Valproic Acid Use Trends, Patterns, and Predictors in Females of Reproductive Age in the United States

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Abstract

Objective: To provide an up-to-date evaluation of valproic acid (VPA) use trends, patterns, and predictors in females of reproductive age in ambulatory care settings in the US.

Methods: A retrospective, cross-sectional study was conducted using 2017 through 2022 Medical Expenditure Panel Survey data to examine trends in VPA use. Prescription rates were calculated per 1,000 prescription events with 95% confidence intervals. VPA prescriptions were stratified by clinical indication and recipient group (females aged 12–49 years, females aged ≥50 years, and males aged 12–49 years). Multivariable logistic regression was used to identify predictors of VPA use among females aged 12–49 years and all females with comorbid bipolar disorder, headache, or seizure conditions.

Results: The cumulative total of VPA prescription events across the 2017–2022 study period was 29,754,849 (95% CI, 23,843,243–35,666,455). Of these, 5,442,682 (95% CI, 2,879,340–8,006,024) were issued to females aged 12–49 years (18.3% of all VPA prescriptions). From 2017 to 2022, VPA prescribing decreased by nearly 50% ($P = .037$). Most VPA prescriptions filled by females aged 12–49 years were for migraine or other headache syndromes (27.2%), followed by bipolar disorder (24.6%) and convulsions or epilepsy (20.7%). Of the estimated 153,120 females aged 12–49 years who filled a prescription for VPA between 2017–2022, 85.9% were not using contraception.

Conclusion: Approximately 1 in 5 VPA prescriptions between 2017 to 2022 were prescribed to females of reproductive age. VPA was most commonly used for the treatment of migraine or other headache syndrome, followed by bipolar disorder and convulsive disorder. Only 14.1% of females of reproductive age using VPA were also using contraception. Interventional studies aimed at reducing VPA use in females of reproductive age are needed.

J Clin Psychiatry 2026;87(1):25m16009

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Despite a documented risk of birth defects and developmental disorders in children exposed to valproic acid (VPA) in the womb,[1–3] there are unique clinical scenarios that may require VPA use in females of reproductive age. Examples of clinical indications for VPA are treatment of epilepsy, migraine, and bipolar disorder.[4] In 2013, the US Food and Drug Administration (FDA) issued a Drug Safety Communication stating that VPA should only be used during pregnancy for epilepsy and bipolar disorder if there is no other viable medication for the patient.[5] Additionally, the package insert states that VPA should not be used in females of childbearing potential for conditions that are not usually associated with permanent injury or death, eg, migraine.[5] In situations where VPA is deemed clinically indicated for a female of reproductive age, concurrent effective contraception use is recommended.[6] However, it is strongly encouraged that VPA be avoided in this population altogether, with a recent 2022 editorial boldly stating this in the title "Prescribing Guideline for Valproic Acid and Women of Reproductive Potential: Forget It Exists."[7]

There are clinical encounters where it can be challenging to find alternative treatment options to VPA. For example, in the case of acute mania secondary to bipolar disorder, patients often need 2 mood stabilizers to achieve treatment response/remission.[8] Because of this, treatment guidelines have a "combination therapy" section as first-line treatment options for acute mania, including lithium or VPA in addition to a second-generation antipsychotic (SGA).[8] While this would

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Clinical Points

- The extent to which valproic acid (VPA) is used in females of reproductive age and factors influencing its use in this population are unknown.
- VPA continues to be used in females of reproductive age for indications in which it is contraindicated, such as for the treatment of migraines.
- Most females of reproductive age using VPA are not using contraception.

suggest using lithium in combination with an SGA in females of reproductive age with severe mania, there are scenarios where lithium is ineffective or contraindicated (eg, elevated risk of toxicity due to recurring acute kidney injury on chronic kidney disease, concurrent drug-drug interactions with erratic medication adherence, history of repeated toxicity). For patients with severe refractory epilepsy, multiple agents may be needed in combination to reduce seizure episodes.[9] And while it may not be recommended to use VPA for migraine prophylaxis in females of reproductive age, it is possible that some prescribers may still choose to prescribe VPA in this population.[10] Based on a study by Rizvi and colleagues, an estimated 28.3% of all VPA prescriptions in the US were prescribed to females of reproductive age (aged 15–44 years), with over half of patient visits having been for a seizure disorder, 10.6% for a mood disorder, and 0.6% for migraine.[11] This study utilized data from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) for 2018 and 2019 and concluded that VPA prescribing in females of reproductive age remained unchanged in the last decade.[11] However, since the study only utilized 2 years' worth of data, ongoing investigation into VPA use trends, patterns, and predictors is needed. Furthermore, nearly one-third of the visits had no matching diagnosis for which VPA is commonly used, with no indication of what these "other" diagnoses were.[11] Other recent studies investigating VPA prescription trends in females of reproductive age have taken place outside the US, including Finland,[12] the United Kingdom,[13] India,[14] Italy,[15,16] Germany,[17] Japan,[18] Ireland,[19] New Zealand,[20,21] Poland,[22] France,[23] and Estonia,[24] many of which conclude that VPA use in females of reproductive age continues to be an issue in need of addressing.

