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Proton pump inhibitors (PPI) in Germany: Status quo of a growing market

Proton pump inhibitors (PPIs) have been the leading therapy for upper gastrointestinal diseases, including gastroesophageal reflux disease and gastritis, for several decades. However, previous studies have shown that PPIs are often prescribed in the outpatient setting for too long a period of time without an indication or without following guidelines (1). In recent years, studies have been published that have pointed to positive associations between long-term PPI use and risks of chronic disease. In a prospective analysis conducted in China with 204,689 participants, regular use of PPIs was associated with a higher risk of type 2 diabetes, and the risk increased with increasing duration of use (2). The results of another retrospective, population-based cohort study in Taiwan, involving 56,785 PPI users and 56,785 control subjects, suggested that PPI use was associated with the risk of developing PD (3). Zhang et al. conducted a comprehensive literature search that included six studies with a total of 166,146 participants. The authors found a significant association between long-term use of PPIs and dementia risk in Europe in participants aged ≥ 65 years (4). More recently, Ahn et al. designed a real-world study with performance data from 7,696,127 individuals aged 40 years or older in Germany that supports the hypothesis that PPI use is associated with an increased risk of dementia (5).

>> In fact, there is no mention of dangerous side effects or worrying associations with serious illness when PPIs are prescribed according to guidelines and for a defined period of time. Each study concluded that physicians should exercise caution when prescribing PPIs for the long term (2-5). The key to mitigating adverse effects is the rational use of PPIs at the lowest effective dose and for the shortest possible duration.

A recent study from the UK shows that the volume of PPI prescribing remains high, although there is increasing evidence in the literature thatover-prescribing is occurring in relation toguideline recommendations (6) (7). No very recent data are available on the situation in Germany. The aim of this study was therefore to determine the actual quantity of prescribed and over-the-counter PPIs in Germany.

Methods

Several IQVIA databases were used for this retrospective study, covering all prescriptions billed to statutory and private health insurance funds in Germany as well as over-the-counter (OTC) sales. The analyses were conducted for the period November 2020 to October 2021 and in some cases November 2018 to October 2021 and were descriptive in nature. Data was mainly collected from IQVIATM 'PharmaScope National' (PSN) and IQVIA 'TM DPM' databases ('Der pharmazeutische Markt Deutschland').

IQVIATM 'PSN' data includes the dispensing of medicines by pharmacies for the SHI market, private prescriptions and cash sales based on the dispensing by public pharmacies. The data basis for the SHI market are SHI invoices issued by the pharmacy data centres. The proportion of private prescriptions and sales without a prescription are collected on the basis of a random sample of around 6,500 pharmacies. Market information on the mail-order business included German consumers' purchases from online pharmacies. A mail order panel forms the basis for this, which is supplemented by a projection.

IMSTM 'DPM' provides information on the purchasing behaviour of public pharmacies in Germany. The survey is based on a complete survey of wholesalers, supplemented by a projection of direct sales by pharmaceutical manufacturers to pharmacies. It is a full wholesale survey and a representative sample of pharmacies.

Results

During the one-year study period, 2.87 billion PPI tablets were sold, 97% of which were sold as prescriptions. Pantoprazole and omeprazole together accounted for 92% of prescription PPIs and 98% of over-the-counter sales (Fig. 1).

More than 93% of PPI prescriptions are issued by general practitioners. The prescribing market is very diverse - 94% of GPs prescribe PPIs with a low concentration level; 48% of GPs issue 80% of prescriptions. Nevertheless, there are also frequent prescribers, as around 20% of doctors issue around 45% of total prescriptions (Fig. 3)

95 million PPI tablets were sold over the counter; 96% of the over-the-counter PPI market was for self-medication.

The German over-the-counter (OTC) PPI market grew by an average of 14% per year over a three-year period (+11% from 2019 to 2020 and +16% from 2020 to 2021, Figure 4). Although the prescription market stagnated at a high level (+0.3% per year over four years until 2018), there was a decline in 2019 (-1.6%), which eventually reversed to growth of 2.0% in 2020. Larger packs proved to be more stable over time and are the most recent driver of growth in reimbursement in the PPI prescription market.I.

