

# Trends in valproate use in patients in Germany between 2009 and 2017

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## ABSTRACT

**Objective:** The goal of this study was to analyze trends in valproate use in patients followed by neurologists and general practitioners in Germany between 2009 and 2017.

**Methods:** This study included all patients aged  $\geq 15$  years followed in 2009, 2013, and 2017 in neurological ( $N = 99$ ) and general ( $N = 499$ ) practices in Germany. Trends in valproate use were estimated based on the mean number of patients per practice who were prescribed valproate and the proportion of physicians prescribing it. Covariables included gender, age, and physician. This cross-sectional study uses descriptive statistics only.

**Results:** In total, 1,298,446 patients were followed in general and neurological practices in 2009, 1,358,160 in 2013, and 1,413,286 in 2017. The mean number of patients aged 15–45 years per practice with at least one valproate prescription decreased in neurological (men: 11.07 versus 9.92; women: 9.27 versus 5.88) and general practices (men: 0.82 versus 0.75; women: 0.60 versus 0.37) between 2009 and 2017. Moreover, the proportion of neurologists prescribing valproate in women between 15 and 45 years of age decreased over time (94% in 2009 versus 86% in 2017), and there was also a substantial decrease in the share of general practitioners prescribing valproate in men (47% versus 41%) and women between 15 and 45 years of age (37% versus 22%).

**Conclusion:** The proportion of men and women between 15 and 45 years of age receiving valproate decreased in neurological and general practices in Germany between 2009 and 2017.

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## 1. Introduction

Around one million people worldwide are taking valproate everyday [1]. Valproate, a  $\gamma$ -aminobutyric acid (GABA) agonist, was first approved in patients with epilepsy in France in the late 1960s, and its effectiveness in the context of severe epilepsy was documented in a randomized trial a few years later [2]. Currently, valproate is not only prescribed for epilepsy [3] but also for bipolar disorder [4] and migraine [5].

In recent years, there has been a growing evidence showing that valproate is a teratogenic drug and that the prescription of this molecule can have important deleterious effects in pregnant women [6]. A systematic review and meta-analysis found that the calculated incidence of births with congenital malformations was higher in women with epilepsy than in healthy women (7.08% versus 2.28%) and that the antiepileptic drug (AED) with the highest incidence was valproate (10.73%) [7]. Another meta-analysis of 29 cohort studies including 5100 infants and children exposed to AEDs in utero or during breastfeeding showed

that the use of valproate was associated with cognitive developmental delays, autism, and psychomotor developmental delays [8]. The teratogenic effects of valproate are likely to be explained by increased levels of GABA in the brain, inhibition of voltage-gated sodium channels, and inhibition of histone deacetylases [9].

As a result of the growing concern about the safety of valproate, there has been a recent decrease in the prevalence of use of this drug in different countries [10–14]. However, data from Germany are scarce [14], and, since more than 15,700 people living in this country were prescribed valproate in 2009 [15], this scarcity of data is of particular concern. Therefore, the goal of this study was to analyze trends in valproate use in patients followed by neurologists and general practitioners in Germany between 2009 and 2017.

## 2. Methods

### 2.1. Database

This study was based on data from the Disease Analyzer database (IQVIA), which compiles drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners and specialists [16]. Diagnoses (International Classification of Diseases,

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10th revision [ICD-10]), prescriptions (Anatomical Therapeutic Chemical [ATC] Classification system), and the quality of reported data are being monitored by IQVIA based on a number of criteria (e.g., completeness of documentation, linkage between diagnoses, and prescriptions).

In Germany, the sampling methods used for the selection of physicians' practices were appropriate for obtaining a representative database of general and specialized practices [16]. Prescription statistics for several drugs were very similar to data available from pharmaceutical prescription reports. The age groups for the given diagnoses in the Disease Analyzer database were also commensurate with those in corresponding disease registries. Finally, this database has already been used in previous studies focusing on AEDs [17–19].

## 2.2. Study population, outcomes, and covariables

This study included all patients aged  $\geq 15$  years followed in 2009, 2013, and 2017 in neurological ( $N = 99$ ) and general practices ( $N = 499$ ) in Germany. Trends in valproate use (ATC: N03AG01) in patients followed in neurological and general practices in Germany in 2009, 2013, and 2017 were analyzed using four outcomes: 1) mean number of patients per practice with at least one prescription for valproate; 2) mean number of patients per practice with at least one initial prescription for valproate; 3) proportion of physicians prescribing valproate to at least one patient; and 4) proportion of physicians prescribing valproate for the first time to at least one patient. Covariables included gender, age, and physician.