Considering that there are unique clinical scenarios that may warrant VPA use in females of reproductive age, it is important to evaluate VPA and contraception use patterns in this population. Therefore, the purpose of this study is to examine the trends, patterns, and predictors of VPA use in females of reproductive age in the US.

METHODS

Data Source

The Medical Expenditure Panel Survey (MEPS) is a nationally representative survey of US noninstitutionalized populations, sponsored by the Agency for Healthcare Research and Quality (AHRQ).[25] As MEPS data are deidentified and publicly available, institutional review board approval was not required. MEPS uses an overlapping panel design to collect data on health conditions, health care utilization, insurance coverage, and expenditures. New households are selected annually from the National Health Interview Survey and followed for 2 years through 5 rounds of interviews. Data from 2 panels are combined annually to create national estimates. More information on the MEPS design and public-use data is available elsewhere.[26]

MEPS includes 3 core components: the Household Component (HC), the Medical Provider Component (MPC), and the Insurance Component (IC).[27] The HC collects data on demographics, health conditions, health care expenditures, and access to care. The MPC and IC provide supplementary data from medical providers and employers on health insurance plans. The HC includes the Prescribed Medicines file, detailing unique prescribed medicine events reported by respondents, with additional data imputed from respondents' pharmacies (eg, on medicine names, dates filled, and expenditures).[28]

Study Design and Definitions

A retrospective, cross-sectional analysis of VPA prescribing was conducted using 2017 to 2022 data from the MEPS. To link demographic and medical condition data with prescription records, we merged the HC full-year consolidated file, medical conditions file, and prescribed medicines event file using the unique person identifier (DUPERSID) and condition-event link file. Fatty acid derivative anticonvulsants, defined as any VPA or its derivatives (eg, divalproex sodium), and contraceptive prescriptions (eg, oral contraceptives, patches, vaginal rings) were classified using the Multum Lexicon database (Cerner Multum, Inc.) and generic names in the Prescribed Medicines file.[28] Contraceptive management encounters were identified in the Medical Conditions file using *ICD-10-CM* Z30 codes. A composite indicator of contraceptive use was then created, defined as the presence of either a relevant prescription or a documented contraceptive management encounter. Medical conditions in MEPS are coded using *ICD-10-CM* or Clinical Classifications Software Refined (CCSR) codes, which were linked to

corresponding medical events, including prescribed medicines.[28]

Sociodemographic data were self-reported and included sex (female or male), age, race (White only, Black only, Multiracial or other race), ethnicity (Hispanic or non-Hispanic), marital status (married or not married), region (Midwest, Northeast, South, or West), insurance status (insurance coverage or no insurance coverage), poverty category (poor to low income or middle to high income), general health status (good to excellent or poor to fair), and mental health status (good to excellent or poor to fair). Individual-level clinical characteristics were characterized by the presence of diagnoses for bipolar disorder (*ICD-10-CM* F31, CCSR1X MBD003), epilepsy or recurrent seizures (*ICD-10-CM* G40, NVS009), headache or migraines (*ICD-10-CM* G43, R51, CCSR1X NV010), and depression (*ICD-10-CM* F32, F33, CCSR1X MBD002),[28] which was included since depression/mood disorders are common in individuals with neurologic disorders such as epilepsy/migraine and may account for VPA use as opposed to other neurologic treatment options.

Statistical Analysis

Annual VPA prescription rates per 1,000 prescription events (with 95% confidence intervals) were estimated from 2017 to 2022 using unpooled event-level data, calculated as the number of VPA prescriptions divided by all prescribed medicine events in the US civilian noninstitutionalized population. Rates were not pooled to preserve annual variability. Poisson regression was used to model VPA prescribing by year, with prescription events as the unit of analysis and VPA prescribing as the outcome. This approach estimates the relative change in VPA prescribing over time while accounting for overdispersion. To examine prescribing patterns by indication, we used pooled prescription-level event files from 2017, 2019, and 2021 only and reported the distribution of VPA prescriptions across 3 demographic groups (females aged 12–49 years, females aged ≥50 years, and males aged 12–49 years). Within each group, the proportion of prescriptions by clinical indication was reported based on associated diagnosis codes.

