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Trends in Valproate Prescriptions for Non-Epilepsy Indications among Women Aged 15 – 44 Years U.S. 1996 – 2007:
[A Population-Based Study]

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2011

Abstract

Trends in Valproate Prescriptions for Non-Epilepsy Indications among Women Aged 15 – 44 Years U.S. 1996 – 2007:
[A Population-Based Study]

By Demilade A. Adedinsewo

Background: Scientific evidence has consistently shown taking valproate (VPA) during pregnancy increases the risk of neural tube defects. This study was conducted to estimate the prevalence and trends in VPA prescriptions for non-epilepsy indications among U.S. women of childbearing age.

Methods: We obtained data on individual prescriptions for women aged 15 – 44 years from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007. Women were classified as having epilepsy/seizure (WWE) or not (WWNE) using ICD-9-CM diagnostic codes. Using sampled case specific weights and variances; we estimated the number of anti-epileptic drug (AED) prescriptions, VPA prescriptions, patient visits, and the prevalence of AED and VPA prescriptions to women with no epilepsy or seizure.

Results: Eighty-eight percent of all AED prescriptions and 83% of all VPA prescriptions were for non-epilepsy/non-seizure indications. The prevalence of all AED prescriptions among WWNE more than tripled between 1996 and 2007 (10.3 vs. 34.9 per 1000 patient visits), while the prevalence of VPA prescriptions in this group remained stable over time- 3.1 per 1000 patient visits (95% CI: 2.3 - 3.9) in 1996-1998 vs. 3.7 per 1000 patient visits (95% CI: 2.8 - 4.7) in 2005-2007. Eight-three percent of all VPA prescriptions were to WWNE-- most for psychiatric indications

Conclusion: Our data showed that between 1996 and 2007, in the United States, the use of the teratogen--VPA did not decline among women of childbearing age who did not have a diagnosis of epilepsy or seizure. Thus far, prevention guidelines have been developed for WWE while little attention has been given to women with psychiatric disorders who may be prescribed VPA. The results of this study suggest the need for guidelines to either avoid or reduce significantly the use of VPA among women of childbearing potential who do not have epilepsy or seizure disorders. Interventions to prevent birth defects associated with VPA use during pregnancy are urgently needed and should be targeted towards women receiving VPA for psychiatric indications as well as toward women with epilepsy and seizure disorders.

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TABLE OF CONTENTS

BACKGROUND

Anti-epileptic Drugs (AEDs) are medications used to control seizures and are the mainstay of treatment for the management of patients with epilepsy- a brain disorder associated with repeated disruptions in normal brain function, known as epileptic seizures(1). AEDs are very effective and they have been shown to adequately control seizures in up to 80% of persons with this disorder(2). AEDs have been frequently described in terms how long they have been on the market- with those available before 1990 classified as “older” generation AEDs while those developed afterward are termed “newer’ generation AEDs(3, 4).

Although AEDs are effective in control of seizures, their use during early pregnancy is associated with a spectrum of birth defects, with the type of birth defect usually depending on the AED used (2). Valproate and Carbamazepine (older generation AEDs) have been associated with multiple congenital anomalies such as: neural tube defects (NTDs), cardiovascular and urinary tract anomalies, and orofacial clefts (5-7). More recently, lamotrigine (a newer generation AED) has been linked with an increased risk of oral clefts in babies born to women who take this medication during pregnancy (6, 8).

While AEDs were developed for the treatment of seizure disorders, they are also effective in the treatment of patients with non-epilepsy disorders such as trigeminal neuralgia, neuropathic pain syndromes, migraine, bipolar disorder, and essential tremor (9, 10). As a result, many AEDs are used off-label to treat these diseases or have subsequently received secondary indications for the treatment of non-epilepsy disorders (11). For example, valproate (VPA) was first approved for the treatment of epilepsy in 1978, but

has now been approved for the treatment of manic episodes associated with bipolar disorder and for migraine prophylaxis (12, 13). VPA has become one of the most commonly utilized AED in the treatment of bipolar disorder due to its anti-manic efficacy and a probable long-term, mood-stabilizing effect (14).

