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Title:

Prescribing practice of newer antiepileptic drugs in pain therapy – a routine data evaluation

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Abstract

Objectives: What are the prevalence and incidence for pregabalin and gabapentin (P/G) prescriptions? What are the typical areas of application for P/G? Which pain-related diagnoses are available for P/G users? How high is the rate of discontinuation for P/G?

Design: A secondary data analysis.

Setting: Primary and secondary care in Germany.

Participants: Anonymous accounting data of 4 million insured persons from under the statutory health insurance scheme in 2009-2015.

Intervention: None.

Primary and secondary outcome measures: None.

Results: In 2015, 1.6% of insured persons were given a P/G prescription. Among the pain patients with new P/G prescriptions, only 21.7% had a typical neuropathic pain disorder. For the remaining new P/G recipients (78.3%), there was either no diagnosis of neuropathic pain or a diagnosis in which a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of P/G. The rate of discontinuation for P/G was high (85%). Among the patients, who have discontinued medication, 61.1% did not receive one follow-up prescription within two years.

Conclusion: The results show that P/G is widely used in cases of chronic pain irrespective of neuropathic pain diagnoses. The high rate of discontinuation indicates that the anticipated therapeutic effects are lacking and/or adverse effects occur.

Trial registration: None.

Strengths and limitations of this study

- The findings of this study are based on a routine data evaluation which was carried out for the accounting of services. This can lead to systematic restrictions.
- Due to following reasons, the pain-related indications may have been insufficiently coded in individual cases, e.g. mistakes in the daily routine, clear neuropathic diagnoses may have been specifically identified to justify a prescription.
- The diagnosis coding of unspecific low back pain were often routinely coded as "lumboischialgia" or unspecific neck pain as "cervical neuralgia". This systematic misclassification tend towards overestimation of neuropathic diagnosis.

1. Introduction

The active ingredient pregabalin and gabapentin, hereinafter referred to as pregabalin/gabapentin or P/G, belong to the group of "newer antiepileptic drugs", which were developed for the treatment of epilepsy. Pregabalin/gabapentin was also later approved for the treatment of neuropathic pain (gabapentin: 2001; pregabalin: 2004), which is now the main indication for these active ingredients [1].

Controlled randomised studies showed a slight improvement of neuropathic pain disorder in patients treated with pregabalin/gabapentin compared to placebo; the effects are about as great as those of amitriptyline [2–4]. Adverse effects occur significantly more frequently in the P/G intervention group than in the placebo comparison group [5]. The evidence for the rather small therapeutic effects of P/G, which are approved for the treatment of rare medical conditions, contradicts the prescription figures, which have been increasing steadily for years. According to the medication report, a total of 128 million daily doses of pregabalin/gabapentin were prescribed in 2015 [1]. The Lyrica product by Pfizer (pregabalin) was ranked 26th in 2015 on the list of the highest-revenue medicines under patent-protection with net GKV (statutory health insurance) costs of 170.3 million euros [1]. Prescription data from England describe the same trends [6].

The current study presents an analysis of the prescription situation. The following research questions are the main focuses:

1.) How high is the **annual prevalence** for the prescription of pregabalin/gabapentin among all insured persons from 2009 to 2015?

2.) How high is the **annual incidence** for new prescriptions of pregabalin/gabapentin among all insured persons from 2009 to 2015?

3.) What are the **areas of application** (epilepsy/generalised anxiety disorder/pain) for patients with new pregabalin/gabapentin prescriptions from 2009 to 2015?

4.) Which **pain-related diagnoses** (neuropathic pain/non-neuropathic pain/mixed pain/no pain) are applicable to patients without epilepsy diagnosis with new pregabalin/gabapentin prescriptions in 2015?

5.) What is the **proportion** of patients for whom pregabalin/gabapentin was discontinued within two years after a new prescription for the treatment of pain?

- How many follow-up prescriptions were given to patients for whom pregabalin/gabapentin was discontinued?

2. Methods

2.1. Study design and database

The research questions were analysed in a cross-sectional design. The research database of the InGef – Institute for Applied Health Research was used as the data basis for this project. The InGef research database (formerly HRI Research Database) contains accounting data on the utilisation and resource consumption of approx. 6.7 million anonymous insured persons from around 65 health insurance funds and company health insurance funds [7]. The present analysis was based on a sample of almost 4 million random samples from the research database, which closely represents the age and gender structure of Germany for the year 2013 (according to Destatis – Federal Statistical Office – 31.12.2013). The random sampling enables a longitudinal analysis of insured persons over the years 2009-2015; in addition to sociodemographic data, it contains information on medicines prescribed by doctors and dispensed by pharmacies in the form of central pharma numbers (PZN) and ATC codes, ICD diagnoses from outpatient and inpatient areas as well as invoiced medical services.
The diagnoses and prescriptions can be linked to the anonymous insured person's name at the end of each quarter.

2.2. Random sample analysis

The inclusion criteria, which vary according to the question, are presented below (for insured persons who meet the following criteria):

Sample 1 (Question 1 – ANNUAL PREVALENCE):

- insured for at least one day in the first quarter of the respective reporting year

Sample 2 (Question 2 – ANNUAL INCIDENCE):

- insured for at least one day in the first quarter of the respective reporting year
- insured for 365 days in the previous year

Sample 3 (Question 3 – AREAS OF APPLICATION FOR NEW PRESCRIPTION):

- insured for at least one day in the first quarter of the respective reporting year
- insured for 365 days in the previous year
- at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) in the reporting year, but not in the four previous quarters

Sample 4 (Question 4 – PAIN DIAGNOSES IN THE NEW PRESCRIPTION):

- insured for at least one day in the first quarter of 2015

- no coded epilepsy diagnosis (G40.- | G41.-) in the years 2014-2015
- no prescription of antiepileptic medication (all N03 codes) in 2014
- at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) in 2015

Sample 5 (Question 5 – DISCONTINUATION):

- insured for at least one day in the first quarter of 2013
- no coded epilepsy diagnosis (G40.- | G41.-) in the years 2011-2013
- no prescription of antiepileptic medication (all N03 codes) in the years 2011-2012
- at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16), and in the same quarter of the prescription, at least one pain diagnosis in 2013

2.3 Data evaluation

The annual prevalence was calculated individually for each reporting year from 2009 to 2015. All insured persons who received at least one P/G prescription (ATC code: N03AX12 or N03AX16) within one year were divided by the total number of all insured persons from sample 1 of the respective reporting year.

The annual incidence was calculated individually for each year from 2010 to 2015 (except for the first reporting year: 2009, as no new prescriptions could be identified due to missing data for the previous year). To this end, all insured persons who received a pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) within one year, but not in the previous year, were compared to the total number of all patients from sample 2 of the respective reporting year.

The areas of application approved for P/G were analysed individually for each possible combination of the diagnoses "Epilepsy (G40.- | G41.-)","Generalised anxiety disorder (F41.1)" and "Pain (for selection of ICD-10 codes, see all pain diagnoses in the last row of Table 1)".

Table 1: **Pain-related diagnoses** in patients with new pregabalin/gabapentin prescriptions in 2015 (n=25,251)

	Pain-related diagnoses	**Number of insured persons**	**As a percentage**
1	Non-neuropathic pain * (exclusive)	2,951	11.7
2	Typical neuropathic pain disorder ** (exclusive) (demonstrable benefit of a P/G therapy)	1,218	4.8
3	Pain with possible neuropathic or partial-neuropathic cause *** (exclusive) (no demonstrable benefit of P/G)	3,025	12.0

1 and 2	1,295	5.1
1 and 3	10,756	42.6
2 and 3	1,010	4.0
1 and 2 and 3	2,990	11.8
neither 1, 2 nor 3	2,006	7.9

Typical neuropathic pain disorder

* ICD-10 pain code "not neuropathic":

R522	Other chronic pain
M545	Low back pain
F4541	Chronic pain disorder related to somatic and psychological factors
R51	Headache
R529	Pain, unspecified
R104	Other and unspecified abdominal pain
R103	Pain localised in other parts of lower abdomen
R521	Chronic intractable pain
M5499	Back pain, unspecified: Localisation not specified in more detail
R101	Pain localised in upper abdomen
R074	Chest pain, not specified in more detail
M2556	Pain in joint: Lower leg [fibula, tibia, knee joint]
M7969	Pain in extremities: Localisation not specified in more detail
G442	Tension-type headache
M2559	Pain in joint: Localisation not specified in more detail
F4540	Persistent somatoform pain disorder
M546	Pain in area of thoracic spine
M2555	Pain in joint: Pelvic region and thigh [pelvis, femur, buttocks, hip, hip joint, sacroiliac joint]
M7967	Pain in the extremities: Ankle and foot [tarsal, metatarsal, toes, ankle, joints of the foot]
R520	Acute pain
M2551	Pain in joint: Shoulder region [clavicle, scapula, acromioclavicular/shoulder/sternoclavicular joints]
I7022	Atherosclerosis of arteries of extremities: Pelvic-leg type, with rest pain
M2550	Pain in joint: Multiple sites
I7021	Atherosclerosis of arteries of extremities: Pelvic-leg type, with load-induced ischaemic pain

** ICD-10 pain codes "typically neuropathic":

G629	Polyneuropathy, not specified in more detail
B029	Zoster without complication
G632	Diabetic polyneuropathy
B022	Zoster with involvement of other parts of the nervous system
G530	Post-Zoster neuralgia
G500	Trigeminal neuralgia
G6288	Other specified polyneuropathies

*** ICD-10 pain code "possibly neuropathic":

M544	Lumbago with sciatica
M5416	Radiculopathy: Lumbar region
M542	Cervicalgia
M511	Lumbar and other intervertebral disc disorders with radiculopathy
G560	Carpal tunnel syndrome
M5419	Radiculopathy: Localisation not specified in more detail
M5412	Radiculopathy: Cervical region
M5417	Radiculopathy: Lumbosacral region
M5414	Radiculopathy: Thoracic region
M543	Sciatica
M501	Cervical disc disorder with radiculopathy
M5410	Radiculopathy: Multiple sites in spine
G573	Lesion of lateral popliteal nerve
M961	Postlaminectomy syndrome, not elsewhere classified
G580	Intercostal neuropathy
G562	Lesion of ulnar nerve

In addition, insured persons in Sample 3, to whom one of the above-mentioned diagnosis groups was assigned in parallel to the P/G prescription within a quarter, were divided by all insured persons in Sample 3. These calculations were made individually for each reporting year from 2010 to 2015.

To answer the question of which pain-related diagnoses P/G was newly prescribed, the percentage distribution of all coded ICD-10 pain diagnoses of the insured persons from sample 4 was presented first. Furthermore, the diagnoses were classified into the three categories "**non-neuropathic** pain"," **typical neuropathic** pain disorders for which there is a demonstrable **benefit of a P/G therapy**" and "pain, **possibly** of **neuropathic** or partial-neuropathic cause for which there is **no demonstrable** benefit of **P/G**" [1–4]. The ICD-10 diagnosis classification is presented in the last line of Table 1.

The calculation of the number of follow-up prescriptions/rate of discontinuation according to new P/G prescriptions was based on sample 5 and relates to the year 2013 plus two years of follow-up observation period (up to max. 2015). If in the two-year follow-up period no P/G prescription occurred for at least two consecutive quarters, this was defined as a discontinuation of therapy. The percentage of insured persons who discontinued therapy and the number of individual prescriptions up to termination were presented.

3. Results

3.1. Prevalence and incidence for P/G prescriptions

From 2009-2015, 1.3% (52,774/3,948,482) of insured persons were prescribed at least one P/G prescription. The prevalence of prescriptions increased from 1.1% in 2009 to 1.6% per annum in 2015 (Table 2a).

Table 2a: **Annual prevalence** for pregabalin/gabapentin prescriptions 2009-2015

Year	Number of insured persons with P/G prescriptions	Number of total insured persons	Prevalence per 100,000 insured persons
2009	41,083	3,822,333	1,074.8
2010	46,225	3,890,247	1,188.2
2011	50,230	4,027,591	1,247.1
2012	53,389	4,019,944	1,328.1
2013	56,358	4,010,383	1,405.3
2014	60,306	3,998,004	1,508.4
2015	61,828	3,870,869	1,597.3
Mean value 2009-2015	52,774	3,948,482	1,335.6

Table 2b: **Prevalence** for pregabalin/gabapentin prescriptions grouped by age and stratified by gender in 2015

Age group	Total prevalence per 100,000 insured persons	Prevalence per 100,000 insured women	Prevalence per 100,000 insured men
0-17	13.4	17.5	9.6
18-35	249.2	289.4	210.0
36-55	1,042.5	1,213.2	874.9
56-75	2,899.6	3,146.0	2,634.9
76+	5,302.1	5,709.5	4,658.1
Total	1,597.3	1,869.7	1,312.8
Total 18+	1,894.0	2,197.1	1,571.7

The prescription rate was highest in the 76+ age group (5,302 persons per 100,000 insured persons in 2015) (Table 2b). The prescription for minors, on the other hand, at 13.4 per 100,000 insured persons, was low. Compared to men, women were prescribed P/G more frequently (women: a total of 1,869.7 per 100,000 insured persons; men: a total of 1,312.8 per 100,000 insured persons). Like prescription prevalence, the rate of new P/G prescription increased annually (Table 3).