Finally, pooled person-level data from 2017, 2019, and 2021 (reflecting MEPS' 2-year follow-up design) were used to characterize the study population and conduct regression analyses. Bivariate analyses compared demographic and clinical characteristics between females aged 12–49 years with and without a VPA prescription; proportions of demographic and clinical characteristics were compared using design-based F tests, with statistical significance set at $P < .05$. Two multivariable logistic regression models were conducted using the same pooled data to identify predictors of VPA prescriptions among 2 subcohorts:

1. females aged 12–49 years with any indication for VPA.
2. females of all ages with bipolar, headache, or seizure disorders.

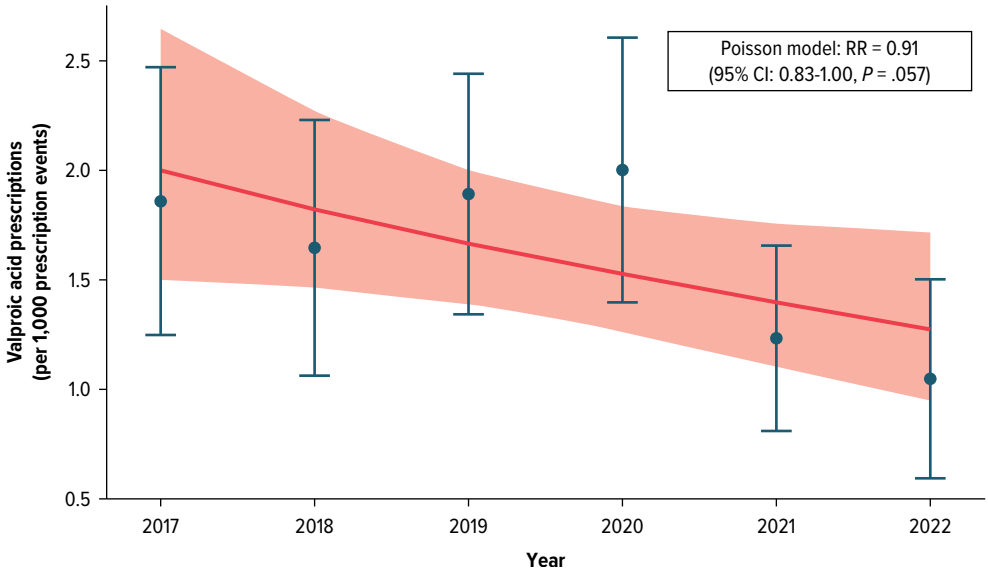
Running both models assessed whether predictors of VPA use are consistent when (*a*) focusing strictly on reproductive age versus (*b*) conditioning on clinical indication across females. Models included socioeconomic and demographic variables including poverty category, marital status, perceived general and mental health, age group, and region. These covariates were selected based on their clinical relevance in practice and reasonable hypotheses regarding their potential influence on treatment decisions (eg, socioeconomic status may affect access to quality care, marital status may shape pregnancy planning behaviors, and perceived health status may reflect treatment-refractory disease burden). Firth's penalized likelihood logistic regression was conducted as a sensitivity analysis; however, this model did not account for the MEPS complex survey design. All primary analyses were conducted in SPSS 29.0 and R 4.5.1, incorporating MEPS survey weights, stratification, and clustering.[25]

RESULTS

The cumulative total of VPA prescription events across the 2017 to 2022 study period was 29,754,849 (95% CI, 23,843,243–35,666,455). Of these, 5,442,682 (95% CI, 2,879,340–8,006,024) were issued to females aged 12–49 years, translating to 18.3% of all VPA prescriptions. The prevalence of VPA prescribing decreased by nearly half from 5,945,500 prescriptions in 2017 versus 2,969,360 prescriptions in 2022 ($P = .037$) and showed a decreasing trend during the study period (Figure 1), with annual prescribing decreasing by about 8.6% per year (rate ratio [RR] 0.91; 95% CI, 0.83–1.00; $P = .057$).

Of the estimated 153,120 (unweighted n = 43) females aged 12–49 years who filled a prescription for VPA based on pooled 2017, 2019, and 2021 data, 85.9% did not have some form of documented contraceptive use via a prescribed medicine event or contraceptive management encounter. Additional demographic and clinical characteristics are detailed in Table 1, with unweighted counts provided in Supplementary Table 1. Among females aged 12–49 years, VPA prescriptions were most commonly associated with migraine or headache syndrome (27.2%), bipolar disorder (24.6%), and convulsive disorder (20.7%). In contrast, bipolar disorder accounted for 29.5% of prescriptions among females aged ≥50 years (followed by depressive episode

Figure 1.
Valproic Acid Prescribing in the United States From 2017 to 2022[a]



[a]Blue points with error bars (95% CI) represent survey estimates. Red line and ribbon indicate the Poisson regression estimate of the prescription rate per year, with shaded ribbon reflecting 95% model-based confidence intervals.
Abbreviations: CI = confidence interval, RR = rate ratio.