In 1982, the CDC published a case control study from the birth defects registry in Lyons, France which showed VPA use in early pregnancy produced a 20 fold increase in the odds of having a baby with spina bifida(15). Soon thereafter, the American manufacturer of the drug wrote a letter to all physicians in the United States informing them of this risk. VPA was subsequently established as a drug known to cause a severe birth defect--spina bifida and it joined the FDA short list of known human teratogens (category D) (16).

In several studies, valproate (VPA) has been shown to be a significant risk factor in the development of NTDs in infants of women who receive this drug during early pregnancy (17-21). Valproate reportedly inhibits the intestinal absorption of folate - which has demonstrated an enormous role in decreasing the risk of NTDs (22, 23).

Data from the United Kingdom (UK) Epilepsy and Pregnancy Registry indicate that VPA monotherapy is associated with the highest frequency of multiple congenital malformations compared to other AEDs. Valproate shows a three-fold increase in the odds of multiple congenital anomalies when compared to carbamzepine (6.2% vs. 2.2%, OR= 2.97, $p<0.001$) and a two-fold increase when compared to lamotrigine (6.2% vs. 3.2%; OR = 1.93, $p=0.015$) (24). Data from the North American Antiepileptic Drug

Pregnancy Registry also show that VPA monotherapy is associated with a high risk of major malformations (25).

Studies have also shown other adverse effects of VPA exposure in utero. A study conducted in the UK among children born to women with epilepsy showed that children exposed to levitiracetam in utero obtained higher developmental scores than children exposed to VPA. Only eight percent of children exposed to levitiracetam in utero fell within the below average range of development (i.e. obtaining a developmental quotient score of < 84), compared with 40 percent of children exposed to VPA ($p < 0.001$) (26). Another multi-center study conducted in the United States and the UK reported in utero exposure to VPA was associated with poorer cognitive outcomes as compared to other commonly used AEDs (lamotrigine, carbamazepine, phenytoin)(27). In this study, the mean IQ score for children exposed to VPA was 9 points (95% CI = 3.1 to 14.6) lower than the mean score of those exposed to lamotrigine at the age of 3 years (27); however, differences seen in IQ between children exposed to VPA, carbamazepine and phenytoin did not demonstrate statistical significance.

Gilboa et al. recently estimated that approximately 40 cases of spina bifida occur annually in the United States as a result of VPA use during pregnancy for all indications, suggesting that significant prevention could occur from a reduction in the use of VPA among women of childbearing potential (2).

Recent clinical guidelines from the American Academy of Neurology and the American Epilepsy Society recommend that VPA be avoided during pregnancy if possible among women with epilepsy (WWE) to reduce the risk of congenital malformations and advised

that women of childbearing age be switched to a less teratogenic regimen (28). Whereas, no current guideline exists, specifically, regarding the management of women without a diagnosis of epilepsy who are also being prescribed VPA.

Meador et al. demonstrated a significant decline in the use of VPA among women with epilepsy who attend specialized epilepsy clinics (29). Similarly, the accumulating evidence for an association between VPA and birth defects and other adverse outcomes has been suggested as an explanation for a marked fall in the prescribing of VPA for adolescent females with epilepsy in the UK and a corresponding increase in the prescription of lamotrigine which is thought to carry lower risks(18). However, there is no evidence demonstrating that this 'fall' in prescriptions translates to women who do not have a diagnosis of epilepsy as well.

There is very little or no information regarding the prescribing patterns and trends in VPA prescriptions among U.S. women of childbearing age who do not have diagnosis of epilepsy o seizure. We thus aimed to estimate the prevalence of and evaluate the trends in VPA prescriptions among women aged 15 – 44 years with non-epilepsy/non-seizure disorders.

Trends in Valproate Prescriptions for Non-Epilepsy Indications among Women Aged 15 – 44 Years U.S. 1996 – 2007:
[A Population-Based Study]

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ABSTRACT

Background: Scientific evidence has consistently shown taking valproate (VPA) during pregnancy increases the risk of neural tube defects. This study was conducted to estimate the prevalence and trends in VPA prescriptions for non-epilepsy indications among U.S. women of childbearing age.