Table 3: **Annual incidence** for pregabalin/gabapentin – **new** prescriptions 2010-2015			
Year	**Number of insured persons with new P/G prescriptions**	**Number of total insured persons**	**Incidence per 100,000 insured persons**
2010	22,776	3,701,696	615.3
2011	23,121	3,717,582	621.9
2012	24,750	3,977,347	622.3
2013	25,784	3,966,813	650.0
2014	27,613	3,952,306	698.7
2015	26,526	3,757,502	705.9
Mean value 2010-2015	25,095	3,845,541	652.4

One exception was the last year accounted for, 2015. This showed a slight drop in incidence.

3.2. Area of application

Considering the three applications approved for P/G, it was found that the majority (77.9%) of P/G recipients had only a pain diagnosis and there was no evidence of epilepsy or anxiety disorder (Table 4).

Table 4: **Diagnoses** in patients with pregabalin/gabapentin prescriptions in 2015 (n=61,828)		
ICD diagnoses	**Number of insured persons with P/G prescriptions**	**As a percentage**
Pain * (exclusive)	48,190	77.9
Epilepsy ** (exclusive)	793	1.3
Anxiety disorder *** (exclusive)	707	1.1
Pain + anxiety disorder	2,404	3.9
Pain + epilepsy	2,222	3.6
Pain + epilepsy + anxiety disorder	162	0.3
Epilepsy + anxiety disorder	49	0.1
No pain, epilepsy or anxiety disorder	7,198	11.6
* all ICD-10 pain diagnoses listed in Table 4 (last row) ** ICD codes: G40.- | G41.- *** ICD codes: F41.1		

There was no evidence for the approved application diagnoses according to Fachinfo for 11.6% of the P/G recipients. P/G recipients exclusively with a diagnosis of epilepsy or anxiety (epilepsy: 1.3%;

anxiety 1.1%) were the minority. The percentage of new P/G recipients (excluding pain diagnoses) increased continuously over the years. The proportion of existing epilepsy and anxiety diagnoses remained relatively constant in the new P/G prescriptions group.

3.3. Application in pain patients

After excluding epilepsy patients, 25,251 insured persons remained under new P/G prescription, whose pain diagnoses were analysed. A typical neuropathic pain disorder was present in one fifth of all new P/G recipients (21.7%), Table 1. For the majority (58.6%) of new recipients, a diagnosis was made in which a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of P/G. The three most frequent representatives in this category were the diagnoses "M544_Lumboischialgia" (5,836/25,251),"M5416_Radiculopathy: Lumbar region" (4,978/25,251) and "M542_Cervical neuralgia" (4,543/25,251). In 19.6% of the cases, there was only a "non-neuropathic pain diagnosis" or "no pain diagnosis".

3.4. Discontinuation

Within the follow-up period, 85% (16,573/19,501) of insured persons who received a new P/G prescription due to pain (excluding patients with epilepsy diagnosis) were again discontinued within two years. For the majority of the persons, who have discontinued, the discontinuation occurred within a short period. Thus, in 61.1% of the cases, there was no follow-up prescription after the initial prescription (number of follow-up-prescriptions / proportion in percent: 1/13.2%; 2/7.5%; 3/5.4%; ≥4/12.8%). The proportion of P/G insured persons with regular follow-up prescriptions over the follow-up period was 15% (2,928/19,501).

4. Discussion

The prescription figures for pregabalin and gabapentin increased annually from 2009 to 2015. The majority of patients (78%) received P/G for the treatment of pain. In patients who received new P/G prescriptions, only about one in five (22%) had a typical neuropathic pain disorder with a demonstrable benefit of a P/G therapy. For the remaining new P/G recipients (78.3%), there was either no diagnosis of neuropathic pain or a diagnosis in which a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of P/G. The rate of discontinuation for P/G was high; based on new prescriptions, 51.9% of cases did not receive a follow-up prescription within two years.

The findings of this study are based on a routine data evaluation, which was carried out independently of the research questions, specifically for the accounting of services in the daily treatment routine. This can lead to systematic restrictions [8]. Regarding the information relevant to this project "P/G consumption", a typical realistic representation can be assumed due to the prescription requirement for P/G-containing medicinal products. However, the pain-related indications may have been insufficiently coded in individual cases. For example, clear neuropathic diagnoses may have been specifically identified to justify a prescription. Presumably, the proportion of evidence-based indications is even lower in reality. In the diagnosis coding of unspecific low back pain as well, systematic misclassifications that tend towards overestimation are likely, since they are often routinely coded as "lumboischialgia" or unspecific neck pain as "cervical neuralgia".

The increase in the number of P/G prescriptions found in this analysis coincides with figures from the IMS health database from the United Kingdom [6]. The steadily increasing number of prescriptions with a constant incidence of purely neuropathic pain disorders indicates that P/G is increasingly being used in patients with "mixed chronic pain ("mixed pain")". This observation has also made by Goodman et al. in an issue of the New England Journal of Medicine in August 2017 [6]. "Mixed pain" refers to chronic pain syndromes in which a mixture of nociceptive and neuropathic pain components is assumed. Instruments specially developed for this purpose, such as the painDETECT questionnaire, are designed to identify the neuropathic pain component [9] and are promoted accordingly. However, the pre-approval P/G studies only included patients with pure neuropathic pain as a result of damage to somatosensory nerve structures, e.g. with post-zoster neuralgia or diabetic polyneuropathy. High-quality qualitative studies on the efficacy of P/G in patients with mixed chronic pain are not yet available [10]. In the current edition of the guideline "Non-specific low back pain", the NVL guideline group also opposes a screening using painDETECT [11] due to a lack of evidence.

In consideration of the pain diagnoses, which are coded in parallel to new P/G prescriptions, the question arises as to which diagnoses should be classified as neuropathic or non-neuropathic.

In the S1 guideline "Diagnostics of neuropathic pain" [12] of the German Society of Neurology, for example, in addition to the pure neuropathic pain syndromes with damage to somatosensory nerve structures, pain diagnoses in which a neuropathic component is pathophysiologically conceivable, such as "lumboischialgia" or “radiculopathy”, are classified as neuropathic. The pain of these conditions is typically caused by nerve irritation, but this does not necessarily constitute damage. In these cases, there is often no evidence of benefit for the application of P/G. In this regard, an RCT published in March 2017 by Mathieson et al. showed the non-benefit of pregabalin [13]. Within the scope of this project, we decided to differentiate between "typical neuropathic pain disorder" with a demonstrable benefit of P/G therapy and "pain, possibly with neuropathic or partially-neuropathic cause" with no evidence for the application of P/G. Subsequently, a typical neuropathic pain disorder is presented exclusively in one fifth of the new P/G prescriptions. This phenomenon is increasingly being described and critically discussed internationally [6, 14]. Abroad, there is also an increasing reference to the fact that P/G is also abused by addicts as a drug booster [15, 16].

The high discontinuation rate suggests two causes. On the one hand, the hoped-for pain-relieving effect is not achieved, and on the other hand the therapy is discontinued due to adverse effects. Ultimately, P/G was prescribed as a long-term therapy only for a small minority. This is thought to be the typical neuropathic pain cases in which P/G has been shown to have an effect. In all other cases, the discontinued therapy trial underlines that the widely practised and promoted strategy of using P/G also in mixed chronic pain patients is not useful. The cause of pain in these cases is multifactorial and usually cannot be solved by medicine.

In view of the discrepancy between the high number of prescriptions and the discontinuation rate, as an indirect parameter of a clinically unconvincing effect, the question arises as to the motives for the high number of prescriptions. The marketing by the pharmaceutical industry [6], among others, which was specifically targeted at the treatment of mixed-pain patients with neuropathic symptoms, may play an important role. The influence of pharmaceutical marketing may also be an explanation for the slight drop in the incidence of new prescriptions in 2015. Pregabalin generics were introduced in December 2014, which could have led to a possible withdrawal of marketing efforts by the patent-holding company.

A further motive for doctors to prescribe it may be the one-sided biomedical understanding of chronic pain, out of which pain symptoms are too often answered with the prescription of a painkiller rather than with non-medicinal measures or counselling. Furthermore, there is no convincing therapeutic approach for the effective treatment of chronic pain patients to date. Multimodal therapy programmes are not sufficiently available and, in their current inpatient or short-term outpatient configuration, do not solve the problems of the continuous care situation in established practices. Frustration among

both doctors and patients may trigger desperate measures such as the use of newer antiepileptic medicine.

5. Study protocol

The study protocol is available on request. Please contact: annika.viniol@staff.uni-marburg.de.

6. Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

7. Competing interests

The authors declare that they have no competing interests.

9. Authors' contributions

AV planned the study, discussed the results and wrote the manuscript. TP and LH analyzed data and discussed the manuscript. KMK gave support to study design and discussed the manuscript. JW, JH, NDB and AB discussed the results and the manuscript.

10. Reporting statement

Data analysis and reporting style is in accordance with the "German Reporting Standard for Secondary Data Analyses" (STROSA).

11. Patient consent

Due to the nature of secondary data analysis, no patient consent is required.

12. Data sharing statement

Data used in the analyses are entrusted in the Institute for Applied Health Research Berlin. Please contact: jochen.walker@hrisk.de

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Cross sectional study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-8*
Bias	9	Describe any efforts to address potential sources of bias	5-8
Study size	10	Explain how the study size was arrived at	Secondary data analysis
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Cross sectional study
		(*b*) Describe any methods used to examine subgroups and interactions	5-8
		(*c*) Explain how missing data were addressed	5-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	5-8

		Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Cross sectional study
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-11
		(b) Give reasons for non-participation at each stage	Secondary data analysis
		(c) Consider use of a flow diagram	Secondary data analysis
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	9-11
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Cross sectional study
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Cross sectional study
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Cross sectional study
		Cross-sectional study—Report numbers of outcome events or summary measures	9-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Cross sectional study
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Cross sectional study
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
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	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
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	13-14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Title:

Prescribing practice of pregabalin / gabapentin in pain therapy – an evaluation of German claim data

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Abstract

Objectives: To describe the prevalence and incidence of pregabalin and gabapentin (P/G) prescriptions, typical therapeutic uses of P/G with careful attention to pain-related diagnoses, and discontinuation rates of P/G.

Design: A secondary data analysis.

Setting: Primary and secondary care in Germany.

Participants: Anonymous health insurance data of 4 million insured persons in the space of time from 2009 to 2015.

Intervention: None.

Primary and secondary outcome measures: We analysed the prescribing practice of P/G in general and investigate the use of P/G in pain therapy. We focused on the question due to which pain-related diagnoses patients get a new P/G prescription and illustrated the discontinuation rate of P/G.

Results: In 2015, 1.6% of insured persons were given a P/G prescription. Among the pain patients with new P/G prescriptions, only 25.7% had a typical neuropathic pain disorder. For the remaining new P/G recipients (74.3%), there was either no diagnosis of neuropathic pain or a diagnosis in which a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of P/G. The rate of discontinuation for P/G was high (85%). Among the patients who had discontinued medication, 61.1% did not receive one follow-up prescription within two years.

Conclusion: The results show that P/G is widely used in cases of chronic pain irrespective of neuropathic pain diagnoses. The high rate of discontinuation indicates that the anticipated therapeutic effects are lacking and/or adverse effects occur.

Trial registration: None.

Strengths and limitations of this study

- The findings of this study are based on accounting data on the utilisation and resource consumption of insured persons from health insurance funds. These secondary data can lead to systematic restrictions.
- The pain-related indications may have been insufficiently coded (documentation errors)
- The diagnosis coding of unspecific low back pain were often routinely coded as "lumboischialgia" or unspecific neck pain as "cervical neuralgia". This systematic misclassification tend towards overestimation of neuropathic diagnosis.

1. Introduction

The active ingredient pregabalin and gabapentin, hereinafter referred to as pregabalin/gabapentin or P/G, belong to the group of "newer antiepileptic drugs", which were developed for the treatment of epilepsy. The European Medicines Agency approved Pregabalin/gabapentin also later for the treatment of neuropathic pain (Pregabalin (2004): “peripheral and central neuropathic pain”; Gabapentin (2001): “peripheral neuropathic pain like painful diabetic neuropathy and post herpetic neuralgia” [1]), which is now a common indication for these active ingredients [2].

Controlled randomised studies showed a slight improvement of specific forms of neuropathic pain disorder in patients treated with pregabalin/gabapentin compared to placebo [3–5]. The evidence for the rather small therapeutic effects of P/G, which are approved for the treatment of a rather minor condition spectrum, contradicts the prescription figures, which have been increasing steadily for years. According to the medication report, a total of 128 million daily doses of pregabalin/gabapentin were prescribed in 2015 [2]. The Lyrica product by Pfizer (pregabalin) was ranked 26th in 2015 on the list of the highest-revenue medicines under patent-protection with net GKV (statutory health insurance) costs of 170.3 million euros [2]. US Prescription data describe the same trends. The gabapentin prescription rate has been raised from 39 million in 2012 to 64 million in 2016 in the United States [6, 7].

The above described increasing P/G prescribing makes us concerned, why we investigate the prescribing practice in this study. The following research questions are the main focuses:

1.) How high is the **annual prevalence** for the prescription of pregabalin/gabapentin among all insured persons from 2009 to 2015?