## 2.3. Statistical analyses

This cross-sectional study used descriptive statistics only. A  $p$ -value  $< 0.05$  was considered statistically significant. All statistical analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC, USA).

## 3. Results

Overall, 1,298,446 patients were followed in general and neurological practices in 2009, 1,358,160 in 2013, and 1,413,286 in 2017. The mean number of patients per practice with at least one prescription for valproate decreased in men (11.07 versus 9.92) and women aged 15–45 years (9.27 versus 5.88) followed in neurological practices between 2009 and 2017 while this number increased in men (12.07 versus 15.10) and women aged  $> 45$  years (13.89 versus 15.91; Fig. 1). In general practices, there was a decrease in the mean number of younger patients per practice with at least one prescription for valproate (men: 0.82 in 2009 versus 0.75 in 2017; women: 0.60 versus 0.37) and an increase in this number in older patients (men: 1.24 versus 1.32; women: 1.19 versus 1.23). Interestingly, the mean number of patients per practice with at least one initial prescription for valproate decreased across all subgroups in neurological and general practices between 2009 and 2017, except in men aged  $> 45$  years followed by neurologists (1.07 versus 1.04) and in men aged 15–45 years followed by general practitioners (0.09 versus 0.07; Fig. 2). Moreover, the proportion of neurologists prescribing valproate in women aged 15–45 years decreased

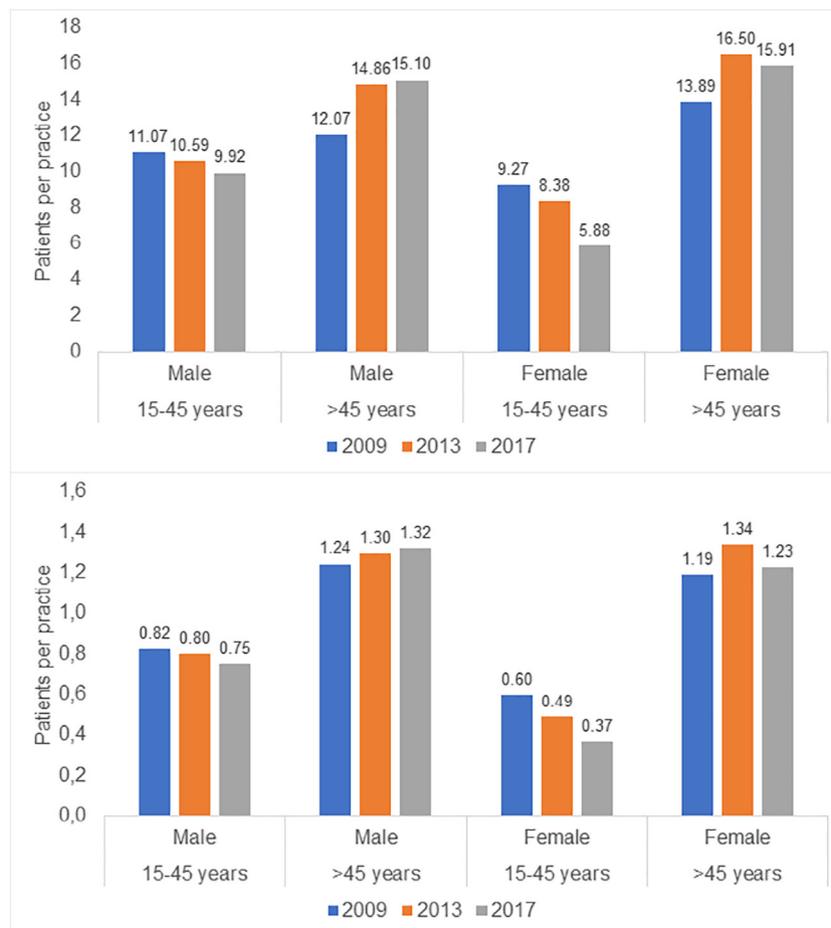
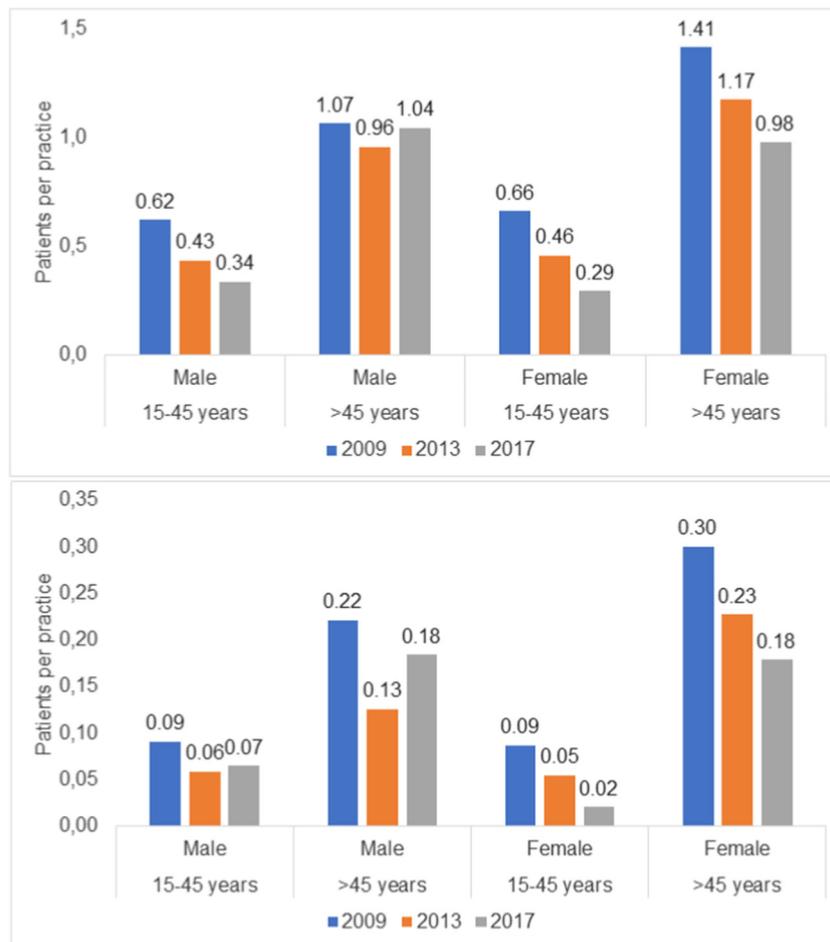