Methods: We obtained data on individual prescriptions for women aged 15 – 44 years from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey from 1996-2007. Women were classified as having epilepsy (WWE) or not (WWNE) using ICD-9-CM diagnostic codes. We estimated the number of anti-epileptic drugs (AEDs), VPA prescriptions, patient visits (PV), and the prevalence of AED and VPA prescriptions to WWNE.

Results: Eighty-three percent of VPA prescriptions were issued to WWNE. The prevalence of AED prescriptions among WWNE tripled between 1996 and 2007 (10.3 vs. 34.9 per 1000 PV), while the prevalence of VPA prescriptions remained stable- 3.1 per 1000 PV (95% CI: 2.3 - 3.9) in 1996-1998 vs. 3.7 per 1000 PV (95% CI: 2.8 - 4.7) in 2005-2007. Of all VPA prescriptions to WWNE, most are for psychiatric indications.

Conclusion: Over the study period, use of the teratogen--VPA did not decline among WWNE. Prevention guidelines have been developed for WWE while little attention has been given to WWNE also receiving VPA. Our results suggest the need for guidelines to either avoid or reduce the use of VPA among WWNE. Interventions to prevent VPA associated birth defects are urgently needed and should be targeted towards women with psychiatric disorders as well as WWE.

INTRODUCTION

In 1982, the CDC published a case control study from the birth defects registry in Lyons, France which showed valproic acid (VPA) use in early pregnancy produced a 20 fold increase in the odds of having a baby with spina bifida(15). Soon thereafter, the American manufacturer of the drug wrote a letter to all physicians in the United States informing them of this risk. Valproic acid was later established as a drug known to cause a severe birth defect--spina bifida and it joined the FDA short list of known human teratogens (category D) (16). More recent studies have also shown VPA to be significant risk factor for multiple congenital anomalies, including spina bifida (2, 5, 17-25, 28) as well as intellectual impairment in the infants of women who receive this drug during pregnancy (26, 27, 30).

Clinical evidence and scientific studies have demonstrated that AEDs cannot usually be discontinued in patients without putting the patient at risk of relapse (31-33) and it has also been argued that VPA was uniquely successful in preventing some seizures types such as idiopathic generalized epilepsies (30, 34). Thus, any seizure resulting from AED discontinuation among pregnant women may adversely affect the outcome of the pregnancy (35). As such, VPA has remained on the market and due to this, there continued to be reports, not only, of increased risk of spina bifida in exposed pregnancies but also increased risk for all major malformations. Clinicians, treating women with epilepsy (WWE), have become increasingly concerned about the risk of congenital malformations due to VPA use in pregnancy and clinical guidelines from the American Academy of Neurology and the American Epilepsy Society recommend that VPA be

avoided during pregnancy among WWE and advised that women of childbearing age be switched to a less teratogenic regimen (28).

While AEDs were developed for the treatment of seizure disorders, they are also effective in the treatment of non-epilepsy disorders such as neuropathic pain syndromes, migraine and bipolar disorder and as a result, many AEDs including VPA are used, either off-label, to treat these disorders, or have subsequently received approval for these secondary indications (9-14). Valproic acid, particularly, has received approval for the treatment of manic episodes associated with bipolar disorder and for migraine prophylaxis and has become one of the most commonly utilized AED in the treatment of bipolar disorder (12-14).

Gilboa et al. recently estimated that approximately 40 cases of spina bifida occur annually in the United States as a result of VPA use during pregnancy for all indications, suggesting that significant prevention could occur from a reduction in the use of VPA (2). While much research has been conducted on the use of VPA among WWE, little is known about the trends in VPA use among women without a diagnosis of epilepsy or seizure in the United States. We sought to determine the trends in the use of VPA among women of childbearing age without a diagnosis of epilepsy or seizure and whether or not its use was decreasing--a trend that would prevent adverse outcomes to the exposed embryos and fetuses.