2.) How high is the **annual incidence** for new prescriptions of pregabalin/gabapentin among all insured persons from 2009 to 2015?

3.) What are the **indications for prescribing** (epilepsy/generalised anxiety disorder/pain) for patients with new pregabalin/gabapentin prescriptions from 2009 to 2015?

4.) Which **pain-related diagnoses** (neuropathic pain/non-neuropathic pain/mixed pain/no pain) are applicable to patients without epilepsy diagnosis with new pregabalin/gabapentin prescriptions in 2015?

5.) What is the **proportion** of patients for whom pregabalin/gabapentin was discontinued within two years after a new prescription for the treatment of pain?

- How many follow-up prescriptions were given to patients for whom pregabalin/gabapentin was discontinued?

2. Methods

2.1. Study design and database

The research questions were analysed in a cross-sectional design. The research database of the InGef – Institute for Applied Health Research was used as the data basis for this project. The InGef research database (formerly HRI Research Database) contains data on the utilisation and resource consumption of approx. 6.7 million anonymous insured persons from around 65 health insurance funds and company health insurance funds [8]. As long as the insured persons are members of these health insurances, their data are all-encompassing available in this database and were no competing to other databases. When insurant change to another insurance which is not linked with this database, their data are still not available in this database. The present analysis was based on a sample of almost 4 million random samples from the research database, which closely represents the age and gender structure of Germany for the year 2013 (according to Destatis – Federal Statistical Office – 31.12.2013). The random sampling enables a longitudinal analysis of insured persons over the years 2009-2015; in addition to sociodemographic data, it contains information on medicines prescribed by doctors and dispensed by pharmacies in the form of central pharma numbers (PZN) and ATC codes, ICD diagnoses from outpatient and inpatient areas as well as invoiced medical services.
The diagnoses and prescriptions can be linked to the anonymous insured person's name at the end of each quarter. In every analysis, all dosage forms and formulations of P/G were included.

2.2. Random sample analysis

The inclusion criteria, which vary according to the question, are presented below (for insured persons who meet the following criteria):

Sample 1 (Question 1 – ANNUAL PREVALENCE):
Persons who were insured for at least one day in the first quarter of the respective reporting year.

Sample 2 (Question 2 – ANNUAL INCIDENCE):
Persons who were insured for at least one day in the first quarter of the respective reporting year and 365 days in the previous year.

Sample 3 (Question 3 – INDICATIONS FOR PRESCRIBING FOR NEW PRESCRIPTION):
Persons who were insured for at least one day in the first quarter of the respective reporting year and 365 days in the previous year with at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) in the reporting year, but not in the four previous quarters (independent from diagnosis).

Sample 4 (Question 4 – PAIN DIAGNOSES IN THE NEW PRESCRIPTION):
Persons who were insured for at least one day in the first quarter of 2015 and fulfil the following criteria: no coded epilepsy diagnosis (G40.- | G41.-) in the years 2014-2015; no prescription of antiepileptic medication (all N03 codes) in 2014; at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) in 2015

Sample 5 (Question 5 – DISCONTINUATION):
Persons who were insured for at least one day in the first quarter of 2013 and fulfil the following criteria: no coded epilepsy diagnosis (G40.- | G41.-) in the years 2011-2013; no prescription of antiepileptic medication (all N03 codes) in the years 2011-2012; at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16), and in the same quarter of the prescription, at least one pain diagnosis in 2013

2.3 Data evaluation

The annual prevalence was calculated individually for each reporting year from 2009 to 2015. All insured persons who received at least one P/G prescription (ATC code: N03AX12 or N03AX16) within one year were divided by the total number of all insured persons from sample 1 of the respective reporting year.

The annual incidence was calculated individually for each year from 2010 to 2015 (except for the first reporting year: 2009, as no new prescriptions could be identified due to missing data for the previous year). To this end, all insured persons who received a pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) within one year, but not in the previous year, were compared to the total number of all patients from sample 2 of the respective reporting year.

The areas of indications for P/G prescribing were analysed individually for each possible combination of the diagnoses "Epilepsy (G40.- | G41.-)","Generalised anxiety disorder (F41.1)" and "Pain (all ICD-codes including the term “pain”)”. The used pain related ICDs are illustrated in the supplementary material. In addition, insured persons in Sample 3, to whom one of the above-mentioned diagnosis groups was assigned in parallel to the P/G prescription within a quarter, were divided by all insured persons in Sample 3. These calculations were made individually for each reporting year from 2010 to 2015.

To answer the question of which pain-related diagnoses P/G was newly prescribed, the percentage distribution of all coded ICD-10 pain diagnoses of the insured persons from sample 4 was presented first. Furthermore, the diagnoses were classified into the following three categories: Diagnoses with an

improved evidence (via controlled randomised studies) for P/G were classified as "**typical neuropathic pain** disorders for which there is a demonstrable **benefit of a P/G** therapy" [2–5]. Diseases with a potentially neuropathic genesis based upon aetiology/anatomical deliberations, independent from the therapeutic benefit of P/G [9] were classified as "pain, **possibly** of **neuropathic** or partial-neuropathic cause for which there is **no demonstrable benefit of P/G**". All other pain diagnose, were labelled as "**non-neuropathic** pain". The ICD-10 diagnosis classification is presented as supplementary data.

The calculation of the number of follow-up prescriptions/rate of discontinuation according to new P/G prescriptions was based on sample 5 and relates to the year 2013 plus two years of follow-up observation period (up to max. 2015). If in the two-year follow-up period no P/G prescription occurred for at least two consecutive quarters, this was defined as a discontinuation of therapy. The percentage of insured persons who discontinued therapy and the number of individual prescriptions up to termination were presented.

2.4 Patient and Public Involvement

This work focusses on the prescribing practice of P/G in pain therapy, which enable a critical reflection of this drugs and probably prevent over- and/or undertreatment. This secondary data analysis does not involve individuals. We did no recruitment. Patients were not involved in the study development. Beside this publication, we present the data of this analysis on conferences.

3. Results

3.1. Prevalence and incidence for P/G prescriptions

From 2009-2015, 1.3% (52,774/3,948,482) of insured persons were prescribed at least one P/G prescription. The prevalence of prescriptions increased from 1.1% in 2009 to 1.6% per annum in 2015 (Table 1a).

Table 1a: **Annual prevalence** for pregabalin/gabapentin prescriptions 2009-2015

Year	Number of insured persons with P/G prescriptions	Number of total insured persons	Prevalence per 100,000 insured persons
2009	41,083	3,822,333	1,074.8
2010	46,225	3,890,247	1,188.2
2011	50,230	4,027,591	1,247.1
2012	53,389	4,019,944	1,328.1
2013	56,358	4,010,383	1,405.3
2014	60,306	3,998,004	1,508.4
2015	61,828	3,870,869	1,597.3
Mean value 2009-2015	52,774	3,948,482	1,335.6

Table 1b: **Prevalence** for pregabalin/gabapentin prescriptions grouped by age and stratified by gender in 2015

Age group	Total prevalence per 100,000 insured persons	Prevalence per 100,000 insured women	Prevalence per 100,000 insured men
0-17	13.4	17.5	9.6
18-35	249.2	289.4	210.0
36-55	1,042.5	1,213.2	874.9
56-75	2,899.6	3,146.0	2,634.9
76+	5,302.1	5,709.5	4,658.1
Total	1,597.3	1,869.7	1,312.8
Total 18+	1,894.0	2,197.1	1,571.7

The prescription rate was highest in the 76+ age group (5,302 persons per 100,000 insured persons in 2015) (Table 1b). The prescription for minors, on the other hand, at 13.4 per 100,000 insured persons, was low. Compared to men, women were prescribed P/G more frequently (women: a total of 1,869.7 per 100,000 insured persons; men: a total of 1,312.8 per 100,000 insured persons). Like prescription prevalence, the rate of new P/G prescription increased annually (Table 2).

Table 2: **Annual incidence** for pregabalin/gabapentin – **new** prescriptions 2010-2015			
Year	**Number of insured persons with new P/G prescriptions**	**Number of total insured persons**	**Incidence per 100,000 insured persons**
2010	22,776	3,701,696	615.3
2011	23,121	3,717,582	621.9
2012	24,750	3,977,347	622.3
2013	25,784	3,966,813	650.0
2014	27,613	3,952,306	698.7
2015	26,526	3,757,502	705.9
Mean value 2010-2015	25,095	3,845,541	652.4

3.2. Area of application

Considering the three applications approved for P/G, it was found that the majority (77.9%) of P/G recipients had only a pain diagnosis and there was no evidence of epilepsy or anxiety disorder (Table 3).

Table 3: **Diagnoses** in patients with pregabalin/gabapentin prescriptions in 2015 (n=61,828)		
ICD diagnoses	**Number of insured persons with P/G prescriptions**	**As a percentage**
Pain * (exclusive)	48,190	77.9
Epilepsy ** (exclusive)	793	1.3
Anxiety disorder *** (exclusive)	707	1.1
Pain + anxiety disorder	2,404	3.9
Pain + epilepsy	2,222	3.6
Pain + epilepsy + anxiety disorder	162	0.3
Epilepsy + anxiety disorder	49	0.1
No pain, epilepsy or anxiety disorder	7,198	11.6
* all ICD-10 pain diagnoses listed in the supplementary information ** ICD codes: G40.- | G41.- *** ICD codes: F41.1		

There was no evidence for the approved application diagnoses for 11.6% of the P/G recipients. P/G recipients exclusively with a diagnosis of epilepsy or anxiety (epilepsy: 1.3%; anxiety 1.1%) were the minority. The percentage of new P/G recipients (excluding pain diagnoses) increased continuously

over the years. The proportion of existing epilepsy and anxiety diagnoses remained relatively constant in the new P/G prescriptions group.

3.3. Application in pain patients

After excluding epilepsy patients, 25,251 insured persons remained under new P/G prescription, whose pain diagnoses were analysed. A typical neuropathic pain disorder was present in one quarter of all new P/G recipients (25.7%), Table 4.

Table 4: **Pain-related diagnoses** in patients with new pregabalin/gabapentin prescriptions in 2015 (n=25,251)

Pain-related diagnoses		**Number of insured persons**	**As a percentage**
1	Non-neuropathic pain * (exclusive)	2,951	11.7
2	Typical neuropathic pain disorder ** (exclusive) (demonstrable benefit of a P/G therapy)	1,218	4.8
3	Pain with possible neuropathic or partial-neuropathic cause *** (exclusive) (no demonstrable benefit of P/G)	3,025	12.0
1 and 2		1,295	5.1
1 and 3		10,756	42.6
2 and 3		1,010	4.0
1 and 2 and 3		2,990	11.8
neither 1, 2 nor 3		2,006	7.9

For the majority (70.4%) of new recipients, a diagnosis was made in which a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of P/G. The three most frequent representatives in this category were the diagnoses "M544_Lumboischialgia" (5,836/25,251),"M5416_Radiculopathy: Lumbar region" (4,978/25,251) and "M542_Cervical neuralgia" (4,543/25,251). In 19.6% of the cases, there was exclusively only a "non-neuropathic pain diagnosis" or "no pain diagnosis".

3.4. Discontinuation

Within the follow-up period, 85% (16,573/19,501) of insured persons who received a new P/G prescription due to pain (excluding patients with epilepsy diagnosis) were again discontinued within two years. For the majority of the persons, who have discontinued, the discontinuation occurred within a short period. Thus, in 61.1% of the cases, there was no follow-up prescription after the initial

prescription (number of follow-up-prescriptions / proportion in percent: 1/13.2%; 2/7.5%; 3/5.4%; ≥4/12.8%). The proportion of P/G insured persons with regular follow-up prescriptions over the follow-up period was 15% (2,928/19,501).

4. Discussion

The prescription figures for pregabalin and gabapentin increased annually from 2009 to 2015. The majority of patients (78%), who are receiving P/G, have a pain diagnosis. In patients who received new P/G prescriptions, only about one quarter (25.7%) had a typical neuropathic pain disorder with a demonstrable benefit of a P/G therapy. For the remaining new P/G recipients (74.3%), there was either no diagnosis of neuropathic pain or a diagnosis in which a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of P/G. The rate of discontinuation for P/G was high; based on new prescriptions, 51.9% of cases did not receive a follow-up prescription within two years.

The increasing number of P/G prescriptions found in this analysis coincides with data from the IMS health database from the United States [6, 7]. Goodman et al. state in an issue of the New England Journal of Medicine in August 2017, that growth of P/G prescriptions was likely in “chronic non-cancer pain” as an alternative to opiates [7]. The in our work founded, steadily increasing number of prescriptions with a constant incidence of purely neuropathic pain disorders indicates that P/G is increasingly being used in patients with "mixed chronic pain ("mixed pain")". "Mixed pain" refers to chronic pain syndromes in which a mixture of nociceptive and neuropathic pain components is assumed [10, 11]. Instruments specially developed for this purpose, such as the painDETECT questionnaire, are designed to identify the neuropathic pain component [12] and are promoted accordingly. However, the pre-approval P/G studies only included patients with pure neuropathic pain as a result of damage to somatosensory nerve structures, e.g. with post-zoster neuralgia or diabetic polyneuropathy. High-quality qualitative studies on the efficacy of P/G in patients with mixed chronic pain are not yet available [13]. In the current edition of the guideline "Non-specific low back pain", the NVL guideline group also opposes a screening using painDETECT [14] due to a lack of evidence. The increasing prescribing rate among elderly might depend on the fact that chronic pain diagnosis generally increases by age [15].

