozin, Forxiga |
| A10BJ05 | Dulaglutid, Trulicity |
| B01AF03 | Edoxaban, Lixiana |
| C03DA04 | Eplerenon, Inspra |
| M04AA03 | Febuxostat, Adenuric |
| C01EB17 | Ivabradin, Procoralan |
| N06BA12 | Lisdexamfetamin, Elvanse |
| N03AX16 | Pregabalin, Lyrica |
| B01AF01 | Rivaroxaban, Xarelto |
| C09DX04 | Sacubitril/Valsartan, Entresto |
| A10BH03 | Saxagliptin, Onglyza |
| A10BH01 | Sitagliptin, Januvia |
| N02AX06 | Tapentadol, Palexia |
| B01AC24 | Ticragelor, Brilique |
| C10BA02 | Ezetimib/Simvastatin, Inegy |
| N02AA55 | Oxycodon/Naloxon, Targin |
| M05BX04 | Denosumab, Prolia |
| N06AX21 | Duloxetin, Cymbalta |
| A10BK02 | Canagliflozin, Invokana |
| A10BK03 | Empagliflozin, Jardiance |
| L04AB01 | Etanercept, Enbrel |
| N06BA09 | Atomoxetin, Strattera |
| N07XX09 | Dimethylfumarat, Tecfidera |
| C01BD07 | Dronedaron, Multaq |
| R03AC18 | Indacaterol/Glycopyrronium, Ultibro Breezhaler |
| A10BJ02 | Liraglutid, Victoza |
| B01AC22 | Prasugrel, Efient |
| A10AE04 | Insulin glargin, Toujeo |
| R03AL06 | Tiotropium/Olodaterol, Spiolto |
| R03AL03 | Umeclidinium/Vilanterol, Anoro |
| G04BD08 | Solifenacin, Vesikur |

***Notes:*** *This list was developed within the WirtMed study and comprises drugs with a high price and/or unsure or unproved medical benefit for patients.*