METHODS

Study Design: We obtained data on individual prescriptions given during patient visits to office based physicians and hospital emergency/outpatient departments from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) respectively, available from the National Center for Health Statistics for the years 1996 - 2007 (36). Both NAMCS and NHAMCS provide data describing the use of ambulatory medical care services in the United States. NAMCS data were obtained from a national sample of office-based physicians. Physicians were selected using a multistage probability design based on location, number of physician practices within the primary sampling unit (PSU), and number of patient visits within their practice.(37) NHAMCS contains data on visits to hospital emergency and outpatient departments. Hospitals were selected using a four-stage probability design based on location, number of hospitals within the PSU, number of clinics/emergency service areas within outpatient/emergency departments, and number of patient visits within clinics/emergency service areas. The data from both these surveys include patient demographic information, ICD-9-CM-coded diagnoses related to the visit, and medications prescribed at each sampled visit. (38)

Study Population: We restricted analyses to prescriptions for women of reproductive age (15 - 44 years) and classified these women into two broad diagnostic categories: those with a diagnosis of epilepsy/seizure (ICD-9-CM diagnostic codes 345.xx and 780.3x) and those without a diagnosis of epilepsy/seizure (all other women). The former category was designated as ‘women with epilepsy’ (WWE) and the latter as ‘women with no epilepsy’

(WWNE). Among WWNE, we identified a sub-population of women who received a prescription for at least one of 20 specific AEDs, using documentation provided by the National Center for Health Statistics to identify codes for both generic and brand name formulations(37, 38). AEDs were identified as one of the following: carbamazepine, clonazepam, clorazepate, ethosuximide, felbamate, fosphenytoin, gabapentin, lamotrigine, levetiracetam, mephobarbital, oxcarbazepine, phenobarbital, phenytoin, primidone, tiagabine, topiramate, valproate, zonisamide, or vigabatrin.

Within the sub-population of WWNE with an AED prescription, the subjects were further classified into six mutually exclusive diagnosis categories using a systematic ranking of diagnosis type most likely to receive an AED prescription. Disorders were grouped in the following categories; where a subject had more than one relevant diagnosis recorded, the preference was given to diagnoses in following order:

1. Affective disorders (ICD-9-CM Codes: 296, 298.0, 301.1, 309.1, 331)
2. Schizophrenic disorders (ICD-9-CM Code: 295)
3. Other psychiatric indications (ICD-9-CM Codes: 290–294, 297–302 (excluding 298.1 & 301.1), 306– 310 (excluding 309.1), 312–316)
4. Migraine (ICD-9-CM Code: 346)
5. Pain disorders (ICD-9-CM Codes: 053, 250, 350—359, 720—724)
6. Other non-epilepsy/non-seizure disorders: All non-epilepsy disorders for which an AED was prescribed, not classified above.

Statistical Analysis: We estimated the total number of patient visits and the total number of all AED and VPA prescriptions for the entire sample of women using case-specific weights and variances. The overall prevalence of AED use and VPA use (prescriptions per 1,000 patient-visits) was determined for 3-year time intervals (1996-1998, 1999-2001, 2002-2004, 2005-2007) for the overall population as well as among those with and without epilepsy/seizure.

For all VPA prescriptions among women without epilepsy, we described the distribution of diagnosis categories observed. All analyses were conducted using SURVEY procedures for statistical analysis of data with complex survey designs in SAS 9.3 (Cary, NC).

RESULTS

Over the 12-year period analyzed, an estimated 52 million AED prescriptions were issued to WWNE (i.e., approximately 4.3 million per year). Of these, approximately 17% were for VPA.

Table 1 shows the prevalence and the estimated number of AED and VPA prescriptions overall and for 3-year intervals. We observed a greater than 3 fold increase in the number and prevalence of prescriptions for AEDs among WWNE between 1996 and 2007; from 10.3 per 1000 patient visits (95% CI: 8.4, 12.1) in 1996 – 1998 to 34.9 per 1000 patient visits (95% CI: 30.4, 39.3) in 2005 – 2007.

