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Changes in Antiepileptic Drug Prescribing Patterns in Pregnant Women with Epilepsy

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Abstract

Objective—We analyzed current prescribing patterns for antiepileptic drugs (AEDs) in pregnant women with epilepsy (PWWE) at 20 USA tertiary epilepsy centers.

Methods—The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study is an NIH-funded, prospective, observational, multi-center investigation of pregnancy outcomes for both mother and child, which enrolled women from December 2012 to

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January 2016. Inclusion criteria for PWWE included ages 14–45 years and up to 20 weeks gestational age. Exclusion criteria included history of psychogenic non-epilepstic spells, expected IQ<70, other major medical illness, progressive cerebral disease, and switching AEDs in pregnancy prior to enrollment.

Results—351 PWWE were enrolled in the MONEAD study, which included 259 (73.8%) on monotherapy, 77 (21.9%) on polytherapy, and 15 (4.3%) on no AEDs. The most common AED monotherapy regimens were lamotrigine (42.1% of monotherapies), levetiracetam (37.5%), carbamazepine (5.4%), zonisamide (5.0%), oxcarbazepine (4.6%), and topiramate (3.1%). All other individual monotherapies were each <1%. The most common AED polytherapy combination was lamotrigine + levetiracetam (42.9% of polytherapies), followed by lacosamide + levetiracetam (6.5%), lamotrigine + zonisamide (5.2%), and all other remaining combinations (each <4%); only 5.2% of polytherapy subjects were on ≥3 AEDs (1.1% of total PWWE). Only four subjects (1.1%) were on valproate (1 monotherapy, 3 polytherapy).

Conclusions—The distribution of AED use likely reflects current prescribing patterns for pregnant women with epilepsy cared for in USA tertiary epilepsy centers. This distribution has changed markedly since the turn of the century, but changes in the general population remain uncertain.

Keywords

Pregnancy; Epilepsy; Seizures; Antiepileptic drugs

1. INTRODUCTION

In the 1990's, several pregnancy registries were established to assess the risks of *in utero* exposure to antiepileptic drugs (AEDs) for congenital malformations. In the early 21st century, findings from these registries began to disclose differential risks across AEDs; most notably the highest risk was noted for valproate.[1] In addition, we previously reported that fetal valproate exposure posed the highest risk for cognitive impairments,[2] and others have found that valproate has an increased risk for autism.[3] However, little data exists on the impact of these findings on prescription practices.

The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study is a continuation of the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study, and has now completed enrollment of a new cohort of pregnant women with epilepsy (PWWE) and the children born to them. Here we present analysis of the distribution of AEDs to examine changes in prescribing practices for PWWE.

2. METHODS

2.1. Design

MONEAD study is an NIH-funded, prospective, observational, multi-center investigation of pregnancy outcomes for both PWWE and their children. These outcomes will be reported in the future. The purpose of this publication is to describe current prescribing patterns for AEDs in PWWE at tertiary epilepsy centers in the USA. Enrollment occurred from

December 2012 – January 2016. Twenty clinical sites at tertiary USA epilepsy centers were selected that specialize in management of women with epilepsy during childbearing years. The 20 MONEAD sites included Augusta University, Columbia University, Emory University, Geisinger Clinic, Brigham and Women's Hospital of Harvard University, Henry Ford Health System, Johns Hopkins University, Minnesota Epilepsy Group, New York University, Northwell Health, Northwestern University, Stanford University, University of Alabama, University of Arizona, University of Cincinnati, University of Miami, University of Pittsburgh, University of Southern California, University of Washington, and Wake Forest University.

PWWE were recruited primarily from the 20 epilepsy practices, but also via referral from obstetricians and other physicians. PWWE could also self refer. Inclusion criteria for PWWE were ages 14–45 years and <20 weeks gestational age. Exclusion criteria included history of psychogenic non-epileptic spells, expected IQ<70, other major medical illness, progressive cerebral disease, and switching AEDs in pregnancy prior to enrollment. Unlike the NEAD study which enrolled only PWWE on the most common monotherapies, MONEAD was specifically designed to enroll all PWWE regardless of treatment regimen in order to obtain a representative sample of PWWE and their AED treatments. In addition to PWWE, the MONEAD Study also enrolled two control groups: healthy pregnant women (HPW) and non-pregnant women with epilepsy (NPWWE) as well as the children born to the PWWE and HPW, their fathers, and maternal relatives. Data were collected from subjects and their medical records.

2.2. Standard Protocol Approvals, Registrations, and Patient Consents

This study is registered on clinicaltrials.gov as NCT01730170, and was approved by the individual site IRBs. Signed informed consent was obtained from all adult subjects prior to participation.

2.3. Outcome Measures

For this analysis, the primary outcome was the distribution of AED(s) use in PWWE at enrollment. Other demographics are provided.