In consideration of the pain diagnoses, which are coded in parallel to new P/G prescriptions, the question arises as to which diagnoses should be classified as neuropathic or non-neuropathic. In the S1 guideline "Diagnostics of neuropathic pain" [9] of the German Society of Neurology, for example, in addition to the pure neuropathic pain syndromes with damage to somatosensory nerve structures, pain diagnoses in which a neuropathic component is pathophysiologically conceivable, such as "lumboischialgia" or “radiculopathy”, are classified as neuropathic. The pain of these conditions is typically caused by nerve irritation, but this does not necessarily constitute damage. In these cases, there is often no evidence of benefit for the application of P/G. In this regard, an RCT published in March 2017 by Mathieson et al. showed the non-benefit of pregabalin [16]. Within the scope of this project, we decided to differentiate between "typical neuropathic pain disorder" with a

demonstrable benefit of P/G therapy and "pain, possibly with neuropathic or partially-neuropathic cause" with no evidence for the application of P/G. Subsequently, a typical neuropathic pain disorder is presented exclusively in one fifth of the new P/G prescriptions. This phenomenon is increasingly being described and critically discussed internationally [7, 17]. Abroad, there is also an increasing reference to the fact that P/G is also abused by addicts as a drug booster [18, 19].

The high discontinuation rate suggests three possible causes: First, the pain might be disappeared. Second, the hoped-for pain-relieving effect is not achieved. Thirdly, the therapy is discontinued due to adverse effects. Ultimately, P/G was prescribed as a long-term therapy only for a small minority. This is thought to be the typical neuropathic pain cases in which P/G has been shown to have an effect. In all other cases, the discontinued therapy trial underlines that the widely practised and promoted strategy of using P/G also in mixed chronic pain patients is not useful. The cause of pain in these cases is multifactorial and usually cannot be solved by medicine. Finally, we are not able to perceive the real reasons for the high discontinuation rate on the base of this routine data. To answer the question, a patient-based survey might be the first choice to investigate this question.

The discrepancy between the high number of prescriptions and the discontinuation rate, as a potentially indirect parameter of a clinically unconvincing effect, arises the question to the motives for the high number of prescriptions. We speculate, that one possible motive for doctors to prescribe it may be the one-dimensional biomedical understanding of chronic pain, out of which pain symptoms are too often answered with the prescription of a painkiller rather than with non-medicinal measures or counselling. Furthermore, there is no convincing therapeutic approach for the effective treatment of chronic pain patients to date. Multimodal therapy programmes are not sufficiently available and, in their current inpatient or short-term outpatient configuration, do not solve the problems of the continuous care situation in established practices. Frustration among both doctors and patients may trigger desperate measures such as the use of newer antiepileptic medicine. Furthermore, the marketing by the pharmaceutical industry [7], among others, which was specifically targeted at the treatment of mixed-pain patients with neuropathic symptoms, may play an important role.

Altogether, the results of this analysis provide an indication of overprescribing of P/G. On the one hand, it means that several patients probably take unnecessary drugs going along with the risk of polypharmacy, potential side effects and interaction. An on the other hand, it implies a high economic burden for the health care system. For example, the costs for pregabalin has been doubled from 2012 to $4.4 billion in 2016 in the United States [6, 7]. German data describe the same trends [2]. There are possible savings for health insurance funds.

The secondary data analysis, which is based on accounting data on the utilisation of insured persons from health insurance funds, can lead to systematic restrictions [20]. The variable "P/G consumption" can be considered as a valid indicator because P/G is only available on prescription. However, the operationalisation of the pain-related diagnosis variables is more challenging due to the fact, that the diagnosis coding maybe insufficiently coded in individual cases. One possibility are random errors during the diagnosis coding, which result in a potential bias in both directions (more or less than in reality). Another possibility may be, that doctors prefer to code clear neuropathic diagnoses to justify the prescription even in cases where the neuropathic nature is unclear. This might result in a bias, where the proportion of evidence-based indications is even lower in reality. In the diagnosis coding of unspecific low back pain as well, systematic misclassifications that tend towards overestimation are likely, since they are often routinely coded as "lumboischialgia" / “Radiculopathy: Lumbar region” or unspecific neck pain as "cervical neuralgia”.

According to international literature, G/P has also sometimes used in off-label indications like hot flush, restless leg, multiple sclerosis [21]. Our methodologically approach, does not account these potentially off label indications, which may lead to a bias. Patients would be mistakenly assumed to be using P/G for a non-neuropathic pain condition, when in fact they were using it for such an off-label indication.

Conclusion:

The results show that chronic pain patients often get pregabalin or gabapentin independent from a neuropathic pain diagnose. The high rate of discontinuation indicates that the anticipated therapeutic effects are lacking and/or adverse effects occur.

5. Study protocol

The study protocol is available on request. Please contact: annika.viniol@staff.uni-marburg.de.

6. Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

7. Competing interests

The authors declare that they have no competing interests.

9. Authors' contributions

AV planned the study, discussed the results and wrote the manuscript. TP and LH analyzed data and discussed the manuscript. KMK gave support to study design and discussed the manuscript. JW, JH, NDB and AB discussed the results and the manuscript.

10. Reporting statement

Data analysis and reporting style is in accordance with the "German Reporting Standard for Secondary Data Analyses" (STROSA).

11. Patient consent

Due to the nature of secondary data analysis, no patient consent is required.

12. Data sharing statement

Data used in the analyses are entrusted in the Institute for Applied Health Research Berlin. Please contact: jochen.walker@hrisk.de

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The classification criteria of the pain-related diagnosis	
ICD-10 pain code "not neuropathic"	
F413	fear/tension- type pain syndrome
F4534	psychogenic painful micturition
F4539	psychogenic pain of the abdomen
F4540	continuing somatoform disorder
F4541	chronic pain with somatic and psychological factors
G440	cluster headache
G441	vasomotor headache
G442	tension headache
G443	chronic posttraumatic headache
G444	headache caused by drugs
G448	other headache without detailed specification
G501	atypical facial pain
H571	eye pain
I702	arteriosclerosis of the extremities: physical stress induced leg pain
L905	cicatrix pain
M2550	joint pain: multiple sites
M2551	joint pain: shoulder region (clavicula, scapula, acromioclavicular-/shoulder-/sternoclavicular joints)
M2552	joint pain: upper arm (humerus, elbow joint)
M2553	joint pain: forearm (radius, ulna, wrist)
M2554	joint pain: hand (finger, carpus, metacarpus)
M2555	joint pain: pelvic region and tigh (pelcis, femur, buttocks, hip, hip joint, sacroiliac joint)
M2556	joint pain: lower leg (fibula, tibia, knee joint)
M2557	joint pain: ankle and foot (tasal, metratarsal, toes, ankle, subtalar joint, other ankle joints)
M2558	joint pain: multiple sites (neck, head, rips, torso, spine)
M2559	joint pain: multiple localisation
M545	back pain
M546	pain in area of thoracal spine
M5480	other back pain: different areas of the spine
M5481	other back pain: atlanto-occipital joint
M5482	other back pain: cervical area
M5483	other back pain: cervical-thoracal area
M5484	other back pain: thoracal area
M5485	other back pain: thoracal-lumbar area
M5486	other back pain: lumbar area
M5487	other back pain: lumbar-sacral area
M5488	other back pain: sacral area
M5489	other back pain: not detailed localisation
M5490	back pain- nondetailed specification: several localisations of the spine
M5491	back pain- no detailed specification: atlanto-occipital joint
M5492	back pain- no detailed specification: cervical area
M5493	back pain- no detailed specification: cervical-thoracal area
M5494	back pain- no detailed specification: thoracal area
M5495	back pain- no detailed specification: thoracal-lumbar area
M5496	back pain- no detailed specification: lumbar area
M5497	back pain- no detailed specification: lumbar-sacral area
M5498	ankle and foot (tasal, metratarsal, toes, ankle, subtalar joint, other ankle joints)
M5499	back pain- not detailed specification: area not detailed localisation
M7960	pain in extremities: several localisations
M7961	pain in extremities: shoulder region (clavicula, scapula, acromioclavicular-/shoulder-/sternoclavicular joint)
M7962	pain in extremities: upper arm (humerus, elbow joint)
M7963	pain in extremities: forearm (radius, ulna, wrist)
M7964	pain in extremities: hand (finger, carpus, metacarpus)
M7965	pain in extremities: pelvic region and tigh (pelcis, femur, buttocks, hip, hip joint, sacroiliac joint)
M7966	pain in extremities: lower leg (fibula, tibia, knee joint)
M7967	pain in extremities: ankle and foot (tasal, metratarsal, toes, ankle, subtalar joint, other ankle joints)
M7969	pain in extremities: no detailed localisation
M961	post disection syndome
N3981	flank pain
N940	intermenstrual pain
O294	headache after spinal cord anesthesia during pregnancy
O745	headache after spinal cord anesthesia during pregnancy
O894	headache after spinal cord anesthesia during childbed
R070	sore throat

R071	chest pain while breathing
R072	precordial pain
R073	other kind of chest pain
R074	chest pain: no detailed specification
R101	pain in the area of upper abdomen
R102	pain in the area of pelvis and perineum
R103	pain in other areas of lower abdomen
R104	other pains without detailed specification
R309	pains passing water without detailed specification
R51	headache
R520	acute pain
R521	chronic unswayable pain
R522	other chronic pain
R529	pain without detailed specification
ICD-10 pain codes "typically neuropathic" (Diagnoses with an improved evidence via controlled randomised studies)	
B02	herpes zoster
G500	trigeminal neuralgia
G530	post zoster neuralgia
G546	phantom pain
G9585	deafferentation pain due to spinal cord impairment
M797	fibromyalgia
T926	stump pain after traumatically arm amputation
T936	stump pain after traumatically leg amputation
ICD-10 pain code "possibly neuropathic" (diseases with a potentially neuropathic genesis based upon aetiology/anatomical deliberations, independent from the therapeutic benefit of P/G according to the guideline "diagnostic for neuropathic pain" from the German Society of Neurology [1]	
G130	paraneoplastic neuromyopathy and neuropathy
G521	diseases of N. glossopharyngeus and glossopharyngeus neuralgia
G56	mono neuropathy of the upper extremity
G57	mono neuropathy of the lower extremity
G58	other mono neuropathies
G59	mono neuropathy parallel to other illness
G60	hereditary and idiopathic neuropathy
G61	polyneuritis
G62	other polyneuropathies
G63	polyneuropathy parallel to other illness
G990	autonomous neuropathy through endokrinal and metabolic diseases
M501	cervical intervertebral disc degeneration with radiculopathy
M511	lumbal intervertebral disc degeneration with radiculopathy
M541	radiculopathy
M542	cervical neuralgia
M543	ischialgia
M544	lumboischialgia

1 Deutsche Gesellschaft für Neurologie. Diagnostik neuropathischer Schmerzen: S1-Leitlinie 2012.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Cross sectional study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-8*
Bias	9	Describe any efforts to address potential sources of bias	5-8
Study size	10	Explain how the study size was arrived at	Secondary data analysis
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Cross sectional study
		(*b*) Describe any methods used to examine subgroups and interactions	5-8
		(*c*) Explain how missing data were addressed	5-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	5-8

		Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Cross sectional study
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-11
		(b) Give reasons for non-participation at each stage	Secondary data analysis
		(c) Consider use of a flow diagram	Secondary data analysis
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	9-11
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Cross sectional study
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Cross sectional study
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Cross sectional study
		Cross-sectional study—Report numbers of outcome events or summary measures	9-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Cross sectional study
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Cross sectional study
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
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	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
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	13-14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prescribing practice of pregabalin / gabapentin in pain therapy – an evaluation of German claim data

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Prescribing practice of pregabalin / gabapentin in pain therapy – an evaluation of German claim data

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Abstract

Objectives: To describe the prevalence and incidence of pregabalin and gabapentin (P/G) prescriptions, typical therapeutic uses of P/G with careful attention to pain-related diagnoses, and discontinuation rates of P/G.

Design: A secondary data analysis.

Setting: Primary and secondary care in Germany.

Participants: Anonymous health insurance data of 4 million insured persons in the space of time from 2009 to 2015.

Intervention: None.

Primary and secondary outcome measures: We analysed the prescribing practice of P/G in general and investigate the use of P/G in pain therapy. We focused on the question due to which pain-related diagnoses patients get a new P/G prescription and illustrated the discontinuation rate of P/G.

Results: In 2015, 1.6% of insured persons were given a P/G prescription. Among the pain patients with new P/G prescriptions, only 25.7% had a typical neuropathic pain disorder. For the remaining new P/G recipients (74.3%), there was either no diagnosis of neuropathic pain or a diagnosis in which a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of P/G. The rate of discontinuation for P/G was high (85%). Among the patients who had discontinued medication, 61.1% did not receive one follow-up prescription within two years.

Conclusion: The results show that P/G is widely used in cases of chronic pain irrespective of neuropathic pain diagnoses. The high rate of discontinuation indicates that the anticipated therapeutic effects are lacking and/or adverse effects occur.

Trial registration: None.