As seen in both table 1 and figure 1, the number and prevalence of VPA prescriptions among WWNE has remained relatively stable, showing a modest but statistically insignificant increase over the years, ranging from 3.1 per 1,000 patient visits (95% CI: 3.2, 4.2) to 3.7 per 1000 patient visits (95% CI: 2.8, 4.7).

Figure 2 shows the proportions of VPA prescriptions for all women of childbearing age by diagnosis category (WWNE and WWE). It demonstrates that the vast majority (83%) of all VPA prescriptions to women of childbearing age, were issued for non-epilepsy/non-seizure indications and this ratio has remained the same over the year intervals studied.

Figure 3 shows the different indications for which VPA is being prescribed among WWNE with almost three-quarters of VPA prescriptions made for psychiatric diagnoses. Of all VPA prescriptions to WWNE, 57% were for an affective disorder, 7% for

schizophrenic disorders, and 10% for other psychiatric diagnoses. Three percent of the total VPA prescriptions were for migraine, while the remaining 21% were for other non-epilepsy/non-seizure indications.

DISCUSSION / CONCLUSION

Our data showed that between 1996 and 2007, in the United States, the use of the teratogen--VPA did not decline among women of childbearing age who did not have a diagnosis of epilepsy or seizure. In addition, we show that 83% of VPA prescriptions are to WWNE and most of these prescriptions were for psychiatric indications. Interventions to prevent birth defects associated with VPA use during pregnancy are urgently needed and should be targeted towards women receiving VPA for psychiatric indications as well as toward women with epilepsy and seizure disorders (11).

Thus far, prevention guidelines have been developed for WWE while little attention has been given to women with psychiatric disorders who may be prescribed VPA. The results of this study suggest the need for guidelines to either avoid or reduce significantly the use of VPA among women of childbearing potential who do not have epilepsy or seizure disorders.

The prevalence of AED prescriptions among WWNE has more than tripled between 1996 and 2007. Newer generation AEDs with better therapeutic effects and side effect profiles than the older generation AEDs have been introduced. Also, the marketing of these drugs has shifted from use in the management of only epilepsy/seizures to other conditions ranging from psychiatric disorders to musculoskeletal disorders (10, 11, 39). For instance, two AEDs, gabapentin and pregabalin (both AEDs), are first line treatments in peripheral neuropathic pain(10) and pregabalin is the first FDA-approved drug for the management fibromyalgia (40).

Contrary to what we expected, given that VPA is a known human teratogen, we found that the prevalence of VPA prescriptions has remained relatively stable among women with and without epilepsy.

Since about half of all pregnancies in the United States are unplanned (41), there is an urgent need to reduce the use of VPA among women of childbearing age. Avoiding the use of VPA by women of childbearing age will eliminate exposure during pregnancy. We argue that any physician considering using VPA among women of childbearing age carefully consider the considerable risk VPA causes exposed embryos and fetuses. We call attention to all women of childbearing age, because by the time that pregnancy is known, much of the damage to the embryo or fetus has already happened, as VPA does most damage in the first trimester of pregnancy (19). For women currently on the drug, they should consult with their health care provider, seeking to find safer medications for the management of their ailment.

To our knowledge, this is the first study to investigate VPA prescriptions for non-epilepsy indications among women of childbearing age in the United States. Use of recent data from a nationally representative sample of AED prescriptions in women of childbearing age allows us to accurately describe the current prescribing patterns of VPA in this population.

These datasets, however, are subject to certain limitations. With any large database, errors with entry of diagnosis codes when abstracting data or recording information are a concern, but given the large sample size and infrequency of errors, we believe this will have little effect on results. In this dataset, information was available only on the

prescriptions and not for the women themselves. As a result, we cannot know for certain if the number of women receiving VPA or AED prescriptions has changed over time, only that there have been changes in the absolute numbers of prescriptions.