[19.7%]), while convulsion-related diagnoses represented 32.5% of VPA prescriptions among males aged 12–49 years (with other psychiatric or neurologic disorder [27.1%] and bipolar disorder [23.5%] as the next most frequent) (Figure 2). Definitions used to classify psychiatric and neurologic conditions are provided in Supplementary Box 1.

In multivariable logistic regression, females aged 12–49 years reporting fair/poor general health had significantly higher odds of VPA use compared to those reporting good, very good, or excellent health (odds ratio [OR] 5.53; 95% CI, 2.11–14.52; $P < .001$) (Table 2). Similarly, fair/poor perceived mental health was associated with higher odds of VPA use (OR 3.51; 95% CI, 1.30–9.50; $P = .013$). These associations remained significant in the sensitivity analysis using Firth's logistic regression, and being unmarried (vs. married) also emerged as a significant predictor (OR 4.63; 95% CI, 2.01–12.93; $P < .001$) (Supplementary Table 2). In a separate multivariable model among females of all ages with bipolar, headache, or seizure disorders (unweighted n = 70), those residing in the Northeast had significantly higher odds of receiving a VPA prescription compared to those in the South (OR 2.71; 95% CI, 1.38–5.29; $P = .004$) (Table 3). However, this association was not statistically significant in the sensitivity analysis using Firth's logistic regression (OR 1.68; 95% CI, 0.88–3.15; $P = .114$) (Supplementary Table 3).

DISCUSSION

This study reports national-level data and predictors regarding VPA use patterns in females of reproductive age in the US using recent, multiyear national data from MEPS. There have been many publications emphasizing the importance of avoiding VPA use in females of reproductive age, calling attention to ongoing VPA use in this population despite the well-known teratogenic risks. However, most recent studies were conducted outside of the US,[12–24] and the last US study examining VPA prescribing trends utilized only 2 years' worth of data from 2018 and 2019.[11] Thus, this study provides a much-needed update on VPA use trends, patterns, and predictors in the US.

A recent study by Smolinski and colleagues found that pregnancy rates more than doubled between 2005 to 2020 among females using VPA for the treatment of a mood disorder or migraine compared with epilepsy.[29] This is noteworthy considering data from our study indicate that migraine or other headache syndromes and bipolar disorder are the indications that VPA is most commonly used for in females of reproductive age, despite VPA being associated with anatomical, behavioral, and cognitive teratogenicity.[30] In fact, VPA use in females of reproductive age for the treatment of headache/migraine was far greater than that in males of the same age group (27.2% vs 0.8%). There are many pharmacologic treatment options for treating headache/migraines,[31] so it

Table 1.

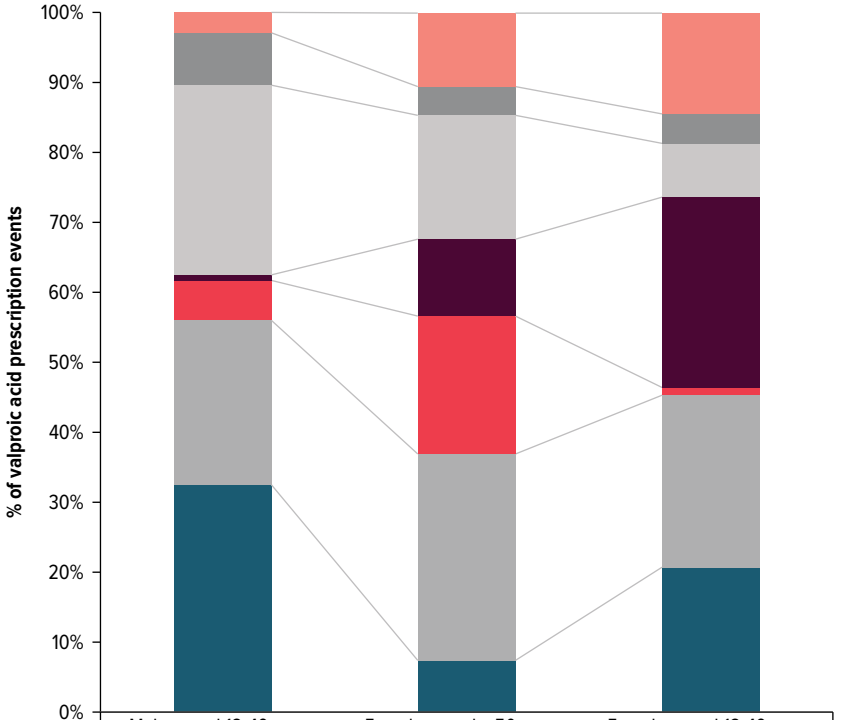
Demographic and Clinical Characteristics of Females Aged 12–49 Years in the United States From 2017, 2019, and 2021