Strengths and limitations of this study

- A secondary data analysis can lead to systematic restrictions.
- Diagnosis may have been insufficiently coded (documentation errors).
- The diagnosis coding of unspecific low back pain were often routinely coded as "lumboischialgia" or unspecific neck pain as "cervical neuralgia", which can cause a systematic misclassification tend towards overestimation of neuropathic diagnosis.
- We cannot conclude about the reasons of the detected prescribing practice.
- According to the secondary nature of the data, we have no information about the discontinuation reasons of P/G.

1. Introduction

Pregabalin and gabapentin, hereinafter referred to as pregabalin/gabapentin or P/G, belong to the group of "newer antiepileptic drugs", which were developed for the treatment of epilepsy. The European Medicines Agency approved pregabalin/gabapentin later also for the treatment of neuropathic pain (pregabalin (2004): “peripheral and central neuropathic pain”; gabapentin (2001): “peripheral neuropathic pain like painful diabetic neuropathy and post herpetic neuralgia” [1, 2]), which is now a common indication for these active ingredients [3].

Randomised controlled studies showed a slight improvement of specific forms of neuropathic pain disorder in patients treated with pregabalin/gabapentin compared to placebo [4–6]. The evidence for the rather small therapeutic effects of P/G, which are approved for the treatment of a rather minor condition spectrum, contradicts the prescription figures, which have been increasing steadily for years. According to the medication report, a total of 128 million daily doses of pregabalin/gabapentin were prescribed in 2015 [3]. The Lyrica product by Pfizer (pregabalin) was ranked 26th in 2015 on the list of the highest-revenue medicines under patent-protection with net GKV (statutory health insurance) costs of 170.3 million Euros [3]. US Prescription data describe the same trends. The gabapentin prescription rate has been raised from 39 million in 2012 to 64 million in 2016 in the United States [7, 8].

Increased P/G prescribing prompted us to further investigate prescribing practices. In this study, we answer the following questions:

1.) How high is the **annual prevalence** for the prescription of pregabalin/gabapentin among all insured persons from 2009 to 2015?

2.) How high is the **annual incidence** for new prescriptions of pregabalin/gabapentin among all insured persons from 2009 to 2015?

3.) What are the **indications for prescribing** (epilepsy/generalised anxiety disorder/pain) for patients with new pregabalin/gabapentin prescriptions from 2009 to 2015?

4.) Which **pain-related diagnoses** (neuropathic pain/non-neuropathic pain/mixed pain/no pain) are applicable to patients without epilepsy diagnosis with new pregabalin/gabapentin prescriptions in 2015?

5.) What is the **proportion** of patients for whom pregabalin/gabapentin was discontinued within two years after a new prescription for the treatment of pain?

- How many follow-up prescriptions were given to patients for whom pregabalin/gabapentin was discontinued?

2. Methods

2.1. Study design and database

The research questions were analysed in a cross-sectional design. The research database of the InGef – Institute for Applied Health Research was used as the data basis for this project. The InGef research database (formerly HRI Research Database) contains data on the utilisation and resource consumption of approx. 6.7 million anonymous insured persons from around 65 health insurance funds and company health insurance funds [9]. As long as the insured persons are members of these health insurances, their data are all-encompassing available in this database and were no competing to other databases. When insurant change to another insurance which is not linked with this database, their data are not available in this database. The present analysis was based on a sample of almost 4 million random samples from the research database, which closely represents the age and gender structure of Germany for the year 2013 (according to Destatis – Federal Statistical Office – 31.12.2013). The random sampling enables a longitudinal analysis of insured persons over the years 2009-2015. Beside sociodemographic data, it contains information on medicines prescribed by doctors and dispensed by pharmacies in the form of central pharma numbers (PZN) and ATC codes, ICD diagnoses from outpatient and inpatient areas as well as invoiced medical services.
The diagnoses and prescriptions can be linked to the anonymous insured person's name at the end of each quarter. In every analysis, all dosage forms and formulations of P/G were included.

2.2. Random sample analysis

The inclusion criteria, which vary according to the question, are presented below (for insured persons who meet the following criteria):

Sample 1 (Question 1 – ANNUAL PREVALENCE):
Persons who were insured for at least one day in the first quarter of the respective reporting year.

Sample 2 (Question 2 – ANNUAL INCIDENCE):
Persons who were insured for at least one day in the first quarter of the respective reporting year and 365 days in the previous year.

Sample 3 (Question 3 – INDICATIONS FOR PRESCRIBING FOR NEW PRESCRIPTION):
Persons who were insured for at least one day in the first quarter of the respective reporting year and 365 days in the previous year with at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) in the reporting year, but not in the four previous quarters (independent from diagnosis).

Sample 4 (Question 4 – PAIN DIAGNOSES IN THE NEW PRESCRIPTION):
Persons who were insured for at least one day in the first quarter of 2015 and fulfil the following criteria: no coded epilepsy diagnosis (G40.- | G41.-) in the years 2014-2015; no prescription of antiepileptic medication (all N03 codes) in 2014; at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) in 2015

Sample 5 (Question 5 – DISCONTINUATION):
Persons who were insured for at least one day in the first quarter of 2013 and fulfil the following criteria: no coded epilepsy diagnosis (G40.- | G41.-) in the years 2011-2013; no prescription of antiepileptic medication (all N03 codes) in the years 2011-2012; at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16), and in the same quarter of the prescription, at least one pain diagnosis in 2013

2.3 Data evaluation

The annual prevalence was calculated individually for each reporting year from 2009 to 2015. All insured persons who received at least one P/G prescription (ATC code: N03AX12 or N03AX16) within one year were divided by the total number of all insured persons from sample 1 of the respective reporting year.

The annual incidence was calculated individually for each year from 2010 to 2015 (except for the first reporting year: 2009, as no new prescriptions could be identified due to missing data for the previous year). To this end, all insured persons who received a pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) within one year, but not in the previous year, were compared to the total number of all patients from sample 2 of the respective reporting year.

The areas of indications for P/G prescribing were analysed individually for each possible combination of the diagnoses "Epilepsy (G40.- | G41.-)","Generalised anxiety disorder (F41.1)" and "Pain (all ICD-codes of pain syndromes)". The used pain related ICDs are illustrated in the supplementary material. In addition, insured persons in sample 3, to whom one of the above-mentioned diagnosis groups was assigned in parallel to the P/G prescription within a quarter, were divided by all insured persons in sample 3. These calculations were made individually for each reporting year from 2010 to 2015.

To answer the question of which pain-related diagnoses P/G was newly prescribed, the percentage distribution of all coded ICD-10 pain diagnoses of the insured persons from sample 4 was presented first. Furthermore, the diagnoses were classified into the following three categories: Diagnoses with an improved evidence for P/G via controlled randomised studies (assessed by the authors) were classified

as "**typical neuropathic pain** disorders for which there is a demonstrable **benefit of a P/G** therapy" [3–6]. Diseases with a potentially neuropathic genesis based upon aetiology/anatomical deliberations, independent from the therapeutic benefit of P/G [10] were classified as "pain, **possibly** of **neuropathic** or partial-neuropathic cause for which there is **no demonstrable benefit of P/G**". All other pain diagnose, were labelled as "**non-neuropathic** pain".

The calculation of the number of follow-up prescriptions/rate of discontinuation according to new P/G prescriptions was based on sample 5 and relates to the year 2013 plus two years of follow-up observation period (up to max. 2015). If in the two-year follow-up period no P/G prescription occurred for at least two consecutive quarters, this was defined as a discontinuation of therapy. The percentage of insured persons who discontinued therapy and the number of individual prescriptions up to termination were presented.

2.4 Patient and Public Involvement

This is a retrospective, secondary data analysis, so patients and the public were not involved directly. Beside this publication, we present the data of this analysis on conferences.

3. Results

3.1. Prevalence and incidence for P/G prescriptions

From 2009-2015, 1.3% (52,774/3,948,482) of insured persons were prescribed at least one P/G prescription. The prevalence of prescriptions increased from 1.1% in 2009 to 1.6% per annum in 2015 (Table 1a).

Table 1a: **Annual prevalence** for pregabalin/gabapentin prescriptions 2009-2015

Year	Number of insured persons with P/G prescriptions	Number of total insured persons	Prevalence per 100,000 insured persons
2009	41,083	3,822,333	1,074.8
2010	46,225	3,890,247	1,188.2
2011	50,230	4,027,591	1,247.1
2012	53,389	4,019,944	1,328.1
2013	56,358	4,010,383	1,405.3
2014	60,306	3,998,004	1,508.4
2015	61,828	3,870,869	1,597.3
Mean value 2009-2015	52,774	3,948,482	1,335.6

Table 1b: **Prevalence** for pregabalin/gabapentin prescriptions grouped by age and stratified by gender in 2015

Age group	Total prevalence per 100,000 insured persons	Prevalence per 100,000 insured women	Prevalence per 100,000 insured men
0-17	13.4	17.5	9.6
18-35	249.2	289.4	210.0
36-55	1,042.5	1,213.2	874.9
56-75	2,899.6	3,146.0	2,634.9
76+	5,302.1	5,709.5	4,658.1
Total	1,597.3	1,869.7	1,312.8
Total 18+	1,894.0	2,197.1	1,571.7

The prescription rate was highest in the 76+ age group (5,302 persons per 100,000 insured persons in 2015) (Table 1b). The prescription for minors, on the other hand, at 13.4 per 100,000 insured persons, was low. Compared to men, women were prescribed P/G more frequently (women: a total of 1,869.7 per 100,000 insured persons; men: a total of 1,312.8 per 100,000 insured persons). Like prescription prevalence, the rate of new P/G prescription increased annually (Table 2).

Table 2: **Annual incidence** for pregabalin/gabapentin – **new** prescriptions 2010-2015			
Year	**Number of insured persons with new P/G prescriptions**	**Number of total insured persons**	**Incidence per 100,000 insured persons**
2010	22,776	3,701,696	615.3
2011	23,121	3,717,582	621.9
2012	24,750	3,977,347	622.3
2013	25,784	3,966,813	650.0
2014	27,613	3,952,306	698.7
2015	26,526	3,757,502	705.9
Mean value 2010-2015	25,095	3,845,541	652.4

3.2. Area of application

Considering the three applications approved for P/G, it was found that the majority (77.9%) of P/G recipients had only a pain diagnosis and there was no evidence of epilepsy or anxiety disorder (Table 3).

Table 3: **Diagnoses** in patients with pregabalin/gabapentin prescriptions in 2015 (n=61,828)		
ICD diagnoses	**Number of insured persons with P/G prescriptions**	**As a percentage**
Pain * (exclusive)	48,190	77.9
Epilepsy ** (exclusive)	793	1.3
Anxiety disorder *** (exclusive)	707	1.1
Pain + anxiety disorder	2,404	3.9
Pain + epilepsy	2,222	3.6
Pain + epilepsy + anxiety disorder	162	0.3
Epilepsy + anxiety disorder	49	0.1
No pain, epilepsy or anxiety disorder	7,198	11.6
* all ICD-10 pain diagnoses listed in the supplementary information ** ICD codes: G40.- | G41.- *** ICD codes: F41.1		

There was no evidence for the approved application diagnoses for 11.6% of the P/G recipients. P/G recipients exclusively with a diagnosis of epilepsy or anxiety (epilepsy: 1.3%; anxiety 1.1%) were the minority. The percentage of new P/G recipients (excluding pain diagnoses) increased continuously

over the years. The proportion of existing epilepsy and anxiety diagnoses remained relatively constant in the new P/G prescriptions group.

3.3. Application in pain patients

After excluding epilepsy patients, 25,251 insured persons remained under new P/G prescription, whose pain diagnoses were analysed. A typical neuropathic pain disorder was present in one quarter of all new P/G recipients (25.7%), Table 4.

Table 4: **Pain-related diagnoses** in patients with new pregabalin/gabapentin prescriptions in 2015 (n=25,251)

Pain-related diagnoses		**Number of insured persons**	**As a percentage**
1	Non-neuropathic pain * (exclusive)	2,951	11.7
2	Typical neuropathic pain disorder ** (exclusive) (demonstrable benefit of a P/G therapy)	1,218	4.8
3	Pain with possible neuropathic or partial-neuropathic cause *** (exclusive) (no demonstrable benefit of P/G)	3,025	12.0
1 and 2		1,295	5.1
1 and 3		10,756	42.6
2 and 3		1,010	4.0
1 and 2 and 3		2,990	11.8
neither 1, 2 nor 3		2,006	7.9

For the majority (70.4%) of new recipients, a diagnosis was made in which a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of P/G. The three most frequent representatives in this category were the diagnoses "M544_Lumboischialgia" (5,836/25,251),"M5416_Radiculopathy: Lumbar region" (4,978/25,251) and "M542_Cervical neuralgia" (4,543/25,251). In 19.6% of the cases, there was exclusively only a "non-neuropathic pain diagnosis" or "no pain diagnosis".

The percentage distribution of the pain-related diagnoses showed slightly variation over the time. The portion of typical neuropathic pain disorders was 17.8% in 2011 and 18.6% in 2013; the portion of pain disorder with a potentially neuropathic component was 72.4 in 2011 and 73.8% in 2013; the portion of cases with "non-neuropathic pain diagnosis" or "no pain diagnosis" war 18.8% in 2011 and 20.6% in 2013.