Our data suggest that the largest opportunity for prevention of VPA induced birth defects would come from a major reduction in the use of this drug by women of childbearing potential who do not have a diagnosis of epilepsy or seizure, as we found that WWNE received a prescription for this teratogen 4 times as often as WWE. Our findings suggest there is an urgent need for clinicians and health care providers particularly those who manage patients with psychiatric disorders to reduce VPA prescriptions among these women. Women on this medication should also work with their clinicians to minimize the use of this drug thereby decreasing the incidence of preventable congenital malformations and increasing the likelihood that their pregnancies will be normal.

REFERENCES

1. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;46(4):470-2.
2. Gilboa SM, Broussard CS, Devine OJ, et al. Influencing clinical practice regarding the use of antiepileptic medications during pregnancy: Modeling the potential impact on the prevalences of spina bifida and cleft palate in the United States. *Am J Med Genet C Semin Med Genet* 2011;157(3):234-46.
3. Beghi E. Efficacy and tolerability of the new antiepileptic drugs: comparison of two recent guidelines. *Lancet Neurol* 2004;3(10):618-21.
4. Hsieh LP, Huang CY. Trends in the use of antiepileptic drugs in Taiwan from 2003 to 2007: A Population-Based National Health Insurance study. *Epilepsy Res* 2011.
5. Werler MM, Ahrens KA, Bosco JL, et al. Use of Antiepileptic Medications in Pregnancy in Relation to Risks of Birth Defects. *Ann Epidemiol* 2011;21(11):842-50.
6. Holmes LB, Baldwin EJ, Smith CR, et al. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. *Neurology* 2008;70(22 Pt 2):2152-8.
7. Matalon S, Schechtman S, Goldzweig G, et al. The teratogenic effect of carbamazepine: a meta-analysis of 1255 exposures. *Reprod Toxicol* 2002;16(1):9-17.

8. FDA News release: Risk of oral birth defects in children born to mothers taking topiramate 2011. (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm245594.htm). (Accessed).

9. Zaremba PD, Bialek M, Blaszczyk B, et al. Non-epilepsy uses of antiepileptic drugs. *Pharmacol Rep* 2006;58(1):1-12.

10. Johannessen Landmark C. Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. *CNS Drugs* 2008;22(1):27-47.

11. Kaufman KR. Antiepileptic drugs in the treatment of psychiatric disorders. *Epilepsy Behav* 2011;21(1):1-11.

12. FDA US. Stavzor(valproic acid) prescribing information. 2009. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022152s002lbl.pdf). (Accessed 10/27/2011).

13. Friedman BW, Grosberg BM. Diagnosis and management of the primary headache disorders in the emergency department setting. *Emerg Med Clin North Am* 2009;27(1):71-87, viii.

14. Spina E, Perugi G. Antiepileptic drugs: indications other than epilepsy. *Epileptic Disord* 2004;6(2):57-75.

15. Valproic acid and spina bifida: a preliminary report--France. *MMWR Morb Mortal Wkly Rep* 1982;31(42):565-6.

16. Bjerkedal T, Czeizel A, Goujard J, et al. Valproic acid and spina bifida. *Lancet* 1982;2(8307):1096.

17. Perucca E. Birth defects after prenatal exposure to antiepileptic drugs. *Lancet Neurol* 2005;4(11):781-6.

18. Ackers R, Besag FM, Wade A, et al. Changing trends in antiepileptic drug prescribing in girls of child-bearing potential. *Arch Dis Child* 2009;94(6):443-7.

19. Harden CL, Meador KJ, Pennell PB, et al. Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology* 2009;73(2):133-41.

20. Ornoy A. Valproic acid in pregnancy: how much are we endangering the embryo and fetus? *Reprod Toxicol* 2009;28(1):1-10.

21. Jentink J, Loane MA, Dolk H, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. *N Engl J Med* 2010;362(23):2185-93.

22. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. *Lancet* 1991;338(8760):131-7.

23. De Wals P, Tairou F, Van Allen MI, et al. Reduction in neural-tube defects after folic acid fortification in Canada. *N Engl J Med* 2007;357(2):135-42.