Fig. 1. Mean number of patients per neurological (upper panel) and general practice (lower panel) in Germany with at least one prescription for valproate in 2009, 2013, and 2017.



**Fig. 2.** Mean number of patients per neurological (upper panel) and general practice (lower panel) in Germany with at least one initial prescription for valproate in 2009, 2013, and 2017.

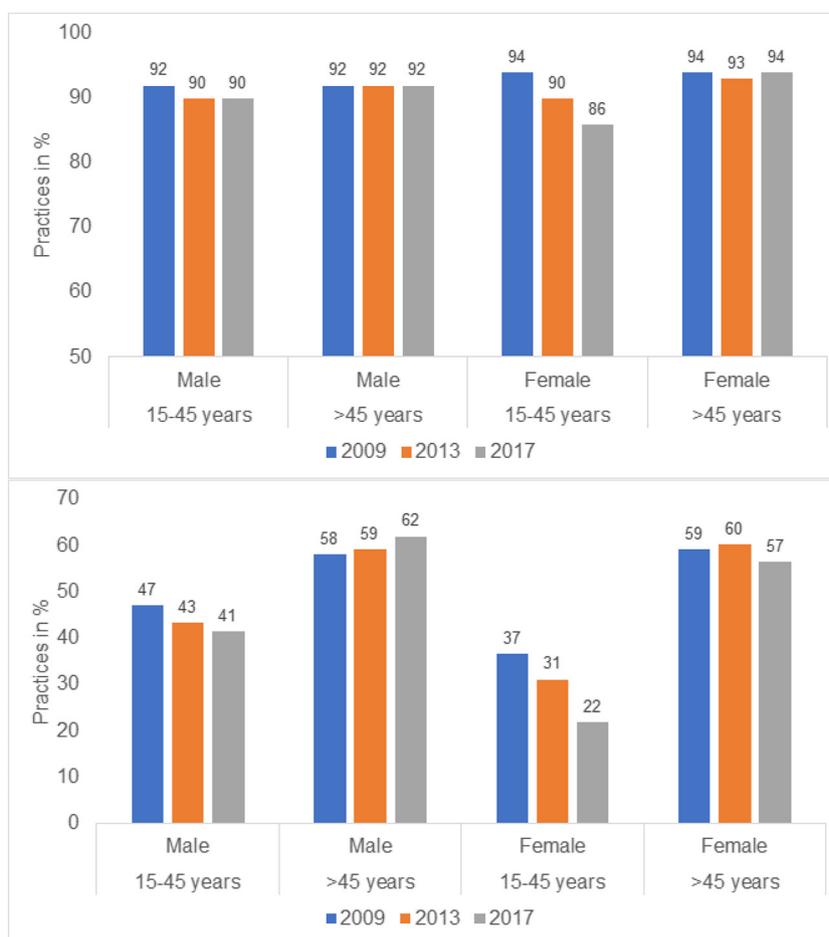
over time (94% in 2009 versus 86% in 2017) whereas there was no significant decreasing trend in women aged >45 years (94% versus 94%), men aged 15–45 years (92% versus 90%), and men aged >45 years (92% versus 92%; Fig. 3). On the other hand, a substantial decrease was found in the rate of general practitioners prescribing valproate in men (47% in 2009 versus 41% in 2017) and women aged 15–45 years (37% versus 22%) whereas an increase of this rate was seen in men aged >45 years (58% versus 62%). No significant trend was detected in women aged >45 years (59% versus 57%). Furthermore, there was a drop in the proportion of neurologists and general practitioners prescribing valproate for the first time to at least one patient in all subgroups, except in men aged 15–45 years who attended general practices (8% in 2009 versus 6% in 2017; Fig. 4). Finally, there was no substantial change in the diagnoses motivating the prescription of valproate between 2009 and 2017. There were 82% of valproate users with epilepsy and 11% with bipolar disorder in 2009, 2013, and 2017 while a small proportion was affected by migraine, schizophrenia, or dementia.