## Supplemental material 2

| | | All patients prescribed pregabalin | Groups of patients with average doses | | Patients with >600mg/day | |
|---|---|---|---|---|---|---|
| | | | ≤600mg/day | >600mg/day | One provider (practice) | Multiple providers (practices) |
| | | N (%) / M (SD) | N (%) / M (SD) | N (%) / M (SD) | N (%) / M (SD) | N (%) / M (SD) |
| **Number of patients per group** | | **53,049** | **52,172** | **877** | **295** | **582** |
| **Patient characteristics** | | | | | | |
| **Gender** | Male | 21,004 (39.6) | 20,468 (39.2) | 536 (61.1) | 190 (64.4) | 346 (59.5) |
| | Female | 32,045 (60.4) | 31,704 (60.8) | 341 (38.9) | 105 (35.6) | 236 (40.5) |
| **Age (years)** | 12–17 | 22 (0.0) | 22 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 18–29 | 867 (1.6) | 782 (1.5) | 85 (9.7) | 26 (8.8) | 59 (10.1) |
| | 30–39 | 1,996 (3.8) | 1,808 (3.5) | 188 (21.4) | 40 (13.6) | 148 (25.4) |
| | 40–49 | 4,472 (8.4) | 4,271 (8.2) | 201 (22.9) | 56 (19.0) | 145 (24.9) |
| | 50–59 | 9,434 (17.8) | 9,252 (17.7) | 182 (20.8) | 71 (24.1) | 111 (19.1) |
| | 60–69 | 9,768 (18.4) | 9,677 (18.5) | 91 (10.4) | 47 (15.9) | 44 (7.6) |
| | ≥ 70 | 26,490 (49.9) | 26,360 (50.5) | 130 (14.8) | 55 (18.6) | 75 (12.9) |
| **Place of residence** | Urban area | 23,862 (45.0) | 23,413 (44.9) | 449 (51.2) | 137 (46.4) | 312 (53.6) |
| | Rural area | 29,119 (54.9) | 28,694 (55.0) | 425 (48.5) | 157 (53.2) | 268 (46.0) |
| **Approved indications** | | | | | | |
| | Epilepsy | 1,968 (3.7) | 1,882 (3.6) | 86 (9.8) | 18 (6.1) | 68 (11.7) |
| | Generalised anxiety disorder | 3,068 (5.8) | 2,958 (5.7) | 110 (12.5) | 25 (8.5) | 85 (14.6) |
| | Neuropathic pain | 39,829 (75.1) | 39,249 (75.2) | 580 (66.1) | 184 (62.4) | 396 (68.0) |
| | Neuropathic pain (broad definition) | 42,120 (79.4) | 41,505 (79.6) | 615 (70.1) | 203 (68.8) | 412 (70.8) |
| | Multiple | 3,293 (6.2) | 3,186 (6,1) | 107 (12.2) | 21 (7.1) | 86 (14.8) |
| | None of the indications recorded in the records | 9,283 (17.5) | 9,098 (17.4) | 185 (21.1) | 71 (24.1) | 114 (19.6) |
| **Medical pre-conditions with increased risk of abuse** | | | | | | |
| | Substance use disorders | 6,414 (12.1) | 6,049 (11.6) | 365 (41.6) | 104 (35.3) | 261 (44.8) |
| | Addictive disorder drug (alcohol) | 43 (0.1) | 41 (0.1) | 2 (0.2) | 0 (0.0) | 2 (0.3) |
| | Addictive disorder drug (tobacco) | 2 (0.0) | 2 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Addictive disorder drug (opioids) | 258 (0.5) | 182 (0.3) | 76 (8.7) | 16 (5.4) | 60 (10.3) |
| **Drugs with potential for abuse** | | | | | | |
| | Benzodiazepine | 9,665 (18.2) | 9,367 (18.0) | 298 (34.0) | 69 (23.4) | 229 (39.3) |
| | Opioids | 23,886 (45.0) | 23,527 (45.1) | 359 (40.9) | 108 (36.6) | 251 (43.1) |
| | Psychostimulants | 288 (0.5) | 263 (0.5) | 25 (2.9) | 9 (3.1) | 16 (2.7) |
| **Contemporaneous prescription of gabapentin** | | 2,973 (5.6) | 2,890 (5.5) | 83 (9.5) | 25 (8.5) | 58 (10.0) |
| **Prescription networks and structural characteristics** | | | | | | |
| | Number of prescriptions | 6.34 (3.28) | 6.23 (2.91) | 12.70 (10.17) | 8.76 (5.46) | 14.69 (11.35) |
| | Number of prescribers (physicians) | 1.79 (1.03) | 1.77 (0.89) | 3.12 (3.91) | - | - |
| | Number of prescribers (practices) | 1.59 (0.87) | 1.57 (0.73) | 2.86 (3.61) | - | - |
| **Medical specialty of initial prescriber** | | | | | | |
| | GP | 32,911 (62.0) | 32,344 (62.0) | 567 (64.7) | 204 (69.2) | 363 (62.4) |
| | Anaesthesiology | 1,935 (3.6) | 1,908 (3.7) | 27 (3.1) | 11 (3.7) | 16 (2.7) |
| | Orthopaedics | 1,209 (2.3) | 1,192 (2.3) | 17 (1.9) | 2 (0.7) | 15 (2.6) |
| | Neuroscience | 4,292 (8.1) | 4,223 (8.1) | 69 (7.9) | 20 (6.8) | 49 (8.4) |
| | Neurology | 5,039 (9.5) | 4,984 (9.6) | 55 (6.3) | 26 (8.8) | 29 (5.0) |
| | Psychiatry and psychotherapy | 2,341 (4.4) | 2,289 (4.4) | 52 (5.9) | 18 (6.1) | 34 (5.8) |
| | Other | 5,322 (10.0) | 5,232 (10.0) | 90 (10.3) | 14 (4.7) | 76 (13.1) |
| | Proportion of specialists among prescribers | 0.31 (0.40) | 0.31 (0.40) | 0.31 (0.38) | 0.30 (0.46) | 0.31 (0.34) |
| | Care density among physicians[1] | 47.97 (70.61) | 48.29 (70.67) | 33.23 (66.43) | - | - |
| | Care density among practices[1] | 17.42 (35.77) | 17.54 (35.84) | 12.90 (32.76) | - | - |
| | Maximal geographic distance [in kilometres] | 6.86 (26.63) | 6.71 (26.24) | 15.98 (43.27) | - | - |

**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

| | Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|---|---|---|---|---|---|
| **Title and abstract** | | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.<br><br>RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.<br><br>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | p. 2<br><br>p. 2<br><br>p. 2 |
| **Introduction** | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | | | p. 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | | | p. 4 |
| **Methods** | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | | | p. 4 ff. |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | | | p. 4 ff. |

| | | | | | |
|---|---|---|---|---|---|
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | | RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.<br><br>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | p. 4 ff.<br><br>p. 5<br><br>p. 4 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | p. 5-6 |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement).<br>Describe comparability of assessment methods if there is more than one group | | | p. 5-6 |

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|---|---|---|---|---|---|
| Bias | 9 | Describe any efforts to address potential sources of bias | | | p. 7 |
| Study size | 10 | Explain how the study size was arrived at | | | p. 7 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | | | p. 7 |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | | | p. 7 |
| Data access and cleaning methods | | .. | | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. | p. 4 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | |
| Linkage | | .. | | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | p. 4ff. |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | p. 7-9 |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | | | p. 7-9 |
| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure | | | p. 7-9 |

| | | | | | |
|---|---|---|---|---|---|
| | | category, or summary measures of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | | | p. 7-9 |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | | | |
| **Discussion** | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | | | p. 9-ff. |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | p. 11 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, | | | p. 11 |

| | | | | | |
|---|---|---|---|---|---|
| | | limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | | | p. 9 ff. |
| **Other Information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | | | p. 13 |
| Accessibility of protocol, raw data, and programming code | | .. | | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | p. 13 |

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.