24. Morrow J, Russell A, Guthrie E, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006;77(2):193-8.

25. Wyszynski DF, Nambisan M, Surve T, et al. Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurology* 2005;64(6):961-5.

26. Shallcross R, Bromley RL, Irwin B, et al. Child development following in utero exposure: levetiracetam vs sodium valproate. *Neurology* 2011;76(4):383-9.

27. Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 2009;360(16):1597-605.

28. Harden CL, Meador KJ, Pennell PB, et al. Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2009;50(5):1237-46.

29. Meador KJ, Penovich P, Baker GA, et al. Antiepileptic drug use in women of childbearing age. *Epilepsy Behav* 2009;15(3):339-43.

30. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 2004;75(11):1575-83.

31. Schmidt D. AED discontinuation may be dangerous for seizure-free patients. *J Neural Transm* 2011;118(2):183-6.

32. Hixson JD. Stopping antiepileptic drugs: when and why? *Curr Treat Options Neurol* 2010;12(5):434-42.

33. Shih JJ, Ochoa JG. A systematic review of antiepileptic drug initiation and withdrawal. *Neurologist* 2009;15(3):122-31.

34. Nicolson A, Appleton RE, Chadwick DW, et al. The relationship between treatment with valproate, lamotrigine, and topiramate and the prognosis of the idiopathic generalised epilepsies. *J Neurol Neurosurg Psychiatry* 2004;75(1):75-9.

35. Pennell PB. Antiepileptic drug pharmacokinetics during pregnancy and lactation. *Neurology* 2003;61(6 Suppl 2):S35-42.

36. Ambulatory health care data. NCHS, Centers for Disease Control and Prevention. National Center for Health Statistics. 2010. (http://www.cdc.gov/nchs/ahcd.htm.). (Accessed 07/07 2011).

37. National Ambulatory Medical Care Survey (NAMCS) public use micro-data file documentation, National Center for Health Statistics,. 2007. (Accessed).

38. National Hospital Ambulatory Medical Care Survey (NHAMCS) public use micro-data file documentation. National Center for Health Statistics. 2007.

39. Johannessen Landmark C, Larsson PG, Rytter E, et al. Antiepileptic drugs in epilepsy and other disorders--a population-based study of prescriptions. *Epilepsy Res* 2009;87(1):31-9.

40. Living with Fibromyalgia, Drugs Approved to Manage Pain. 2008. (http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107802.htm). (Accessed 10/27 2011).

41. Finer LB, Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. *Perspectives on sexual and reproductive health* 2006;38(2):90-6.

TABLES

Table 1. Prevalence and Number of AED and valproate prescriptions for U.S women without a diagnosis of Epilepsy/Seizure (WWNE) aged 15-44 years from 1996 – 2007

	Overall	**1996 – 1998**	**1999 – 2001**	**2002 – 2004**	**2005 – 2007**
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Prevalence (*per 1,000 patient visits)*					
- All AEDs	22.0 (20.0, 24.1)	10.3 (8.4, 12.1)	18.3 (15.4, 21.3)	24.2 (21.0, 27.3)	34.9 (30.4, 39.3)
-Valproate	3.7 (3.2, 4.2)	3.1 (2.3, 3.9)	4.1 (3.0, 5.2)	4.0 (3.0, 5.1)	3.7 (2.8, 4.7)
Number of Prescriptions (*estimated in ten thousands)* [a]					
- All AEDs	5201.7 (4587.8, 5815.6)	609.5 (478.3, 740.6)	1039.0 (830.3, 1247.8)	1453.0 (1225.8, 1680.2)	2100.2 (1666.9, 2533.6)
- Valproate	881.8 (744.4, 1019.2)	182.0 (128.1, 236.0)	233.4 (164.1, 302.6)	241.6 (175.7, 307.6)	224.8 (156.3, 293.3)

All estimates calculated with analytical weights.

a All prescriptions made to a sample of U.S. women without epilepsy/seizure aged 15 - 44 years based on the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007