Discussion

This study shows the size and recent strong growth of the PPI market in Germany. In addition, for some years now it has been possible to purchase PPI preparations without a prescription in pharmacies, meaning that their consumption cannot be controlled by doctors. On the one hand, PPIs are an important therapy for numerous gastrointestinal diseases, on the other hand, it has been shown that unnecessarily prolonged PPI therapy can be associated with severe chronic diseases, even if no causal relationship has

been proven. Our results indicate a massive overuse of PPIs by patients in Germany.

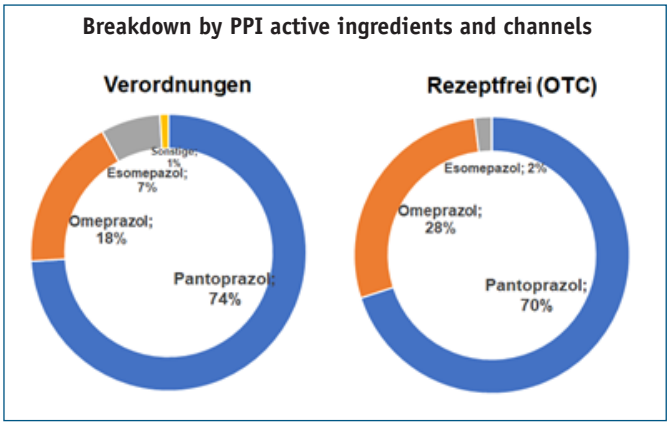


Fig. 1: *Breakdown by PPI active ingredients and channels: prescriptions versus over-the-counter (OTC) dispensing. Source: own illustration.*

However, this is not a purely German phenomenon. In addition to the study from the UK (7), reference should be made to a review of excessive medication consumption in low- and middle-income countries.

Its authors included 367 studies reporting on 5.1 million prescriptions in 80 countries. The most commonly over-utilised drug classes included antibiotics, psychotropic drugs, PPIs and antihypertensives. The main reasons for this were limited knowledge of side effects, polypharmacy, poor regulation and financial influences. Overuse of PPIs was reported in 53 studies (10).

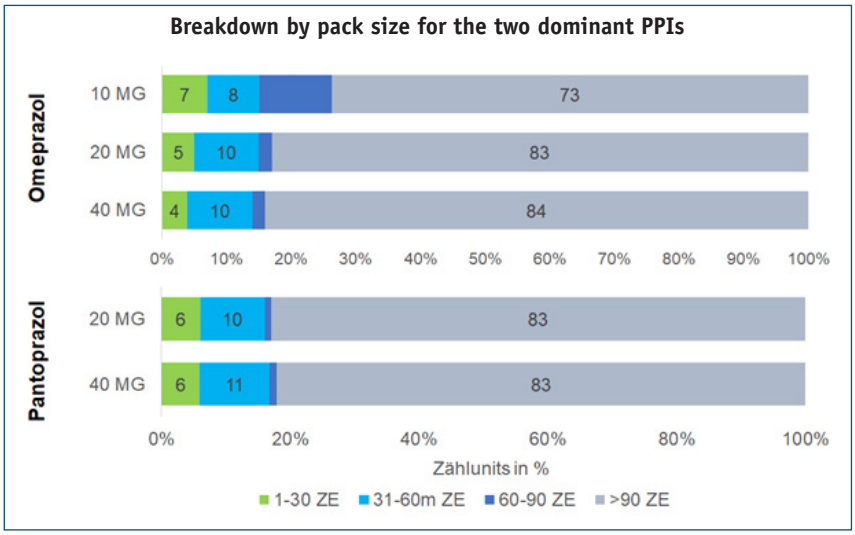


Fig 2: *Aufteilung nach Packungsgröße für die beiden dominierenden PPI: Pantoprazol und Omeprazol. Quelle: eigene Darstellung.*

The most common conditions for which PPIs are prescribed are gastro-oesophageal reflux disease, dyspepsia and eradication of Helicobacter pylori. In the case of eradication of Helicobacter pylori, a combination therapy with antibiotics is usually used to kill Helicobacter pylori (8). prazol and Omepra-However,immediate discontinuation of PPIs is not always advisable. It is recommended to start with a gradual dose reduction before discontinuing PPIs and to treat expected breakthrough symptoms associated with acid hypersecretion after discontinuation with an alginate preparation (11). This gradual approach may allay patients' fears of symptom return and increase patient confidence in the weaning process (6).