	No valproic acid		Valproic acid		
	Wt%	95% CI	Wt%	95% CI	*P* value[a]
Total, n (%); population size	8,368 (99.6); 34,312,505		43 (0.4); 153,120		
Age, mean (SE), y	32.3 (0.13)		33.6 (1.64)		**<.001**
Race					
White only	77.2	75.7–78.7	71.7	52.7–85.2	.547
Black only	12.3	11.2–13.6	19[b]	8.4–37.6[b]	
Multiracial/other	10.5	9.6–11.5	NA[c]	NA[c]	
Ethnicity					
Hispanic	16.8	15.4–18.3	7.4[b]	2.8–18.1[b]	.065
Not Hispanic	83.2	81.7–84.6	92.6	81.9–97.2	
Marital status					
Married	42.9	41.6–44.2	18.5[b]	7.3–39.6[b]	**.019**
Not married	57.1	55.8–58.4	81.5	60.4–92.7	
Region					
Midwest	22.6	20.1–25.4	16.2[b]	7.2–32.5[b]	.788
Northeast	16.7	14.6–18.9	NA[c]	NA[c]	
South	38.5	35.5–41.6	36.5[b]	20.9–55.6[b]	
West	22.2	19.7–25	26.7[b]	13.8–45.5[b]	
Insurance status					
Insurance coverage	95.9	95.3–96.4	94.8	80.9–98.7	.728
No insurance	4.1	3.6–4.7	NA[c]	NA[c]	
Poverty category					
Poor to low income	29.5	28–31.1	45.9	28.6–64.3	.060
Middle to high income	70.5	68.9–72	54.1	35.7–71.4	
General health status					
Good to excellent	86.9	86–87.9	38.5	24.3–55.1	**<.001**
Poor to fair	13.1	12.1–14	61.5	44.9–75.7	
Mental health status					
Good to excellent	87.4	86.4–88.3	43	26.6–61.1	**<.001**
Poor to fair	12.6	11.7–13.6	57	38.9–73.4	
Bipolar disorder					
No	97.5	97.1–97.8	77.6	63.1–87.5	**<.001**
Yes	2.5	2.2–2.9	22.4[b]	12.5–36.9[b]	
Epilepsy/seizure disorders					
No	98.3	98–98.6	75.3	56.1–87.9	**<.001**
Yes	1.7	1.4–2	24.7[b]	12.1–43.9[b]	
Headache/migraine					
No	90.7	89.8–91.5	65.1	46.2–80.3	**<.001**
Yes	9.3	8.5–10.2	34.9[b]	19.7–53.8[b]	
Depressive disorders[d]					
No	83.8	82.7–84.8	56.3	39.3–71.9	**<.001**
Yes	16.2	15.2–17.3	43.7	28.1–60.7	
Prescribed contraceptive use[e]					
No	80.6	79.4–81.6	85.9	68.5–94.4	.462
Yes	19.4	18.4–20.6	14.1[b]	5.6–31.5[b]	
Contraceptive management encounter[f]					
No	87.5	86.4–88.4	91.6	75.3–97.5	.493
Yes	12.5	11.6–13.6	NA[c]	NA[c]	
Any contraceptive use[g]					
No	78.8	77.7–79.9	85.9	68.5–94.4	.347
Yes	21.2	20.1–22.3	14.1	5.6–31.5	

[a]Boldface indicates statistical significance.
[b]Estimates with relative standard error between 30% and 50% indicate that their precision is questionable.
[c]Estimates with relative standard error >50% were not reported (NA) due to large sampling error.
[d]Includes *ICD-10* F32 (depressive episode), F33 (major depressive disorder, recurrent), or CCSR1X MBD002 (depressive disorders).
[e]Includes events in the prescribed medicines file (Multum Lexicon codes).
[f]Includes *ICD-10-CM* Z30 from the medical conditions file.
[g]Any contraceptive use defined as having either a prescribed contraceptive or a contraceptive management encounter.

Figure 2.

Valproic Acid Prescribing in the United States, by Condition and Demographic Group, From Pooled 2017, 2019, and 2021 Data



	Males aged 12-49 years	Females aged ≥ 50 years	Females aged 12-49 years
Missing or unspecified	2.9%[a]	10.5%	14.4%
Other nonpsychiatric or neurologic disorder	7.5%[a]	4.1%[a]	4.2%[a]
Other psychiatric or neurologic disorder	27.1%	17.7%	7.7%[a]
Migraine or headache syndrome	0.8%[a]	11.0%	27.2%
Depressive episode	5.7%[a]	19.7%	1.1%[a]
Bipolar disorder	23.5%	29.5%	24.6%
Convulsive disorder	32.5%	7.4%[a]	20.7%

[a]Estimates with n < 60 or relative standard error >50% should be interpreted with caution and are typically not reported. However, exceptions may be made for rare outcomes (eg, <10% prevalence).

is unclear why VPA continues to be used in this population. It is also worth noting that there was only a small difference in VPA use rates for bipolar disorder in females aged 12 to 49 years (24.6%) versus males aged 12 to 49 years (23.5%).[8] Future studies are needed to determine how often females of reproductive age who use VPA have failed to respond to alternative, safer treatment options.

