

Valproate Prescribed to Reproductive-Age Women in Ambulatory Care:

Analysis of 2018–2019 National Ambulatory Health Care Data

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Reproductive-age women exposed to valproate have an increased risk of polycystic ovarian syndrome, which can cause pelvic pain, abnormal periods, hirsutism, acne, and infertility.¹ In addition, valproate is a human teratogen, and exposure during pregnancy was shown to increase the risk of congenital malformations 5-fold compared to controls.^{2,3} Valproate products comprise sodium valproate, divalproex sodium, valproic acid, and other generics (hereafter collectively called valproate). With the increased awareness about its teratogenicity, several countries have decreased prescriptions of valproate to reproductive-age women.^{4,5} In the United States, 45% of pregnancies

are unintended, and several states restrict elective abortion, making it more critical to decrease valproate prescriptions.^{6,7} However, in the last 10 years, no study has been done on the latest trend in valproate prescription for reproductive-age women. Therefore, this study aims to fill this gap in the literature.

METHODS

This study was a secondary analysis of publicly available de-identified data from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) for 2018 and 2019.⁸ NAMCS data are obtained from a national sample of

office-based physician visits, while NHAMCS contains data on visits to hospital emergency departments in the United States. Multum Lexicon (Cerner Multum, Inc) third-level therapeutic category codes were used to define valproate (code 345). Survey data were analyzed using the sampled visit weight, adjusted to yield an unbiased national estimate. Because of the complex sample design, sampling errors were determined using IBM SPSS statistics version 28 with a complex sampling module, which considers the clustered nature of the sample.

Visits of reproductive-age women aged 15–44 years in which valproate was prescribed were extracted and further grouped using *ICD-10-CM* codes as follows: (1) seizure disorders, (2) mood disorders, (3) schizophrenia and other psychosis, (4) migraine/headache, (5) other psychiatric indications, (6), and others (see Supplementary Table 1 for a list of *ICD-10-CM* codes). Since the dataset is de-identified and publicly available, the study was exempt from review by the institutional review board. The data analysis was conducted in the United States.

RESULTS

Valproate was prescribed more during female visits than in male visits (3.68 million vs 2.62 million). Of the 1.7 billion female visits, 373 million (29%) were of reproductive age (aged 15–44 years). Valproate was prescribed in 1.78 million reproductive-age female visits (4.8 visits, 95% CI, 4.5–5.2 per 1,000 reproductive-age female visits). Of those visits, 53.6%

Table 1.

Valproate Prescribed During Ambulatory Care Visits in the United States: 2018–2019^a

Visits	Unweighted	Weighted (thousands)	Standard Error (thousands)	95% CI (thousands)	
				Lower	Upper
Total visits	57,975	2,177,494	64,581	2,050,764	2,304,224
Female visits	31,797	1,266,754	44,613	1,179,209	1,354,299
Reproductive-age female visits	12,095	373,256	19,546	334,892	411,621
Valproate visits					
Male	121	2,616	152	2,312	2,920
Female	106	3,679	162	3,355	4,003
Total	227	6,295	166	5,963	6,627
Reproductive-age female valproate visits	47	1,785	25	1,731	1,839
Weighted Percentage of Reproductive-Age Female Visits in Which Valproate Was Prescribed					
Diagnosis					
Seizure disorder			53.6		
Mood disorder			10.6		
Schizophrenia spectrum			1.1		
Migraine			0.6		
Others			30.7		
Other psychiatric indication			1.6		
≥ 2 diagnoses ^b			1.8		

^aData from the Centers for Disease Control and Prevention National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey 2018 and 2019.⁸

^bMigraine and epilepsy (1%), epilepsy and bipolar disorder (0.6%), schizophrenia and migraine and convulsion (0.2%).

had a seizure disorder and 10.6% had a mood disorder, while in 30.7% of visits, there was a diagnosis for which valproate does not have a US Food and Drug Administration–approved or common off-label use (Table 1).

DISCUSSION

Prescription of valproate to reproductive-age women in 2018–2019 in ambulatory care across the United States remained unchanged compared to the study by Adedinsewo et al² 10 years prior, which found 4.45 visits (95% CI, 3.8–5.06).

The prescription of valproate has decreased for psychiatric diagnoses and increased for seizure diagnoses. Of total valproate visits between 1996 and 2007, 61% had a psychiatric diagnosis, and 17% had a seizure diagnosis.² In our study, these rates changed to 14% for psychiatric disorders and 54% for seizure disorders. The decrease in valproate prescriptions for psychiatric diagnosis is possibly due to second-generation antipsychotics being preferred over mood stabilizers for mood disorders over the last decade.⁹

Interestingly, for about 30% of the visits, there was no matching diagnosis for which valproate is FDA approved or has common off-label use. Since the survey's primary focus is on the content of the individual visit, chronic diseases may have not been accurately recorded. However,

given the teratogenic potential of valproate, these are concerning findings that deserve further study.