3. RESULTS

Demographics for the PWWE are depicted in Table 1. The majority (74%) of PWWE were on monotherapy, and the most common type of epilepsy was focal epilepsy (62%). The distributions of monotherapy, polytherapy, and no AED use in PWWE were similar across different epilepsy types: 1) focal epilepsy: 75% monotherapy, 20% polytherapy, and 5% no AED, 2) generalized epilepsy: 73% monotherapy, 25% polytherapy, and 2% no AED, 3) unclassified or mixed seizures: 70% monotherapy, 19% polytherapy, and 11% no AED. The distributions of specific AEDs used in PWWE are depicted in Tables 2 and 3. Note that depicted AED use reflects use at time of enrollment in the MONEAD study. The most commonly used monotherapies were lamotrigine and levetiracetam, and the most commonly prescribed polytherapy combination was lamotrigine and levetiracetam. Use of other AEDs was much less and variable, especially for polytherapy. The median number of PWWE

enrolled at each center was 13 (min=3, max=41). AEDs were grouped into five categories (LTG monotherapy, LEV monotherapy, other monotherapy, polytherapy, no AED) to analyze for potential differences in AEDs across the duration of the study (i.e., December 2012 – January 2016) and across regions in the USA (i.e., northeast, southeast, midwest, and west). There were no significant difference in AED prescribing patterns by year of enrollment (p = 0.7009, chi-square test), and no significant difference in AED prescribing patterns by geographic region (p = 0.5622, chi-square test).

4. DISCUSSION

The distribution of AEDs employed likely reflects current prescribing patterns for PWWE cared for in USA tertiary epilepsy centers given our sample of 20 centers across the country. Lamotrigine and levetiracetam are the most commonly prescribed AEDs in monotherapy and also in two-drug polytherapy. A variety of other AEDs were each prescribed to only small numbers of PWWE, especially for other polytherapy combinations, which suggests that the present lack of evidence for many AEDs on maternal and fetal risks during pregnancy leaves physicians without clear choices after lamotrigine and levetiracetam.

The cohort of PWWE from our preceding NEAD study was collected from October 1999 to February 2004. The four most commonly used monotherapies from tertiary epilepsy centers at that time were carbamazepine, lamotrigine, phenytoin and valproate. Only PWWE on one of these monotherapy regimens were enrolled in NEAD. No other AED monotherapies were prescribed in numbers that would have been adequate to analyze. The 25 NEAD centers included two from the UK, but the overall distribution remains the same if the UK centers are removed.

AED use in pregnancy registries in the late 20th and early 21st century was similar overall to the NEAD study. For example, the most commonly used AEDs in PWWE were carbamazepine, lamotrigine, phenytoin and valproate in the UK Epilepsy and Pregnancy Register from 1996–2005;[4] carbamazepine, lamotrigine, phenytoin and valproate in the Australian AED Pregnancy Registry from 1999–2006;[5] and carbamazepine, lamotrigine, phenobarbital and valproate in the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) from 1999–2010.[6]

In contrast to distributions in NEAD and the pregnancy registries in the late 20th and early 21st century, the MONEAD study which enrolled from December 2012 – January 2016 had a markedly different distribution with the most commonly used monotherapies being lamotrigine (42.1%) and levetiracetam (37.5%), followed distantly by carbamazepine (5.4%), zonisamide (5.0%), oxcarbazepine (4.6%), and topiramate (3.1%). The reduction in valproate use likely reflect response to findings of teratogenic rsks and new treatment guidelines.[1,2,7,8] Similarly, the increase use of lamotrigine and levetiracetam are likely due to findings of low teratogenic risks for both anatomical and behavioral outcomes.[1] However, the decline in use of carbamazepine does not reflect its relatively low anatomical and behavioral teratogenic risks.[1]

Data on changes in AED use across time from the pregnancy registries are limited. The Australian AED Pregnancy Registry noted that from 1999–2005 the most commonly used AEDs were carbamazepine (38.5%), lamotrigine (32.7%), valproate (31.3%) and phenytoin (6.7%), but from 2006–2012 they were lamotrigine (37.0%), carbamazepine (27.55%), valproate (24.4%), levetiracetam (17.9%), and topiramate (11.0%).[9] By 2012, the Australian AED Pregnancy Registry noted that the most commonly used AEDs were lamotrigine and levetiracetam (each over 30% of all women), followed by carbamazepine and valproate (each over 20% of women);[10] percentages include polytherapies. The increase use of levetiracetam and topiramate is also reflected in the North American AED Pregnancy Registry (NAAPR), which first published its AED distributions in 2012, depicting totals for 1997–2011, but did not report AED changes across time.[11] Recent preliminary data from the NAAPR[12] and UK Epilepsy and Pregnancy Register[13] mirrored the changes in NEAD to MONEAD. Further, in preparation for the MONEAD study, we conducted a survey of AED use in women of childbearing age at eight of our NEAD centers in 2007.[14] We surveyed a total of 932 women of childbearing age with epilepsy and found that 53% were on monotherapy, 41% on polytherapy, and 6% on no AED. The most common monotherapies were lamotrigine (36%), levetiracetam (18%), carbamazepine (14%), topiramate (9%), and valproate (8%). Thus, it appears that changes at USA tertiary epilepsy centers were already occurring by 2007.