The FDA and European Medicines Agency recommend contraception in females of reproductive age using VPA.[5,32] The Centers for Disease Control and Prevention estimates that about 27% of females of reproductive age (ages 15–49) use contraceptives (14.0% use oral contraceptives, 10.4% use reversible long-acting contraception, and 3.1% use injections, patches, or rings).[33] In this study, only 14.1% of reproductive-age females prescribed VPA had documentation of prescribed contraception. However, this likely underestimates true coverage, as MEPS does not capture over-the-counter methods (eg, Opill), and long-acting methods or sterilization procedures, which are often recorded via Current Procedural Terminology (CPT) codes limited to the MEPS MPC. While prescription data were supplemented with *ICD-10* Z30 codes for contraceptive management, these limitations constrain full ascertainment. Regardless, these data emphasize a need for targeted interventions to encourage co-contraceptive prescribing for females using VPA. Considering half of pregnancies are unintended in the US,[34] with several states restricting elective abortion,[35] it is critical to develop and implement interventions to reduce VPA use in this population and increase contraception use in those where VPA use is unavoidable. Some have suggested a need to develop a formal Risk Evaluation

Table 2.

Logistic Regression Model of Predictors of Valproic Acid Use Among Females Aged 12–49 Years[a]

	Estimate (n)	Odds ratio	95% CI	*P* value[b]
Poverty category				
Middle to high income	24,256,616	(Ref)	(Ref)	(Ref)
Poor or near poor or low income	10,209,009	0.96	0.44–2.10	.912
Marital status				
Married	14,747,030	(Ref)	(Ref)	(Ref)
Not married	19,718,594	2.90	0.97–8.65	.057
Perceived general health				
Good or very good or excellent	29,892,063	(Ref)	(Ref)	(Ref)
Fair or poor	4,573,562	5.53	2.11–14.52	**<.001**
Perceived mental health				
Good or very good or excellent	30,047,602	(Ref)	(Ref)	(Ref)
Fair or poor	4,418,022	3.51	1.30–9.50	**.013**

[a]Analyses were based on 8,411 valid cases; among females aged 12–49 years, n = 43 were VPA users, and n = 8,368 were nonusers.
[b]Boldface indicates statistical significance.

Table 3.

Logistic Regression Model of Predictors of Valproic Acid Use Among Females with Bipolar, Headache, or Seizure Disorders[a]

	Estimate	Odds ratio	95% CI	*P* value[b]
Age group, y				
Under 12 years or over 49 years	3,390,404	(Ref)	(Ref)	(Ref)
12–49 years	4,532,081	0.65	0.338–1.26	.202
Marital status				
Married	3,340,391	(Ref)	(Ref)	(Ref)
Not married	4,582,094	1.18	0.609–2.29	.621
Poverty category				
Middle to high income	5,151,080	(Ref)	(Ref)	(Ref)
Poor or near poor or low income	2,771,406	1.65	0.768–3.55	.198
Region				
South	2,914,553	(Ref)	(Ref)	(Ref)
Northeast	1,372,727	2.71	1.384–5.29	**.004**
West	1,732,253	1.38	0.624–3.03	.428
Midwest	1,902,953	0.87	0.387–1.97	.745
Perceived general health				
Good or very good or excellent	2,271,119	(Ref)	(Ref)	(Ref)
Fair or poor	5,651,366	2.04	0.94–4.43	.071
Perceived mental health				
Good or very good or excellent	6,053,094	(Ref)	(Ref)	(Ref)
Fair or poor	1,869,392	1.89	0.84–4.25	.123

[a]Analyses were based on 2,171 valid cases. Among females with bipolar disorder, headache, or seizure indications, n = 70 were VPA users and n = 2,101 were nonusers.
[b]Boldface indicates statistical significance.

and Mitigation Strategy (REMS) program to mitigate prenatal exposure to VPA,[36] although it is unclear to what degree this type of intervention would mitigate the issue.

Females of reproductive age who reported having fair/poor general health had higher odds of using VPA compared to those with good/very good/excellent general health. This was also the case for females of reproductive age who reported having fair/poor mental health compared to those with good/very good/excellent mental health. Since VPA use is not recommended in females of reproductive age, it is plausible that females who use VPA are more likely to be "treatment refractory," meaning they have failed to respond to multiple trials of alternative recommended treatment options. It makes sense that females who fail to achieve

treatment response with their medication(s) may be more likely to perceive themselves as having poorer general/mental health quality. However, these findings should be interpreted cautiously; it is unknown how many medication trials females in the current study sample had before using VPA, and possible explanations as to why certain factors may be associated with VPA use in females of reproductive age are merely speculative in nature.