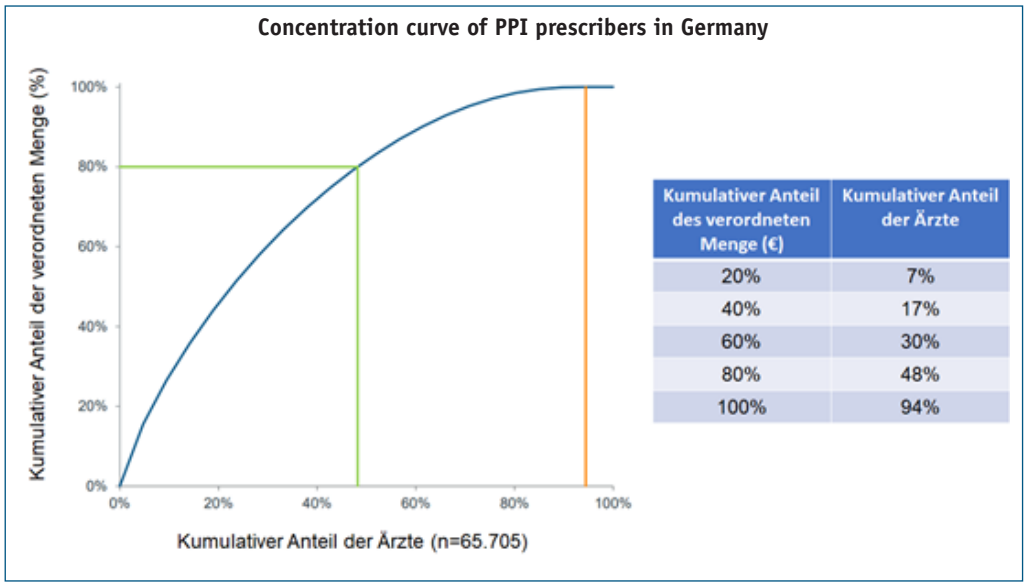
Del-Pino & Sanz conducted a narrative review to evaluate PPI discontinuation strategiesimplemented exclusively or in collaboration with primary careand to identify factors that may influence the success of these strategies. They concluded that the clarity and simplicity of de-escalation protocols, in which patients were informed of the actions to be taken in the event of symptom recurrence, and the training of clinicians responsible for de-escalation were the two most important factors (9).

Our study is one of the first in Germany to look at key market research analyses on PPI consumption in its clinical context.

The use of databases with partial full coverage of pharmacy data centres and wholesalers with the simultaneous analysis of prescriptions and OTC dispensing as well as physicians are the main strengths of these studies.

At the same time, the study also has some limitations, such as the lack of hypothesis-testing statistical methods and the lack of information on diagnoses and thus the possibility of differentiating between necessary and unnecessary PPI therapy.

In summary, the results of this study suggest the considerable size of the PPI market in Germany (based on prescriptions) and a simultaneous increase in over-the-counter PPI purchases and a recent increase in prescriptions. Further studies are needed, but it is even more important to use measures to regulate the overuse of PPIs by patients. <<



Kumulativer Anteil des verordneten Menge (€)	Kumulativer Anteil der Ärzte
20%	7%
40%	17%
60%	30%
80%	48%
100%	94%

Fig 3: *KConcentration curve of PPI prescribers in Germany. Source: own illustration.*