#### 4. Discussion

To the best of our knowledge, this was the first study to analyze trends in valproate use among both men and women in Germany. The major finding of this retrospective study is that there was a decrease in the use of valproate among women of childbearing age. Interestingly, several authors have obtained similar results in other countries and settings. For example, Ackers and colleagues found in a 2009 population-based observational study conducted in the United Kingdom that the prevalence of valproate use in girls aged 12–18 years decreased from

0.94 to 0.63 per 1,000 persons between 1993 and 2006 [10]. One year later, in 2010, Vajda et al. reported, using data from an Australian register, that there was a decrease in the proportion of pregnancies exposed to valproate between 1999 (28.2%) and 2007 (23.6%) [11]. More recently, researchers from Ireland examined prescriptions dispensed by community pharmacies and estimated that the rate of valproate use in women aged 16–44 years declined from 3.50 in 2008 to 3.14 per 1,000 individuals in 2013 [12]. Finally, a recent study conducted among women of childbearing age from Finland showed that the prevalence of valproate use decreased by 19% between 2012 and 2016 [13]. Taken together, these findings highlight the fact that the prescription of valproate in young women has been deeply impacted by the growing evidence showing that this drug is a teratogenic molecule [1]. This decreasing trend in valproate use has been reported in patients followed in neurological practices and in those followed in general practices, suggesting that general practitioners are also aware of the potential deleterious effects of valproate in women of childbearing age.

We further observed a trend towards decreasing valproate use in men aged 15–45 years between 2009 and 2017. This finding must be interpreted with great caution because opposite trends have been found in previous studies. In the study by Ackers and colleagues, the proportion of male adolescents being prescribed valproate increased from 0.86 to 1.10 per 1,000 persons between 1993 and 2006 [10]. This result was corroborated in a UK cohort study of 63,586 participants with epilepsy, as valproate was prescribed more frequently in men aged between 15 and 55 years in 2008 (43.8%) than in 1993 (35.1%) [20]. By contrast, Virta et al. found that the annual prevalence rate of valproate users tended to decrease in men aged 15–44 years between 2008 and 2016 [13]. Although trends in valproate use among young



**Fig. 3.** Proportion of physicians in neurological (upper panel) and general practices (lower panel) in Germany, prescribing valproate to at least one patient in 2009, 2013, and 2017.

male adults should be reanalyzed in other settings and countries, our results might be explained by the fact that several authors have recently claimed that valproate may also be deleterious in men. For example, in 2013, Xiaotian and colleagues found in Chinese Han men with epilepsy that abnormal sperm morphology and motility were more common in valproate users than in controls [21]. More recently, in a 2018 systematic review and meta-analysis of six studies, the levels of follicle-stimulating hormone and testosterone were found to be lower in valproate users compared with healthy controls [22]. Valproate further altered the concentrations of luteinizing hormone, dehydroepiandrosterone sulfate, sex hormone-binding globulin, and androstenedione. Therefore, the conclusions of these studies may motivate physicians to avoid prescribing valproate to young men whenever possible.