The last US study to investigate VPA prescribing patterns was a secondary analysis of data from the NAMCS and the NHAMCS for 2018 and 2019.[11] This study found that VPA was prescribed more during female office–based physician visits compared to male visits (3.68 million vs. 2.62 million), and 29% of the female visits were in those of reproductive age (aged 15–44 years). Of those visits where VPA was prescribed in females of reproductive age, 53.6% had a seizure disorder, 10.6% had a mood disorder, and 0.6% had migraines; 30.7% were prescribed VPA for an "other" unspecified indication. The authors concluded that VPA prescribing in females of reproductive age remains unchanged, referencing a study by Adedinsewo et al that was conducted 10 years prior.[37] However, in the study by Adedinsewo and colleagues, which also utilized NHAMCS data (but from 1996–2007), most females of reproductive age prescribed VPA did not have epilepsy. In the current study, epilepsy was similarly not the most common indication for VPA use. Neither of the previous studies reported predictors of VPA use in females of reproductive age, though this is difficult to reliably determine due to the low sample size of VPA users for each independent variable. Another study by Wisner and colleagues utilized 2009 New York State Medicaid claims for persons with psychiatric disorders and found that 20% of females receiving mood stabilizers were treated with VPA.[38] In the current study, just over 20% of reproductive-aged females using VPA had comorbid bipolar disorder, which further begs the question of whether VPA use patterns for females with mood disorders have significantly changed in the past 2 decades.

These data indicate a need to test interventions that aim to reduce VPA prescribing and/or encourage co-contraceptive prescribing to females of reproductive age. Colas and colleagues published an article in 2024 investigating the impact of the 2018 European additional risk minimization measures for VPA use in females of reproductive age among health care professionals (neurologists, psychiatrists, pediatricians, general practitioners, gynecologists, and pharmacists) and patients.[39] Self-reported levels of awareness, knowledge, and behavior varied considerably by health care professional type and among patients.[39] This suggests that more translational research is needed to reduce the variance in knowledge and behavior related to VPA prescribing across different health care specialty treatment settings, though these findings may not be generalizable to the US. Studies show that VPA use impacts reproductive decision-making more than other factors, such as treatment-refractory convulsive seizures in patients with epilepsy.[40] As such, it is crucial to ensure all clinicians are trained/prompted to inform patients about the teratogenic risks of VPA use, since it influences reproductive planning decisions.

This study has several limitations. First, the modest number of events in both models—female VPA users aged 12–49 years (n = 43) and female VPA users conditioned by indication (n = 70)—limited statistical power, reduced the precision of our estimates, and constrained generalizability, as not all ages within this range were represented. To address these constraints, we followed the rule of ~10 events per predictor and applied Firth's penalized likelihood method to improve model stability.[41] Despite these challenges, we report the findings in line with AHRQ guidance, which allows exceptions for rare outcomes when prevalence is low (<10%).[42] Second, MEPS data rely on self-reports, which may introduce recall bias. Third, over-the-counter and procedure-based contraceptives (such as IUDs and implants) could not be captured due to lack of access to CPT code data from the MPC, potentially understating contraceptive use.

CONCLUSION

Overall VPA prescriptions declined between 2017 and 2022. VPA was most commonly used for the treatment of migraine or other headache syndrome, followed by bipolar disorder and convulsive disorder in females of reproductive age. Over three-fourths of females of reproductive age using VPA had no documented prescription or clinical encounter for contraception. Future research on the development and implementation of interventions to reduce VPA use in females of reproductive age and/or encourage co-contraceptive prescribing is needed.

Article Information

Published Online: December 15, 2025. https://doi.org/10.4088/JCP.25m16009

Submitted: June 23, 2025; accepted October 15, 2025.

To Cite: Vadiei N, Mercer JA, Cornelison B, et al. Valproic acid use trends, patterns, and predictors in females of reproductive age in the United States. *J Clin Psychiatry* 2026;87(1):25m16009.

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Relevant Financial Relationships: Dr Axon reports grant funding from the American Association of Colleges of Pharmacy, Arizona Department of Health, Merck & Co, National Council for Prescription Drug Programs Foundation, Pharmacy Quality Alliance, Tabula Rasa HealthCare Group, and the US Department of Health and Human Services, outside of this study. Dr. Lee was supported by the National Institutes of Aging (NIA/NIH K23-AG066933). The other authors and contributors have no conflicts of interest to disclose.

Funding/Support: No funding was received for this research.

Acknowledgment: The authors acknowledge Nicholas J. Meyers, PharmD (HonorHealth Scottsdale Thompson Peak Medical Centers, Scottsdale, Arizona) for his assistance with preliminary aspects of the project.