3.4. Discontinuation

Within the follow-up period, 85% (16,573/19,501) of insured persons who received a new P/G prescription due to pain (excluding patients with epilepsy diagnosis) were again discontinued within two years. For the majority of the persons, who have discontinued, the discontinuation occurred within a short period. Thus, in 61.1% of the cases, there was no follow-up prescription after the initial prescription (number of follow-up-prescriptions / proportion in percent: 1/13.2%; 2/7.5%; 3/5.4%; ≥4/12.8%). The proportion of P/G insured persons with regular follow-up prescriptions over the follow-up period was 15% (2,928/19,501).

4. Discussion

The prescription figures for pregabalin and gabapentin increased annually from 2009 to 2015. The majority of patients (78%), who are receiving P/G, have a pain diagnosis. In patients who received new P/G prescriptions, only about one quarter (25.7%) had a typical neuropathic pain disorder with a demonstrable benefit of a P/G therapy. For the remaining new P/G recipients (74.3%), there was either no diagnosis of neuropathic pain or a diagnosis in which a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of P/G. The rate of discontinuation for P/G was high; based on new prescriptions, 51.9% of cases did not receive a follow-up prescription within two years.

The increasing number of P/G prescriptions found in this analysis coincides with data from the IMS health database from the United States [7, 8]. Goodman et al. state in an issue of the New England Journal of Medicine in August 2017, that growth of P/G prescriptions was likely in “chronic non-cancer pain” as an alternative to opiates [8]. Although the incidence of purely neuropathic pain disorders has been slightly increased in the last years, the extent of the increasing number of P/G prescriptions does not disproportionate. The steadily increasing number of prescriptions indicates that P/G is increasingly being used in patients with "mixed chronic pain” (mixed pain). "Mixed pain" refers to chronic pain syndromes in which a mixture of nociceptive and neuropathic pain components is assumed [11, 12]. Instruments specially developed for this purpose, such as the painDETECT questionnaire, are designed to identify the neuropathic pain component [13] and are promoted accordingly. However, the pre-approval P/G studies only included patients with pure neuropathic pain as a result of damage to somatosensory nerve structures, e.g. with post-zoster neuralgia or diabetic polyneuropathy. High-quality qualitative studies on the efficacy of P/G in patients with mixed chronic pain are not yet available [14]. In the current edition of the guideline "Non-specific low back pain", the NVL guideline group also opposes a screening using painDETECT [15] due to a lack of evidence. The increasing prescribing rate among elderly might depend on the fact that chronic pain diagnosis generally increases by age [16].

In consideration of the pain diagnoses, which are coded in parallel to new P/G prescriptions, the question arises as to which diagnoses should be classified as neuropathic or non-neuropathic.
In the S1 guideline "Diagnostics of neuropathic pain" [10] of the German Society of Neurology, for example, in addition to the pure neuropathic pain syndromes with damage to somatosensory nerve structures, pain diagnoses in which a neuropathic component is pathophysiologically conceivable, such as "lumboischialgia" or “radiculopathy”, are classified as neuropathic. The pain of these conditions is typically caused by nerve irritation, but this does not necessarily constitute damage. In these cases, there is often no evidence of benefit for the application of P/G. In this regard, an RCT published in March 2017 by Mathieson et al. showed the non-benefit of Pregabalin [17]. Within the

scope of this project, we decided to differentiate between "typical neuropathic pain disorder" with a demonstrable benefit of P/G therapy and "pain, possibly with neuropathic or partially-neuropathic cause" with no evidence for the application of P/G. Subsequently, a typical neuropathic pain disorder is presented exclusively in one fifth of the new P/G prescriptions. This phenomenon is increasingly being described and critically discussed internationally [8, 18]. Abroad, there is also an increasing evidence of P/G as drugs of abuse [19, 20].

Due to the nature of a routine data analysis, we are finally not able to perceive the real reasons for the high discontinuation rate on the base of this routine data. P/G might has been discontinued because of adverse effects, the resolution of pain by the reason that the hoped for pain-relieving effect has not been achieved. We speculate, that the high discontinuation rate reflects an ineffectiveness of P/G in chronic pain therapy.

The discrepancy between the high number of prescriptions and the discontinuation rate, as a potentially indirect parameter of a clinically unconvincing effect, raises the question of why a drug that is seen as ineffective might be so readily prescribed? Due to the complex nature of the doctor-patient-interaction while the treatment of chronic pain disorders, doctors might resort to second line medication to help their patients. Furthermore, the marketing by the pharmaceutical industry [8], among others, which was specifically targeted at the treatment of mixed-pain patients with neuropathic symptoms, may play an important role.

Altogether, the results of this analysis provide an indication of overprescribing of P/G. In consequence, several patients probably take unnecessary drugs going along with the typical polypharmacy risks (e.g. side effects, drug-drug interactions). Furthermore, overprescribing carries a high economic burden for the health care system. For example, the costs for pregabalin has been doubled from 2012 to $4.4 billion in 2016 in the United States [7, 8]. German data describe the same trends [3]. There are possible savings for health insurance funds.

The secondary data analysis, which is based on accounting data on the utilisation of insured persons from health insurance funds, can lead to systematic restrictions [21]. The variable "P/G consumption" can be considered as a valid indicator because P/G is only available on prescription. However, the operationalisation of the pain-related diagnosis variables is more challenging due to the fact, that the diagnosis coding maybe insufficiently coded in individual cases. One possibility are random errors during the diagnosis coding, which result in a potential bias in both directions (more or less than in reality). Another possibility may be, that doctors prefer to code clear neuropathic diagnoses to justify the prescription even in cases where the neuropathic nature is unclear. This might result in a bias, where the proportion of evidence-based indications is even lower in reality. In the diagnosis coding of

unspecific low back pain as well, systematic misclassifications that tend towards overestimation are likely, since they are often routinely coded as "lumboischialgia" / “Radiculopathy: Lumbar region” or unspecific neck pain as "cervical neuralgia”.

According to international literature, P/G has also sometimes used in off-label indications like hot flush, restless leg, multiple sclerosis [22]. Our methodologically approach, does not account these potentially off label indications, which may lead to a bias. Patients would be mistakenly assumed to be using P/G for a non-neuropathic pain condition, when in fact they were using it for such an off-label indication.

Conclusion:

Our analysis indicates that the increasing use of pregabalin and gabapentin is not in typical neuropathic pain conditions. Furthermore, high rates of discontinuation suggest that anticipated therapeutic effects are lacking and/or adverse effects occur. Clinicians and patients should exercise caution with regard to the use.

5. Study protocol

The study protocol is available on request. Please contact: annika.viniol@staff.uni-marburg.de.

6. Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

7. Competing interests

The authors declare that they have no competing interests.

9. Authors' contributions

AV planned the study, discussed the results and wrote the manuscript. TP and LH analyzed data and discussed the manuscript. KMK gave support to study design and discussed the manuscript. JW, JH, NDB and AB discussed the results and the manuscript.

10. Reporting statement

Data analysis and reporting style is in accordance with the "German Reporting Standard for Secondary Data Analyses" (STROSA).

11. Patient consent

Due to the nature of secondary data analysis, no patient consent is required.

12. Data sharing statement

Data used in the analyses are entrusted in the Institute for Applied Health Research Berlin. Please contact: jochen.walker@hrisk.de

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The classification criteria of the pain-related diagnosis	
ICD-10 pain code "not neuropathic"	
F413	fear/tension- type pain syndrome
F4534	psychogenic painful micturition
F4539	psychogenic pain of the abdomen
F4540	continuing somatoform disorder
F4541	chronic pain with somatic and psychological factors
G440	cluster headache
G441	vasomotor headache
G442	tension headache
G443	chronic posttraumatic headache
G444	headache caused by drugs
G448	other headache without detailed specification
G501	atypical facial pain
H571	eye pain
I702	arteriosclerosis of the extremities: physical stress induced leg pain
L905	cicatrix pain
M2550	joint pain: multiple sites
M2551	joint pain: shoulder region (clavicula, scapula, acromioclavicular-/shoulder-/sternoclavicular joints)
M2552	joint pain: upper arm (humerus, elbow joint)
M2553	joint pain: forearm (radius, ulna, wrist)
M2554	joint pain: hand (finger, carpus, metacarpus)
M2555	joint pain: pelvic region and tigh (pelcis, femur, buttocks, hip, hip joint, sacroiliac joint)
M2556	joint pain: lower leg (fibula, tibia, knee joint)
M2557	joint pain: ankle and foot (tasal, metratarsal, toes, ankle, subtalar joint, other ankle joints)
M2558	joint pain: multiple sites (neck, head, rips, torso, spine)
M2559	joint pain: multiple localisation
M545	back pain
M546	pain in area of thoracal spine
M5480	other back pain: different areas of the spine
M5481	other back pain: atlanto-occipital joint
M5482	other back pain: cervical area
M5483	other back pain: cervical-thoracal area
M5484	other back pain: thoracal area
M5485	other back pain: thoracal-lumbar area
M5486	other back pain: lumbar area
M5487	other back pain: lumbar-sacral area
M5488	other back pain: sacral area
M5489	other back pain: not detailed localisation
M5490	back pain- nondetailed specification: several localisations of the spine
M5491	back pain- no detailed specification: atlanto-occipital joint
M5492	back pain- no detailed specification: cervical area
M5493	back pain- no detailed specification: cervical-thoracal area
M5494	back pain- no detailed specification: thoracal area
M5495	back pain- no detailed specification: thoracal-lumbar area
M5496	back pain- no detailed specification: lumbar area
M5497	back pain- no detailed specification: lumbar-sacral area
M5498	ankle and foot (tasal, metratarsal, toes, ankle, subtalar joint, other ankle joints)
M5499	back pain- not detailed specification: area not detailed localisation
M7960	pain in extremities: several localisations
M7961	pain in extremities: shoulder region (clavicula, scapula, acromioclavicular-/shoulder-/sternoclavicular joint)
M7962	pain in extremities: upper arm (humerus, elbow joint)
M7963	pain in extremities: forearm (radius, ulna, wrist)
M7964	pain in extremities: hand (finger, carpus, metacarpus)
M7965	pain in extremities: pelvic region and tigh (pelcis, femur, buttocks, hip, hip joint, sacroiliac joint)
M7966	pain in extremities: lower leg (fibula, tibia, knee joint)
M7967	pain in extremities: ankle and foot (tasal, metratarsal, toes, ankle, subtalar joint, other ankle joints)
M7969	pain in extremities: no detailed localisation
M961	post disection syndome
N3981	flank pain
N940	intermenstrual pain
O294	headache after spinal cord anesthesia during pregnancy
O745	headache after spinal cord anesthesia during pregnancy
O894	headache after spinal cord anesthesia during childbed
R070	sore throat

R071	chest pain while breathing
R072	precordial pain
R073	other kind of chest pain
R074	chest pain: no detailed specification
R101	pain in the area of upper abdomen
R102	pain in the area of pelvis and perineum
R103	pain in other areas of lower abdomen
R104	other pains without detailed specification
R309	pains passing water without detailed specification
R51	headache
R520	acute pain
R521	chronic unswayable pain
R522	other chronic pain
R529	pain without detailed specification
ICD-10 pain codes "typically neuropathic" (Diagnoses with an improved evidence via controlled randomised studies)	
B02	herpes zoster
G500	trigeminal neuralgia
G530	post zoster neuralgia
G546	phantom pain
G9585	deafferentation pain due to spinal cord impairment
M797	fibromyalgia
T926	stump pain after traumatically arm amputation
T936	stump pain after traumatically leg amputation
ICD-10 pain code "possibly neuropathic" (diseases with a potentially neuropathic genesis based upon aetiology/anatomical deliberations, independent from the therapeutic benefit of P/G according to the guideline "diagnostic for neuropathic pain" from the German Society of Neurology [1]	
G130	paraneoplastic neuromyopathy and neuropathy
G521	diseases of N. glossopharyngeus and glossopharyngeus neuralgia
G56	mono neuropathy of the upper extremity
G57	mono neuropathy of the lower extremity
G58	other mono neuropathies
G59	mono neuropathy parallel to other illness
G60	hereditary and idiopathic neuropathy
G61	polyneuritis
G62	other polyneuropathies
G63	polyneuropathy parallel to other illness
G990	autonomous neuropathy through endokrinal and metabolic diseases
M501	cervical intervertebral disc degeneration with radiculopathy
M511	lumbal intervertebral disc degeneration with radiculopathy
M541	radiculopathy
M542	cervical neuralgia
M543	ischialgia
M544	lumboischialgia

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Cross sectional study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-8*
Bias	9	Describe any efforts to address potential sources of bias	5-8
Study size	10	Explain how the study size was arrived at	Secondary data analysis
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Cross sectional study
		(*b*) Describe any methods used to examine subgroups and interactions	5-8
		(*c*) Explain how missing data were addressed	5-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	5-8

		Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Cross sectional study
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-11
		(b) Give reasons for non-participation at each stage	Secondary data analysis
		(c) Consider use of a flow diagram	Secondary data analysis
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	9-11
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Cross sectional study
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Cross sectional study
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Cross sectional study
		Cross-sectional study—Report numbers of outcome events or summary measures	9-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Cross sectional study
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Cross sectional study
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
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	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
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	13-14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prescribing practice of pregabalin / gabapentin in pain therapy – an evaluation of German claim data

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Keywords:	Pain management < ANAESTHETICS, Diabetic neuropathy < DIABETES & ENDOCRINOLOGY, PRIMARY CARE

Title:

Prescribing practice of pregabalin / gabapentin in pain therapy – an evaluation of German claim data

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Abstract

Objectives: To analyse the prevalence and incidence of pregabalin and gabapentin (P/G) prescriptions, typical therapeutic uses of P/G with special attention to pain-related diagnoses and discontinuation rates.

