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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 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 Four 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 patients with pain first 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 2 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.

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 gamma-aminobutyric acid they are classified as 'gabapentinoids'. Originally developed for the treatment of epilepsy, the European Medicines Agency 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 postherpetic neuralgia'[1]), which is now a common indication for their prescription.[2]

Strengths and limitations of this study

- ► Secondary data analysis can lead to systematic restrictions.
- ► Diagnosis may have been coded incorrectly, resulting in either underestimation 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 pregabalin and gabapentin (P/G).
- ► Our methodological approach does not include off-label indications of P/G.

Randomised controlled studies reported a slight improvement in specific forms of neuropathic pain disorder for patients treated with P/G compared with placebo.[3–5] 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 and Paffrath (based on statutory health insurance data), a total of 128 million daily doses of P/G were prescribed in 2015.[2] In 2015, Pfizer's product Lyrica (pregabalin) was ranked 26th on the list of the highest revenue medicines under patent protection and produced net costs of 170.3 million Euro for the statutory health insurance.[2] US Prescription data describe the same trends: from 2012 to 2016, the prescription rate of gabapentin increased from 39 to 64 million annual prescriptions.[6 7]

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 P/G among all insured persons from 2009 to 2015.

2. The annual incidence for new prescriptions of P/G among all insured persons from 2009 to 2015.
3. The indications for new P/G 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 P/G prescriptions to patients without epilepsy in 2015.
5. The proportion of patients who discontinued P/G treatment within 2 years after its new prescription for pain management and the proportion of follow-up prescriptions after discontinuation.

METHODS
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.[8] 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 December 2013). The random sampling enables a longitudinal analysis of insured persons over the years 2009–2015. Besides socio-demographic data, it contains central pharma numbers (PZN) and Anatomical Therapeutic Chemical classification (ATC) codes, International Classification of Diseases (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.

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 1 day in the first quarter of the respective reporting year.

Sample 2 (annual incidence)
Persons who were insured for at least 1 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 1 day in the first quarter of the respective reporting year and 365 days in the previous year with at least one P/G 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 1 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 P/G prescription (ATC code: N03AX12 or N03AX16) in 2015.

Sample 5 (discontinuation, new prescription)
Persons who were insured for at least 1 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 P/G prescription (ATC code: N03AX12 or N03AX16), and at least one pain diagnosis in the same quarter of the prescription in 2013.

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 1 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 P/G prescription (ATC code: N03AX12 or N03AX16) within 1 year, but not in the previous year, were compared with 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 online supplementary file 1). 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:

Table 1A Annual prevalence rates of pregabalin/gabapentin (P/G) 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	1074.8
2010	46 225	3 890 247	1188.2
2011	50 230	4 027 591	1247.1
2012	53 389	4 019 944	1328.1
2013	56 358	4 010 383	1405.3
2014	60 306	3 998 004	1508.4
2015	61 828	3 870 869	1597.3
Mean value 2009–2015	52 774	3 948 482	1335.6

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	1042.5	1213.2	874.9
56–75	2899.6	3146.0	2634.9
76+	5302.1	5709.5	4658.1
Total	1597.3	1869.7	1312.8
Total 18+	1894.0	2197.1	1571.7

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'.[2–5]
2. Diseases from a potentially neuropathic genesis based on aetiology/anatomical deliberations, without 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'.
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 2 years (until 2015). Cases in which the patient had not received a P/G prescription within at least two consecutive quarters, including the 2-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.

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.

RESULTS

Prevalence and incidence of P/G prescriptions

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

In table 1B, 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+ (5302 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 1869.7 per 100 000 insured persons; men: a total of 1312.8 per 100 000 insured persons).

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

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

Table 2 Annual incidence rates for new pregabalin/gabapentin (P/G) 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

Table 3 Diagnostic reasons for pregabalin/gabapentin (P/G) prescriptions in 2015 (n=61 828)

ICD diagnoses	Number of insured persons with P/G prescriptions	%
Pain* (exclusive)	48 190	77.9
Epilepsy† (exclusive)	793	1.3
Anxiety disorder‡ (exclusive)	707	1.1
Pain+anxiety disorder	2404	3.9
Pain+epilepsy	2222	3.6
Pain+epilepsy+anxiety disorder	162	0.3
Epilepsy+anxiety disorder	49	0.1
No pain, epilepsy or anxiety disorder	7198	11.6

*All ICD-10 pain diagnoses listed in the supplementary information.
†ICD codes: G40.- | G41.-.
‡ICD codes: F41.1.

diagnoses remained relatively constant in the new P/G prescriptions group.