The AED prescription changes for PWWE in NEAD-MONEAD and the pregnancy registries may not reflect changes in other patient populations. However, published data on changes in AED prescription practices are limited. Initial monotherapy prescriptions for the three most commonly used AEDs in Sweden from 2007 to 2013 exhibited a modest increase in lamotrigine (18% to 21%) and reductions in carbamazepine (40% to 24%) and valproate (24% to 17% in men and 23% to 11% in women).[15] In Germany from 2007 to 2014, use of levetiracetam (14% to 36%) and lamotrigine (15% to 20%) increased while use of carbamazepoine (40% to 21%) and valproate (32% to 26%) decreased across men and women combined.[16] In Ireland from 2008 to 2013, the rate of prescribing of valproate to women of childbearing age declined only slightly from 3.5/1000 to 3.14/1000 per eligible population.[17] A study of the Florida Medicaid population from 1999–2009 reflects similar overall changes.[18] In 2000, the four most commonly used AEDs in the Florida Medicaid system were carbamazepine, phenobarbital, phenytoin and valproate. In 2009, the four most commonly used AEDs in pregnant women in the Florida Medicaid system were lamotrigine, levetiracetam, carbamazepine, and phenytoin. Valproate fell from 23% to 8%, but this decline was entirely in women taking valproate for epilepsy indications, and there was no decrease in valproate use for other indications (i.e., psychiatric). This finding raises the question as to whether women prescribed valproate for indications other than epilepsy are being adequately advised and consented on valproate's teratogenetic risks. Additional studies in general populations are needed to assess the impact of findings on AED teratogenesis and determine if further educational and health care policy efforts are required to improve knowledge and decisions by patients and physicians.

As noted above, some of the changes in AEDs used during pregnancy are related to improved knowledge on the relative risks for a few AEDs. However, other monotherapies and polytherapy AED regimens are being employed even though they have inadequate data

on teratogenic risks. This is reflected in the MONEAD enrollment data showing that prescriptions to all other AEDs were dispersed across a variety of monotherapies and polytherapies each of which had only small numbers of PWWE. Of the approximately 30 different AEDs available in the USA, only 9 have reasonable data on risks for congenital malformations: lower risks for lamotrigine, levetiracetam, oxcarbazepine, carbamazepine, and possibly gabapentin; intermediate risks for phenobarbital, topiramate and possibly phenytoin; and highest risk for valproate.[1] In regards to risks for impaired neuropsychological development from fetal AED exposure, only 6 AEDs have reasonable data: lower risks for lamotrigine, levetiracetam, and carbamazepine; intermediate risks for phenobarbital and possibly phenytoin; and highest risk for valproate.[1] Note that reasonable data may not imply adequate data as evidenced by the observed possible effects of lamotrigine on cerebral lateralization, and the lack of data on actual fetal exposure in the setting of marked and variable clearance changes for lamotrigine and some other AEDs.[1,2] Clearly, the effects on maternal and fetal outcomes are not yet known for many AEDs in monotherapy and various polytherapies.[1] In addition, there is a great need to expand our knowledge of clearance changes during pregnancy in more AEDs and to understand the effects of those changes on seizure risks. Future studies are needed to delineate differential effects of AEDs on pregnancy outcomes (i.e., obstetrical, neonatal and child). Future findings from the MONEAD study will contribute to expansion of our evidence base.

6. CONCLUSIONS

Patterns of AED use in PWWE were assessed at USA tertiary epilepsy centers from December 2012 to January 2016. The most commonly used monotherapies were lamotrigine and levetiracetam, and the most commonly prescribed polytherapy combination was lamotrigine and levetiracetam. Use of other AEDs was much less and variable, especially for polytherapy. The distribution of AED use likely reflects current prescribing patterns for pregnant women with epilepsy cared for in USA tertiary epilepsy centers. This distribution has changed markedly since the turn of the century, but changes in the general population remain uncertain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Antiepileptic drugs (AEDs) use in pregnant women with epilepsy was assessed.
- AEDs in USA tertiary epilepsy centers from December 2012 to January 2016.
- Lamotrigine and levetiracetam were by far the most commonly prescribed AEDs.
- New information has markedly changed AED use during pregnancy in tertiary centers.
- Further studies are needed to determine pregnancy AED use for general population.