Design: Secondary data analysis.

Setting: Primary and secondary care in Germany.

Participants: 4 million patients in the years 2009-2015 (Anonymous health insurance data).

Intervention: None.

Primary and secondary outcome measures: P/G prescribing rates, P/G prescribing rates associated with pain therapy, analysis of pain-related diagnoses leading to new P/G prescriptions and the discontinuation rate of P/G.

Results: In 2015, 1.6% of insured persons received P/G prescriptions. Among the pain patients firstly treated with P/G, as few as 25.7% were diagnosed with a typical neuropathic pain disorder. The remaining 74.3% had either not received a diagnosis of neuropathic pain or showed a neuropathic component that was pathophysiologically conceivable but did not support the prescription of P/G. High discontinuation rates were observed (85%). Among the patients who had discontinued the drug, 61.1% did not receive follow-up prescriptions within two years.

Conclusion: The results show that P/G is widely prescribed in cases of chronic pain irrespective of neuropathic pain diagnoses. The high discontinuation rate indicates a lack of therapeutic benefits and/or the occurrence of adverse effects.

Trial registration: None.

Strengths and limitations of this study

- Secondary data analysis can lead to systematic restrictions.
- Diagnosis may have been coded incorrectly, resulting in either under- or overestimation of neuropathic diagnoses.
- According to the secondary nature of our data, we cannot conclude about the reasons of the detected prescribing practice.
- We have no information about the discontinuation reasons of P/G.
- Our methodological approach does not include off-label indications of P/G.

1. Introduction

Pregabalin and gabapentin, hereinafter referred to as pregabalin/gabapentin or P/G, belong to the group of "newer antiepileptic drugs". As chemical analogues of the inhibitory neurotransmitter GABA (gamma-aminobutyric acid) they are classified as “gabapentinoids”. Originally developed for the treatment of epilepsy, the European Medicines Agency (EMA) approved P/G also for the treatment of neuropathic pain (pregabalin (2004): “peripheral and central neuropathic pain”; gabapentin (2001): “peripheral neuropathic pain like painful diabetic neuropathy and post herpetic neuralgia” [1, 2]), which is now a common indication for their prescription [3].

Randomised controlled studies reported a slight improvement in specific forms of neuropathic pain disorder for patients treated with pregabalin/gabapentin compared to placebo [4–6]. However, the obviously rather weak therapeutic effects of P/G and their comparatively small application area are contradicted by the prescription figures, which have been increasing steadily over the recent years. According to the German ‘medication report’ from Schwabe et al. (based on statutory health insurance data), a total of 128 million daily doses of pregabalin/gabapentin were prescribed in 2015 [3]. In 2015, Pfizer`s product Lyrica (pregabalin) was ranked 26th on the list of the highest-revenue medicines under patent-protection and produced net GKV (statutory health insurance) costs of 170.3 million Euro [3]. US Prescription data describe the same trends: from 2012 to 2016, the prescription rate of gabapentin increased from 39 to 64 million annual prescriptions. [7, 8].

In view of this general trend, we intended to further investigate the prescribing practices. This study aims to address the following points in question:

1.) The **annual prevalence** for the prescription of pregabalin/gabapentin among all insured persons from 2009 to 2015

2.) The **annual incidence** for new prescriptions of pregabalin/gabapentin among all insured persons from 2009 to 2015

3.) The **indications for new** pregabalin/gabapentin prescriptions (epilepsy/generalised anxiety disorder/pain) from 2009 to 2015

4.) **The Pain related diagnoses** (neuropathic pain/non-neuropathic pain/mixed pain/no pain) that lead to new pregabalin/gabapentin prescriptions to patients without epilepsy in 2015

5.) **The proportion** of patients who **discontinued** pregabalin/gabapentin **treatment within two years** after its new prescription for pain management and the **proportion** of **follow-up prescriptions** after discontinuation.

2. Methods

2.1. Study design and database

For this project, the Institute for Applied Health Research (InGef) database was analysed in a cross-sectional design. This research database (formerly HRI Research Database) contains anonymous data on the utilisation and resource consumption of approx. 6.7 million insured persons from about 65 health insurance funds and company health insurance funds [9]. As long as the insured persons are members of these health insurances, their data are all-encompassing available without overlap with other databases, which also means that if a person changes to an insurance that is not included, his or her data become unavailable. The present analysis is based on a random sample of almost 4 million data sets which closely represents the age and gender structure in Germany for the year 2013 (according to Destatis – Federal Statistical Office – 31.12.2013). The random sampling enables a longitudinal analysis of insured persons over the years 2009-2015. Besides sociodemographic data, it contains central pharma numbers (PZN) and ATC codes, ICD diagnoses from outpatient and inpatient areas as well as invoiced medical services. These data give information on medications prescribed by doctors and dispensed by pharmacies.

The diagnoses and prescriptions can be linked to the anonymous insured person's identification code at the end of each quarter. Each analysis included all dosage forms and formulations of P/G.

2.2. Random sample analysis

The following inclusion criteria vary according to the point in question:

Sample 1 (ANNUAL PREVALENCE):

Persons who were insured for at least one day in the first quarter of the respective reporting year.

Sample 2 (ANNUAL INCIDENCE):

Persons who were insured for at least one day in the first quarter of the respective reporting year and 365 days in the previous year.

Sample 3 (INDICATIONS FOR NEW PRESCRIPTION):

Persons who were insured for at least one day in the first quarter of the respective reporting year and 365 days in the previous year with at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) in the reporting year, but not in the four previous quarters (independent from diagnosis).

Sample 4 (PAIN DIAGNOSES, NEW PRESCRIPTION):

Persons who were insured for at least one day in the first quarter of 2015 and fulfil the following criteria: no coded epilepsy diagnosis (G40.- | G41.-) in the years 2014-2015; no prescription of antiepileptic medication (all N03 codes) in 2014; at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) in 2015.

Sample 5 (DISCONTINUATION, NEW PRESCRIPTION):
Persons who were insured for at least one day in the first quarter of 2013 and fulfil the following criteria: no coded epilepsy diagnosis (G40.- | G41.-) in the years 2011-2013; no prescription of antiepileptic medication (all N03 codes) in the years 2011-2012; at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16), and at least one pain diagnosis in the same quarter of the prescription in 2013.

2.3 Data evaluation

The annual prevalence was calculated individually for each reporting year from 2009 to 2015. The total of insured persons who received at least one P/G prescription (ATC code: N03AX12 or N03AX16) within one year was divided by the number of all insured persons from sample 1 of the respective reporting year.

The annual incidence was calculated individually for each year from 2010 to 2015 (except for the first reporting year 2009, as due to the lack of data for the previous year, new prescriptions could not be identified). To this end, all insured persons who had received a pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) within one year, but not in the previous year, were compared to the total number of all patients from sample 2 of the respective reporting year.

The areas of indications for P/G prescribing were analysed individually for each possible combination of the diagnoses "Epilepsy (G40.- | G41.-)","Generalised anxiety disorder (F41.1)" and "Pain (all ICD-codes of pain syndromes)". (For the pain related ICDs included, see supplementary material). In addition, the number of insured persons from sample 3 that were falling into one of these diagnosis groups and had concurrently received a P/G prescription within a quarter was divided by the number of all insured persons in sample 3. These calculations were applied to each reporting year from 2010 to 2015.

To answer question 4, we first analysed the percentage distribution of all coded ICD-10 pain diagnoses of the insured persons from sample 4, then classified the diagnoses into the following categories:

1) Diagnoses with an improved evidence for P/G (assessed by the authors via controlled randomised studies) were classified as "**typical neuropathic pain** disorders with **demonstrable benefit** from P/G therapy" [3–6].

2) Diseases from a potentially neuropathic genesis based upon aetiology/anatomical deliberations, without therapeutic benefit of P/G [10] were classified as "pain, **possibly** of **neuropathic** or partial-neuropathic cause for which there is **no demonstrable benefit of P/G**".
3) All other pain diagnoses were labelled as "**non-neuropathic pain**".

To calculate the number of follow-up prescriptions and the rate of discontinuation according to new P/G prescriptions, we analysed the sample 5 data from the year 2013 plus a follow-up observation period of two years (until 2015). Cases in which the patient had not received a P/G prescription within at least two consecutive quarters, including the two-year follow-up period, were defined as discontinuation of therapy. This evaluation revealed the percentage of insured persons who discontinued therapy and the number of individual prescriptions before termination.

2.4 Patient and Public Involvement

Because the present study represents a retrospective secondary data analysis, patients and the public were not directly involved. Our work includes the presentation of our research at scientific conferences.

3. Results

3.1. Prevalence and incidence of P/G prescriptions

From 2009-2015, 1.3% (52,774/3,948,482) of insured persons received at least one P/G prescription. As shown in table 1 a, the prevalence rate increased from 1.1% in 2009 to 1.6% per annum in 2015.

Table 1a: **Annual prevalence** rates of pregabalin/gabapentin prescriptions, 2009-2015

Year	Number of insured persons with P/G prescriptions	Total number of insured persons	Prevalence per 100,000 insured persons
2009	41,083	3,822,333	1,074.8
2010	46,225	3,890,247	1,188.2
2011	50,230	4,027,591	1,247.1
2012	53,389	4,019,944	1,328.1
2013	56,358	4,010,383	1,405.3
2014	60,306	3,998,004	1,508.4
2015	61,828	3,870,869	1,597.3
Mean value 2009-2015	52,774	3,948,482	1,335.6

Table 1b: **Prevalence** rates of pregabalin/gabapentin prescriptions in 2015, stratified by age and gender

Age group	Total prevalence per 100,000 insured persons	Prevalence per 100,000 insured women	Prevalence per 100,000 insured men
0-17	13.4	17.5	9.6
18-35	249.2	289.4	210.0
36-55	1,042.5	1,213.2	874.9
56-75	2,899.6	3,146.0	2,634.9
76+	5,302.1	5,709.5	4,658.1
Total	1,597.3	1,869.7	1,312.8
Total 18+	1,894.0	2,197.1	1,571.7

In table 1 b, we present the prevalence rates in the year 2015 stratified by age and gender. The highest prescription rate was seen in the age group 76+ (5,302 persons per 100,000 insured persons in 2015). In contrast, the prescription rate for minors was comparatively low (13.4 per 100,000 insured persons), P/G was prescribed more frequently to women than to men (women: a total of 1,869.7 per 100,000 insured persons; men: a total of 1,312.8 per 100,000 insured persons).

Table 2 shows the annual incidence of P/G prescriptions from 2010-2015. As the prescription rate in general, the rate of new P/G prescriptions increased annually (Table 2).

Table 2: **Annual incidence** rates for **new** pregabalin/gabapentin **prescriptions** 2010-2015

Year	**Number of insured persons with new P/G prescriptions**	**Total Number of insured persons**	**Incidence per 100,000 insured persons**
2010	22,776	3,701,696	615.3
2011	23,121	3,717,582	621.9
2012	24,750	3,977,347	622.3
2013	25,784	3,966,813	650.0
2014	27,613	3,952,306	698.7
2015	26,526	3,757,502	705.9
Mean value 2010-2015	25,095	3,845,541	652.4

3.2. Areas of application

As mentioned earlier, P/G is approved for three applications: epilepsy, anxiety disorders, and neuropathic pain. However, our results show that that the majority (77.9%) of P/G recipients had only received a diagnosis of pain but had suffered neither from epilepsy nor anxiety disorder (Table 3).

Table 3: **Diagnostic reasons** for pregabalin/gabapentin prescriptions in 2015 (n=61,828)

ICD diagnoses	**Number of insured persons with P/G prescriptions**	**in per cent**
Pain * (exclusive)	48,190	77.9
Epilepsy ** (exclusive)	793	1.3
Anxiety disorder *** (exclusive)	707	1.1
Pain + anxiety disorder	2,404	3.9
Pain + epilepsy	2,222	3.6
Pain + epilepsy + anxiety disorder	162	0.3
Epilepsy + anxiety disorder	49	0.1
No pain, epilepsy or anxiety disorder	7,198	11.6
* all ICD-10 pain diagnoses listed in the supplementary information ** ICD codes: G40.- | G41.- *** ICD codes: F41.1		

In 11,6% of the cases, there was no evidence for any of the approved diagnoses for P/G prescription. P/G recipients who were diagnosed exclusively with epilepsy or anxiety (epilepsy: 1.3%; anxiety

1.1%) were in the minority. Although the incidence of P/G prescriptions (excluding pain diagnoses) have increased continuously over the years, the proportion of epilepsy and anxiety diagnoses remained relatively constant in the new P/G prescriptions group.

3.3. P/G application in pain patients

After the number of patients with epilepsy were excluded, 25,251 insured persons with new P/G prescriptions remained. For these we determined the type of pain diagnoses. As presented in table 4, it appears that one quarter of all new P/G recipients (25.7% (line B+D+F+G)) were diagnosed with typical neuropathic pain.