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Supplementary Material: Available at Psychiatrist.com.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Valproic Acid Use Trends, Patterns and Predictors in Females of Reproductive Age in the United States

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DOI Number: 10.4088/JCP.25m16009

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. Unweighted sample sizes of demographic and clinical characteristics of females aged 12 to 49 years in the United States, Medical Expenditure Panel Survey (MEPS) 2017, 2019, and 2021

	No VPA (N = 8,368)	**VPA (N = 43)**
Median age (IQR)	34 (24-42)	36.5 (25.3-45)
Age distribution		
12 to 24	2,136	9
25 to 34	2,157	10
35 to 49	4,075	24
Race		
White only	6,167	30
Black only	1,299	10
Multiracial/other	902	3
Ethnicity		
Hispanic	2,012	6
Not Hispanic	6,356	37
Marital status		
Married	3,428	5
Not married	4,940	38
Region		
Midwest	1,889	7
Northeast	1,279	7
South	3,127	16
West	2,073	13
Insurance status		
Insurance coverage	7,916	41
No insurance	452	2
Poverty category		
Poor to low income	3,220	21
Middle to high income	5,148	22
General health status		
Good to excellent	7,108	22
Poor to fair	1,260	21
Mental health status		
Good to excellent	7,236	23
Poor to fair	1,132	20
Bipolar disorder		
No	8,125	30
Yes	243	13
Epilepsy/seizure		
No	8,221	33
Yes	147	10
Headache/migraine		
No	7,572	32
Yes	796	11
Depressive episode		
No	7,006	25
Yes	1,362	18
Prescribed contraceptive use[a]		
No	6,997	38
Yes	1,371	5
Contraceptive management encounter[b]		
No	7,497	40
Yes	871	3
Any contraceptive use[c]		
No	6,862	38
Yes	1,506	5

[a]Prescribed contraceptive use includes events in the prescribed medicines file (Multum Lexicon codes).

[b]Contraceptive management encounter includes ICD-10-CM Z30 from the medical conditions file.

[c]Any contraceptive use defined as having either a prescribed contraceptive or a contraceptive management encounter.

Supplementary Box 1.

Category	ICD-10-CM Codes
Other non-psych or neurologic disorder	M19, M54, Z76, Z00, E87, Z48, C44, I10, L97, I21, M62, E11, J45, I72
Other psychiatric or neurologic disorder	F34, F39, F91, F84, F43, F42, F99, F41, F20, F90, F03 R45, R25, R41 G30, G20, G47, G45
Migraine or headache syndromes	G43; G44; R51
Depressive episode	F32
Bipolar disorder	F31
Convulsive disorder	R56, G40

Supplementary Table 2. Sensitivity analysis using firth logistic regression for predictors of valproic acid use among females aged 12 to 49 years

	n	Odds Ratio	95% CI	P value
Poverty category				
Middle to high income	5,312	(Ref)	(Ref)	(Ref)
Poor or near poor or low-income	3,342	0.73	(0.39, 1.36)	.318
Marital status				
Married	3,522	(Ref)	(Ref)	(Ref)
Not married	5,132	4.63	(2.01, 12.93)	**<.001**
Perceived general health				
Good or very good or excellent	7,331	(Ref)	(Ref)	(Ref)
Fair or poor	1,323	3.11	(1.54, 6.29)	**.002**
Perceived mental health				
Good or very good or excellent	7,459	(Ref)	(Ref)	(Ref)
Fair or poor	1,195	2.95	(1.45, 5.99)	**.003**

Supplementary Table 3. Sensitivity analysis using firth logistic regression for predictors of valproic acid use among U.S. females with bipolar, headache, or seizure disorders

	n	Odds Ratio	95% CI	*P* value
Age group				
Under 12 years or over 49 years	1,047	(Ref)	(Ref)	(Ref)
12 to 49 years	1,187	.70	(.43, 1.13)	.143
Marital status				
Married	877	(Ref)	(Ref)	(Ref)
Not married	1,357	1.59	(.92, 2.84)	.098
Poverty category				
Middle to high income	1,262	(Ref)	(Ref)	(Ref)
Poor or near poor or low-income	972	1.37	(.82, 2.31)	.238
Region				
South	787	(Ref)	(Ref)	(Ref)
Northeast	379	1.68	(.88, 3.15)	.114
West	538	1.45	(.77, 2.70)	.248
Midwest	530	.98	(.49, 1.89)	.945
Perceived general health				
Good or very good or excellent	1,507	(Ref)	(Ref)	(Ref)
Fair or poor	727	1.16	(.65, 2.04)	.622
Perceived mental health				
Good or very good or excellent	1,651	(Ref)	(Ref)	(Ref)
Fair or poor	583	1.62	(.91, 2.86)	.098