Table 1

Demographics for Pregnant Women with Epilepsy

Total Enrolled	**351**
Mean Age (SD)	31 (5)
Education - n (%)	
No College Degree	104 (30%)
College Degree	159 (45%)
Advanced Degree	88 (25%)
Mean IQ (SD) *	98 (13)
Race - n (%)	
White	295 (84%)
Black or African American	25 (7%)
Other	28 (8%)
Subject desires not to answer	3 (1%)
Ethnicity - n (%)	
Hispanic or Latino	70 (20%)
Non-Hispanic or Non-Latino	281 (80%)
AED Category - n (%)	
AED Monotherapy	259 (74%)
AED Polytherapy	77 (22%)
Without AED	15 (4%)
Seizure Types **	
Generalized	110 (31%)
Focal ***	217 (62%)
Unclassified	27 (8%)

IQ-intelligence quotient, SD=standard deviation, n=number, AED=antiepileptic drug

* Two subjects had missing data for IQ score.

** Three subjects reported multiple seizure types; 2 reported Generalized & Focal seizures and 1 reported Generalized & Unclassified seizures. Percentages represent the proportion of subjects who have that seizure type and total may sum to more than 100%.

*** Incudes focal to bilateral tonic clonic seizures.

Table 2

Use of Specific AEDs in PWWE by Epilepsy Type

	Monotherapy									Polytherapy		
	LTG	**LEV**	**CBZ**	**ZNS**	**OXC**	**TPM**	**LCM**	**VPA**	**Other MonoTx**	**LTG+LEV**	**Other PolyTx Combos**	**No**
Seizure Types *												
Generalized	24	38	0	12	1	3	0	1	1	15	13	2
Focal	79	51	11	1	11	6	2	0	2	14	30	10
Unclassified	7	9	3	0	0	0	0	0	0	4	1	3
Total PWWE	109	97	14	13	12	8	2	1	3	33	44	15
% of Total	31.1%	27.6%	4.0%	3.7%	3.4%	2.3%	0.6%	0.3%	0.9%	9.4%	12.5%	4.3%

Table denotes number of PWWE on each AED at the time of enrollment.

AED=antiepileptic drug, PWWE=pregnant women with epilepsy, LTG=Lamotrigine, LEV=Levetiracetam, CBZ=Carbamazepine, ZNS=Zonisamide, OXC=Oxcarbazepine, TPM=Topiramate, LCM=lacosamide, VPA=Valproate, Other MonoTx=Monotherapies (includes one each of Felbamate, Gabapentin, and Phenobarbital), Other PolyTx Combos=Other Polytherapy Combinations (see Table 3 for details), NA=non-applicable.

* Three subjects reported multiple seizure types; 2 subjects on LTG and TPM reported Generalized & Focal seizures and 1 subject on LEV reported Generalized & Unclassified seizures.

Table 3

Listing of Medications for PWWE Subjects on Polytherapy

AED Regime	Count	% Total of Polytherapy
Lamotrigine, Levetiracetam	33	42.9
Lacosamide, Levetiracetam	5	6.5
Lamotrigine, Zonisamide	4	5.2
Levetiracetam, Phenytoin	3	3.9
Carbamazepine, Lamotrigine	2	2.6
Clonazepam, Lamotrigine	2	2.6
Ethosuximide, Lamotrigine	2	2.6
Lamotrigine, Oxcarbazepine	2	2.6
Levetiracetam, Oxcarbazepine	2	2.6
Levetiracetam, Topiramate	2	2.6
Carbamazepine, Lacosamide	1	1.3
Carbamazepine, Levetiracetam	1	1.3
Ethosuximide, Lamotrigine, Levetiracetam, Zonisamide	1	1.3
Felbamate, Oxcarbazepine, Topiramate	1	1.3
Gabapentin, Lamotrigine	1	1.3
Lacosamide, Lamotrigine	1	1.3
Lacosamide, Topiramate	1	1.3
Lamotrigine, Levetiracetam, Zonisamide	1	1.3
Lamotrigine, Oxcarbazepine, Valproate	1	1.3
Lamotrigine, Phenobarbital	1	1.3
Lamotrigine, Phenytoin	1	1.3
Lamotrigine, Pregabalin	1	1.3
Lamotrigine, Topiramate	1	1.3
Lamotrigine, Valproate	1	1.3
Levetiracetam, Perampanel	1	1.3
Levetiracetam, Phenobarbital	1	1.3
Levetiracetam, Valproate	1	1.3
Lorazepam, Topiramate	1	1.3
Oxcarbazepine, Topiramate	1	1.3
Oxcarbazepine, Zonisamide	1	1.3