P/G application in patients with pain

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 (P/G) prescriptions in 2015 (n=25 251)

		Pain-related diagnoses	Number of insured persons	%
A	1	Non-neuropathic pain (exclusive)	2951	11.7
B	2	Typical neuropathic pain disorder (exclusive) (demonstrable benefit of a P/G therapy)	1218	4.8
C	3	Pain with possible neuropathic or partial-neuropathic cause (exclusive) (no demonstrable benefit of P/G)	3025	12.0
D	1+2		1295	5.1
E	1+3		10 756	42.6
F	2+3		1010	4.0
G	1+2+3		2990	11.8
H	neither 1, 2 nor 3		2006	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' (5836/25 251), 'M5416_Radiculopathy: Lumbar region' (4978/25 251) and 'M542_Cervical neuralgia' (4543/25 251). In 19.6% of the cases (lines A+H 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).

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. About 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 (2928/19 501).

DISCUSSION

Our results reveal two contradictory trends: although the prescription figures for P/G 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 USA.[7]

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.[10 11]

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)[9] of the German Society of Neurology offers a broad catalogue of neuropathic pain diagnoses. Besides classical neuropathic pain syndromes (eg, postherpetic neuralgia) where somatosensory nerve structures are

damaged, the authors[9] 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[12], 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,[7] 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 (eg, side effects, drug–drug interactions). Furthermore, overprescribing is a high economic burden for the healthcare system. For example, the costs for pregabalin has doubled from 2012 to \$4.4 billion in 2016 in the USA.[6 7] German data describe the same trends.[2] 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.[13] 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.[14] 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 P/G 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 P/G prescriptions.

REFERENCES

1. European medicines agency. Lyrica. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000546/human_med_000894.jsp&mid=WC0b01ac058001d124 (Accessed 17 Jul 2018).
2. Schwabe U, Paffrath D. *Arzneiverordnungs-report 2016*. Heidelberg: Springer, 2016.
3. Wiffen PJ, Derry S, Bell RF, *et al*. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2017;6:CD007938.
4. Moore RA, Straube S, Wiffen PJ, *et al*. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev* 2009;3:CD007076.
5. Backonja M, Beydoun A, Edwards KR, *et al*. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* 1998;280:1831–6.
6. QuintilesIMS Institute. Medicines Use and Spending in the U.S.: A Review of 2016 and Outlook to 2021 2017. https://structurecms-staging-psyclone.netdna-ssl.com/client_assets/dwonk/media/attachments/590c/6aa0/6970/2d2d/4182/0000/590c6aa069702d2d41820000.pdf?1493985952 (Accessed 16 Jul 2018).
7. Goodman CW, Brett AS. Gabapentin and pregabalin for pain - is increased prescribing a cause for concern? *N Engl J Med* 2017;377:411–4.
8. Andersohn F, Walker J. Characteristics and external validity of the German Health Risk Institute (HRI) Database. *Pharmacoepidemiol Drug Saf* 2016;25:106–9.

9. Deutsche Gesellschaft für Neurologie. *Diagnostik neuropathischer Schmerzen: S1-Leitlinie*, 2012.

10. Ibor PJ, Sánchez-Magro I, Villoria J, *et al*. Mixed Pain Can Be Discerned in the Primary Care and Orthopedics Settings in Spain: A Large Cross-Sectional Study. *Clin J Pain* 2017;33:1100–8.

11. Junker U, Baron R, Freynhagen R. Chronische Schmerzen: Das „mixed pain concept "als neue Rationale. *Dtsch Arztebl* 2004;101:A-1393 / B-1158 / C-1115.

12. Mathieson S, Maher CG, McLachlan AJ, *et al*. Trial of pregabalin for acute and chronic sciatica. *N Engl J Med* 2017;376:1111–20.

13. Laux G. Grenzen und Chancen der Verwendung von Routinedaten für die Versorgungsforschung. In: *Versorgungsforschung in der Hausarztpraxis. Ergebnisse aus dem CONTENT-Projekt 2006 bis 2009*.

14. Hamer AM, Haxby DG, McFarland BH, *et al*. Gabapentin use in a managed medicaid population. *J Manag Care Pharm* 2002;8:266–71.