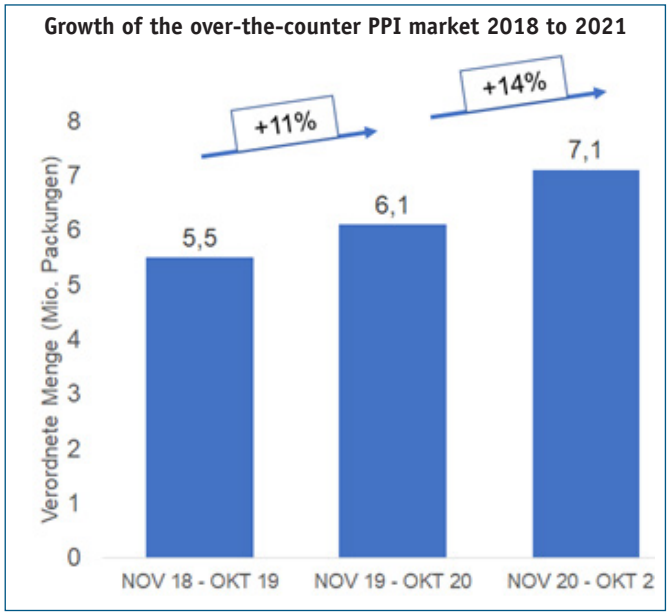


Fig. 4: *Growth of the over-the-counter PPI market in Germany in the period November 2018-October 2021. Source: Own illustration.*

Literature

1. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. Therap Adv Gastroenterol. 2012 Jul;5(4):219-32
2. Yuan J, He Q, Nguyen LH, Wong MCS, Huang J, Yu Y, Xia B, Tang Y, He Y, Zhang C. Regular use of proton pump inhibitors and risk of type 2 diabetes: results from three prospective cohort studies. Gut. 2021 Jun;70(6):1070-1077
3. Chen HL, Lei WY, Wang JH, Bair MJ, Chen CL. Proton pump inhibitor use and the risk for Parkinson's disease: A nationwide population-based study in Taiwan. Medicine (Baltimore). 2023 May 12;102(19):e33711
4. Zhang Y, Liang M, Sun C, Song EJ, Cheng C, Shi T, Min M, Sun Y. Proton pump inhibitors use and dementia risk: a meta-analysis of cohort studies. Eur J Clin Pharmacol. 2020 Feb;76(2):139-147
5. Ahn N, Wawro N, Baumeister SE, Nolde M, Gerlach R, Tauscher M, Günter A, Güntner F, Rückert-Eheberg IM, Meisinger C, Linseisen J. Time-Varying Use of Proton Pump Inhibitors and Cognitive Impairment and Dementia: A Real-World Analysis from Germany. Drugs Aging. 2023 May 13. doi: 10.1007/s40266-023-01031-7
6. Targownik LE, Fisher DA, Saini SD. AGA Clinical Practice Update on De-Prescribing of Proton Pump Inhibitors: Expert Review. Gastroenterology. 2022 Apr;162(4):1334-1342
7. Abrahami D, McDonald EG, Schnitzer M, Azoulay L. Trends in acid suppressant drug prescriptions in primary care in the UK: a population-based cross-sectional study. BMJ Open. 2020 Dec 7;10(12):e041529
8. Suzuki H, Nishizawa T, Hibi T. Helicobacter pylori eradication therapy. Future Microbiol. 2010 Apr;5(4):639-48
9. Del-Pino M, Sanz EJ. Analysis of deprescription strategies of proton pump inhibitors in primary care: a narrative review. Prim Health Care Res Dev. 2023 Feb 15;24:e14
10. Albarqouni L, Palagama S, Chai J, Sivananthajothy P, Pathirana T, Bakhit M, Arab-Zozani M, Ranakusuma R, Cardona M, Scott A, Clark J, Smith CF, Effa E, Ochodo E, Moynihan R; & the Overdiagnosis and Overuse of Healthcare Services in LMICs Network. Overuse of medications in low- and middle-income countries: a scoping review. Bull World Health Organ. 2023 Jan 1;101(1):36-61D
11. S2k-Leitlinie Gastroösophageale Refluxkrankheit und eosinophile Ösophagitis der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) März 2023 – AWMF-Registernummer: 021 – 013; www.dgvs.de/wp-content/uploads/2023/03/LL-Reflux_Leitlinie_final_13.03.23.pdf

Author statement

Kate Plehhova and Monika Häring are employees of Reckitt Benckiser. The data was prepared and analysed by IQVIA on behalf of Reckitt Benckiser. Karel Kostev was responsible for interpreting the data and writing the manuscript.

Citation

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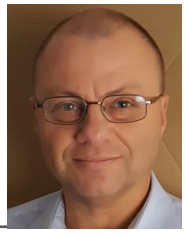
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