Table 4: **Pain-related diagnoses** in patients with new pregabalin/gabapentin prescriptions in 2015 (n=25,251)

Pain-related diagnoses			**Number of insured persons**	**in per cent**
A	1	Non-neuropathic pain (exclusive)	2,951	11.7
B	2	Typical neuropathic pain disorder (exclusive) (demonstrable benefit of a P/G therapy)	1,218	4.8
C	3	Pain with possible neuropathic or partial-neuropathic cause (exclusive) (no demonstrable benefit of P/G)	3,025	12.0
D	1 + 2		1,295	5.1
E	1 + 3		10,756	42.6
F	2 + 3		1,010	4.0
G	1 + 2 + 3		2,990	11.8
H	neither 1, 2 nor 3		2,006	7.9

For the majority (70.4% (line C+E+F+G in table 4)) of new recipients, a neuropathic component was pathophysiologically conceivable, but there was no characteristic indication for P/G treatment. The three most frequent examples of this category were the diagnoses "M544_Lumboischialgia" (5,836/25,251),"M5416_Radiculopathy: Lumbar region" (4,978/25,251) and "M542_Cervical neuralgia" (4,543/25,251). In 19.6% of the cases (lines A+H in table 4), we found only a "non-neuropathic pain diagnosis" or "no pain diagnosis".

The percentage distribution of the pain-related diagnoses varied only marginally over time (typical neuropathic pain disorders: 17.8% (2011) - 18.6% (2013); Pain disorder with a neuropathic component: 72.4 (2011) - 73.8% (2013); non-neuropathic pain diagnosis/no pain diagnosis: 18.8% (2011) - 20.6% (2013).

3.4. Discontinuation of P/G treatment

As many as 85% (16,573/19,501) of insured persons who had received a new P/G prescription due to pain (excluding patients with epilepsy diagnosis) discontinued their treatment within the 2-year follow-up period. In the majority, discontinuation occurred within a short period. 61.1% of the patients did not receive a follow-up prescription (number of follow-up-prescriptions / figures in per cent: 1/13.2%; 2/7.5%; 3/5.4%; ≥4/12.8%). In contrast, as few as 15% of the insured persons received regular follow-up P/G prescriptions (2,928/19,501).

4. Discussion

Our results reveal two contradictory trends: although the prescription figures for pregabalin and gabapentin increased annually in the investigation period, only about 25% of the patients with new P/G prescriptions showed a typical neuropathic pain disorder and a demonstrable benefit of a P/G therapy, in many cases resulting in discontinuation of this therapy.

These findings are in line with data from the United States of America ([8].

Although the incidence of purely neuropathic pain disorders has been slightly increasing in the last years, the increase in the P/G prescription figures does not disproportionate. The steady rise of prescriptions indicates that P/G is being applied progressively in patients with "mixed chronic pain" (mixed pain). "Mixed pain" refers to chronic pain syndromes in which a mixture of nociceptive and neuropathic pain components is assumed [11, 12].

Regarding the pain diagnoses which are coded parallel to new P/G prescriptions, the question arises which chronic pain diagnoses should be classified as neuropathic or non-neuropathic. A clear differentiation between these two definitions does not exist. The S1-guideline "Diagnostics of neuropathic pain" (S1 level: expert group recommendation) [10] of the German Society of Neurology offers a broad catalogue of neuropathic pain diagnoses. Besides classical neuropathic pain syndromes (e.g. post herpetic neuralgia) where somatosensory nerve structures are damaged, the authors [10] also present pain diagnoses in which a neuropathic component is pathophysiologically conceivable (for example by nerve irritation in diagnosis like "lumboischialgia" or "radiculopathy") but do not necessarily comprise damaged nerve structures. Due to the fact that a differentiation is not therapeutically relevant [13]), we decided to differentiate the neuropathic pain diagnoses according to the proven benefit of P/G: "typical neuropathic pain disorder" with a demonstrable benefit of P/G therapy versus "pain, possibly with neuropathic or partially-neuropathic cause" with no evidence for the application of P/G.

Due to the nature of a routine data analysis, we were not able to determine the personal reasons for discontinuation. These possibilities include adverse effects or an absence of the desired pain-relieving effect. We assume that the high discontinuation rate reflects an ineffectiveness of P/G in chronic pain therapy.

The discrepancy between the high number of prescriptions and the discontinuation rate, potentially indicating a clinically unconvincing effect, raises the question why this drug might be so readily prescribed. Due to the complex nature of the doctor-patient-interaction, especially in the face of a chronic pain disorder, doctors might resort to second line medication to help their patients. Furthermore, marketing strategies of the pharmaceutical industry [8], among others, that specifically target mixed-pain patients with neuropathic symptoms, may play an important role in their decision.

Altogether, the results of this analysis suggest an overprescribing of P/G. In consequence, numerous patients probably unnecessarily use medicine that is accompanied with polypharmacy risks (e.g. side effects, drug-drug interactions). Furthermore, overprescribing is a high economic burden for the health care system. For example, the costs for pregabalin has doubled from 2012 to $4.4 billion in 2016 in the United States [7, 8]. German data describe the same trends [3]. This might be a possibility for savings for health insurance funds.

However, secondary data analysis, which is based on accounting data on the utilisation of insured persons from health insurance funds, can lead to systematic restrictions [14]. While the variable "P/G consumption" can be considered a valid indicator (because P/G is only available on prescription), the operationalisation of the pain-related diagnosis variables represents a challenge, because diagnosis coding may happen insufficient. One possible reason are random errors that occur in the course of diagnosis coding, resulting in a potential bias in both directions (diagnoses appear more or less severe than in reality). Another reason may be the fact that doctors probably prefer to code clear neuropathic diagnoses to justify the prescription even in cases where the neuropathic nature is unclear. This can result in a lower proportion of evidence-based indications. On the other hand, misclassifications of unspecific low back pain can produce an overestimation, since these diagnoses are often routinely coded as "lumboischialgia" / “Radiculopathy: Lumbar region” or unspecific neck pain as "cervical neuralgia”.

According to international literature, P/G is sometimes also used in off-label indications like hot flush, restless leg, multiple sclerosis [15]. To avoid counting these cases erroneously as non-neuropathic pain conditions, our methodological approach does not include off-label indications.

Conclusion:

Our analysis leads to the assumption that the increasing use of pregabalin and gabapentin is not based on the diagnosis of typical neuropathic pain conditions. Furthermore, high discontinuation rates suggest that the anticipated therapeutic effect is lacking and/or adverse effects occur. Clinicians and patients should exercise caution regarding pregabalin and gabapentin prescriptions.

5. Study protocol

The study protocol is available on request. Please contact: annika.viniol@staff.uni-marburg.de.

6. Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

7. Competing interests

The authors declare that they have no competing interests.

9. Authors' contributions

AV planned the study, discussed the results and wrote the manuscript. TP and LH analyzed data and discussed the manuscript. KMK gave support to study design and discussed the manuscript. JW, JH, NDB and AB discussed the results and the manuscript.

10. Reporting statement

Data analysis and reporting style is in accordance with the "German Reporting Standard for Secondary Data Analyses" (STROSA).

11. Patient consent

Due to the nature of secondary data analysis, no patient consent is required.

12. Data sharing statement

Data used in the analyses are entrusted in the Institute for Applied Health Research Berlin. Please contact: jochen.walker@hrisk.de

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The classification criteria of the pain-related diagnosis	
ICD-10 pain code "not neuropathic"	
F413	fear/tension- type pain syndrome
F4534	psychogenic painful micturition
F4539	psychogenic pain of the abdomen
F4540	continuing somatoform disorder
F4541	chronic pain with somatic and psychological factors
G440	cluster headache
G441	vasomotor headache
G442	tension headache
G443	chronic posttraumatic headache
G444	headache caused by drugs
G448	other headache without detailed specification
G501	atypical facial pain
H571	eye pain
I702	arteriosclerosis of the extremities: physical stress induced leg pain
L905	cicatrix pain
M2550	joint pain: multiple sites
M2551	joint pain: shoulder region (clavicula, scapula, acromioclavicular-/shoulder-/sternoclavicular joints)
M2552	joint pain: upper arm (humerus, elbow joint)
M2553	joint pain: forearm (radius, ulna, wrist)
M2554	joint pain: hand (finger, carpus, metacarpus)
M2555	joint pain: pelvic region and tigh (pelcis, femur, buttocks, hip, hip joint, sacroiliac joint)
M2556	joint pain: lower leg (fibula, tibia, knee joint)
M2557	joint pain: ankle and foot (tasal, metratarsal, toes, ankle, subtalar joint, other ankle joints)
M2558	joint pain: multiple sites (neck, head, rips, torso, spine)
M2559	joint pain: multiple localisation
M545	back pain
M546	pain in area of thoracal spine
M5480	other back pain: different areas of the spine
M5481	other back pain: atlanto-occipital joint
M5482	other back pain: cervical area
M5483	other back pain: cervical-thoracal area
M5484	other back pain: thoracal area
M5485	other back pain: thoracal-lumbar area
M5486	other back pain: lumbar area
M5487	other back pain: lumbar-sacral area
M5488	other back pain: sacral area
M5489	other back pain: not detailed localisation
M5490	back pain- nondetailed specification: several localisations of the spine
M5491	back pain- no detailed specification: atlanto-occipital joint
M5492	back pain- no detailed specification: cervical area
M5493	back pain- no detailed specification: cervical-thoracal area
M5494	back pain- no detailed specification: thoracal area
M5495	back pain- no detailed specification: thoracal-lumbar area
M5496	back pain- no detailed specification: lumbar area
M5497	back pain- no detailed specification: lumbar-sacral area
M5498	ankle and foot (tasal, metratarsal, toes, ankle, subtalar joint, other ankle joints)
M5499	back pain- not detailed specification: area not detailed localisation
M7960	pain in extremities: several localisations
M7961	pain in extremities: shoulder region (clavicula, scapula, acromioclavicular-/shoulder-/sternoclavicular joint)
M7962	pain in extremities: upper arm (humerus, elbow joint)
M7963	pain in extremities: forearm (radius, ulna, wrist)
M7964	pain in extremities: hand (finger, carpus, metacarpus)
M7965	pain in extremities: pelvic region and tigh (pelcis, femur, buttocks, hip, hip joint, sacroiliac joint)
M7966	pain in extremities: lower leg (fibula, tibia, knee joint)
M7967	pain in extremities: ankle and foot (tasal, metratarsal, toes, ankle, subtalar joint, other ankle joints)
M7969	pain in extremities: no detailed localisation
M961	post disection syndome
N3981	flank pain
N940	intermenstrual pain
O294	headache after spinal cord anesthesia during pregnancy
O745	headache after spinal cord anesthesia during pregnancy
O894	headache after spinal cord anesthesia during childbed
R070	sore throat

R071	chest pain while breathing
R072	precordial pain
R073	other kind of chest pain
R074	chest pain: no detailed specification
R101	pain in the area of upper abdomen
R102	pain in the area of pelvis and perineum
R103	pain in other areas of lower abdomen
R104	other pains without detailed specification
R309	pains passing water without detailed specification
R51	headache
R520	acute pain
R521	chronic unswayable pain
R522	other chronic pain
R529	pain without detailed specification
ICD-10 pain codes "typically neuropathic" (Diagnoses with an improved evidence via controlled randomised studies)	
B02	herpes zoster
G500	trigeminal neuralgia
G530	post zoster neuralgia
G546	phantom pain
G9585	deafferentation pain due to spinal cord impairment
M797	fibromyalgia
T926	stump pain after traumatically arm amputation
T936	stump pain after traumatically leg amputation
ICD-10 pain code "possibly neuropathic" (diseases with a potentially neuropathic genesis based upon aetiology/anatomical deliberations, independent from the therapeutic benefit of P/G according to the guideline "diagnostic for neuropathic pain" from the German Society of Neurology [1]	
G130	paraneoplastic neuromyopathy and neuropathy
G521	diseases of N. glossopharyngeus and glossopharyngeus neuralgia
G56	mono neuropathy of the upper extremity
G57	mono neuropathy of the lower extremity
G58	other mono neuropathies
G59	mono neuropathy parallel to other illness
G60	hereditary and idiopathic neuropathy
G61	polyneuritis
G62	other polyneuropathies
G63	polyneuropathy parallel to other illness
G990	autonomous neuropathy through endokrinal and metabolic diseases
M501	cervical intervertebral disc degeneration with radiculopathy
M511	lumbal intervertebral disc degeneration with radiculopathy
M541	radiculopathy
M542	cervical neuralgia
M543	ischialgia
M544	lumboischialgia

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Cross sectional study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-8*
Bias	9	Describe any efforts to address potential sources of bias	5-8
Study size	10	Explain how the study size was arrived at	Secondary data analysis
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Cross sectional study
		(*b*) Describe any methods used to examine subgroups and interactions	5-8
		(*c*) Explain how missing data were addressed	5-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	5-8

		Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Cross sectional study
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-11
		(b) Give reasons for non-participation at each stage	Secondary data analysis
		(c) Consider use of a flow diagram	Secondary data analysis
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	9-11
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Cross sectional study
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Cross sectional study
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Cross sectional study
		Cross-sectional study—Report numbers of outcome events or summary measures	9-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Cross sectional study
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Cross sectional study
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
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	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
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	13-14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.