The findings of the present retrospective study should be interpreted in light of several limitations. First, since a substantial proportion of valproate users may have been followed at a hospital, and since hospitals are not included in the Disease Analyzer database, this may have introduced a bias in the analyses. Second, diagnoses were only available in a small share of patients, and it was thus not possible to analyze trends in valproate use by diagnosis. Finally, there was no data on prescription doses and durations, and we were unable to analyze any respective trends over the study period. The major strengths of this German study are the number of patients and practices available for analysis and the use of real-world data from primary care practices where diagnoses are continuously documented, allowing for unbiased exposure assessment (no recall bias).

In conclusion, the proportion of men and women aged 15–45 years receiving valproate decreased in neurological and general practices in

Germany between 2009 and 2017. It is likely that physicians are aware of the teratogenic effects of valproate and tend to favor the use of other drugs in young adults.

#### Author contributions

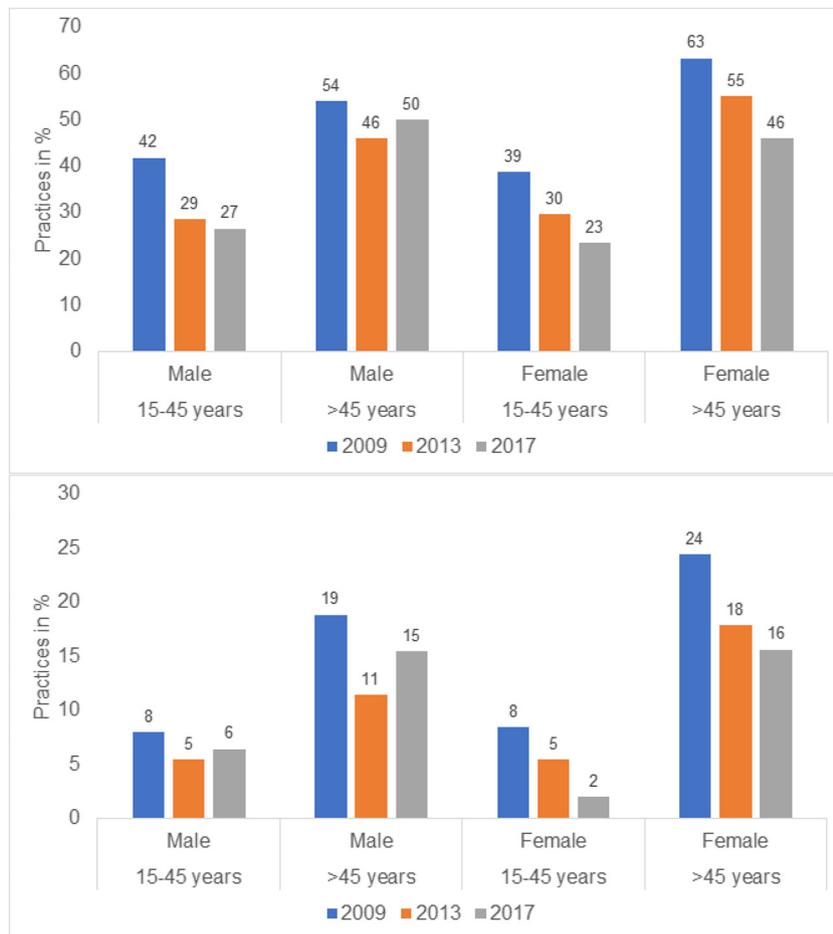
LJ contributed substantially to the conception of the study and the interpretation of the data, and drafted the manuscript. BS and JB contributed substantially to the conception of the study and the interpretation of the data, and revised the manuscript with a critical eye. KK contributed substantially to the conception of the study and the analysis of the data, and revised the manuscript with a critical eye. All authors gave the final approval of the version to be published.

#### Declaration of conflicts of interest

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**Fig. 4.** Proportion of physicians in neurological (upper panel) and general practices (lower panel) in Germany, prescribing valproate for the first time to at least one patient in 2009, 2013, and 2017.

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