CONCLUSION

The prescription of valproate in reproductive-age female visits in ambulatory care in the last decade has remained unchanged. There was a decrease in valproate prescribed for visits with psychiatric disorders but an increase for seizure disorders.

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Supplementary Material

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. Supplementary Table 1. *ICD-10-CM* Code and List of Diagnosis Included

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Supplementary Table 1. *ICD-10-CM* Code and List of Diagnosis Included

ICD10-CM code	Diagnosis
Seizure disorders	
G40.0	Localization-related (focal) (partial) idiopathic epilepsy and epileptic localized onset
G40.1	Localization-related (focal) (partial) symptomatic epilepsy and seizures
G40.2	Localization-related (focal) (partial) symptomatic epilepsy and partial seizures
G40.3	Generalized idiopathic epilepsy and epileptic syndromes
G40.4	Other generalized epilepsy and epileptic syndromes
G40.5	Epileptic seizures related to external causes
G40.8	Other epilepsy and recurrent seizures
G40.9	Epilepsy, unspecified
G40.A	Absence epileptic syndrome
G40.B	Juvenile myoclonic epilepsy [impulsive petit mal]
R56	Convulsions, not elsewhere classified
Mood Disorder	
F30	Manic episode
F30.1	Manic episode without psychotic symptoms
F30.2	Manic episode, severe with psychotic symptoms
F30.3	Manic episode in partial remission
F30.4	Manic episode in full remission
F30.8	Other manic episodes
F30.9	Manic episode, unspecified
	Manic episode in partial remission
F31.0	Bipolar disorder, current episode hypomanic
F31.1	Bipolar disorder, current episode manic without psychotic features
F31.2	Bipolar disorder, current episode manic severe with psychotic features
F31.3	Bipolar disorder, current episode depressed, mild or moderate severity
F31.4	Bipolar disorder, current episode depressed, severe, without psychotic features
F31.5	Bipolar disorder, current episode depressed, severe, with psychotic features
F31.6	Bipolar disorder, current episode mixed
F31.7	Bipolar disorder, currently in remission

F31.8	Other bipolar disorders
F31.9	Bipolar disorder, unspecified
F32	Depressive episode
F32.0	Major depressive disorder, single episode, mild
F32.1	Major depressive disorder, single episode, moderate
F32.2	Major depressive disorder, single episode, severe without psychotic features
F32.3	Major depressive disorder, single episode, severe with psychotic features
F32.4	Major depressive disorder, single episode, in partial remission
F32.5	Major depressive disorder, single episode, in full remission
F32.8	Other depressive Premenstrual dysphoric disorder episodes
F32.9	Major depressive disorder, single episode, unspecified
F32.A	Depression, unspecified
F33	Major depressive disorder, recurrent
F33.0	Major depressive disorder, recurrent, mild
F33.1	Major depressive disorder, recurrent, moderate
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms
F33.4	Major depressive disorder, recurrent, in remission
F33.8	Other recurrent depressive disorders
F33.9	Major depressive disorder, recurrent, unspecified
F34	Persistent mood [affective] disorders
F34.0	Cyclothymic disorder
F34.1	Dysthymic disorder
F34.8	Other persistent mood [affective] disorders
F34.9	Persistent mood [affective] disorder, unspecified
F39	Unspecified mood [affective] disorder
Schizophrenia And Other Psychosis	
F20.0	Paranoid schizophrenia
F20.1	Disorganized schizophrenia
F20.2	Catatonic schizophrenia
F20.3	Undifferentiated schizophrenia
F20.5	Residual schizophrenia
F20.8	Other schizophrenia
F20.9	Schizophrenia, unspecified
F21	Schizotypal disorder
F22	Delusional disorders
F23	Brief psychotic disorder
F24	Shared psychotic disorder

F25.0	Schizoaffective disorder, bipolar type
F25.1	Schizoaffective disorder, depressive type
F25.8	Other schizoaffective disorders
F25.9	Schizoaffective disorder, unspecified
F28	Other psychotic disorder not due to a substance or known physiological condition
F29	Unspecified psychosis
Migraine/headache	
G43.0	Migraine without aura
G43.1	Migraine with aura
G43.4	Hemiplegic migraine
G43.5	Persistent migraine aura without cerebral infarction
G43.6	Persistent migraine aura with cerebral infarction
G43.7	Chronic migraine without aura
G43.A	Cyclical vomiting
G43.C	Periodic headache syndromes in child or adult
G43.D	Abdominal migraine
G43.8	Other migraine
G43.9	Migraine, unspecified
G44	Other headache syndromes
G44.0	Cluster headaches and other trigeminal autonomic cephalgias (TAC)
G44.1	Vascular headache, not elsewhere classified
G44.2	Tension-type headache
G44.3	Post-traumatic headache
G44.4	Drug-induced headache, not elsewhere classified
G44.5	Complicated headache syndromes
G44.8	Other specified headache syndromes
Other Psychiatric Conditions	
This group included all other codes F01-F09 AND Z86.5 not included in the group of mood disorder and schizophrenia and other psychosis	
Others	
This group included all other codes not contained in the above group 1-5	