FIGURES

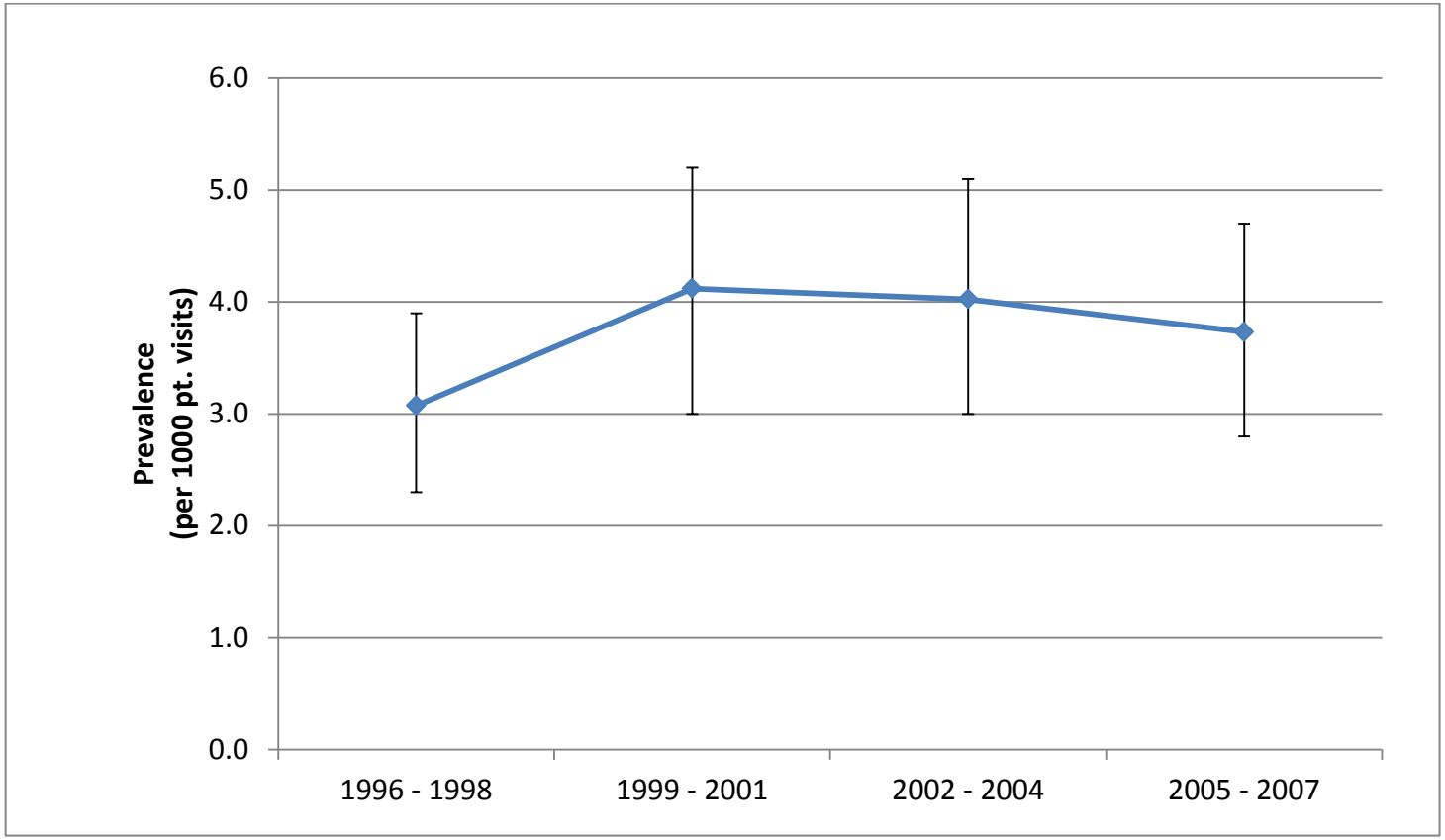


Figure 1. Prevalence (per 1,000 patient visits) of valproate prescriptions for U.S women without a diagnosis of Epilepsy/Seizure (WWNE) aged 15-44 years based on the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007.

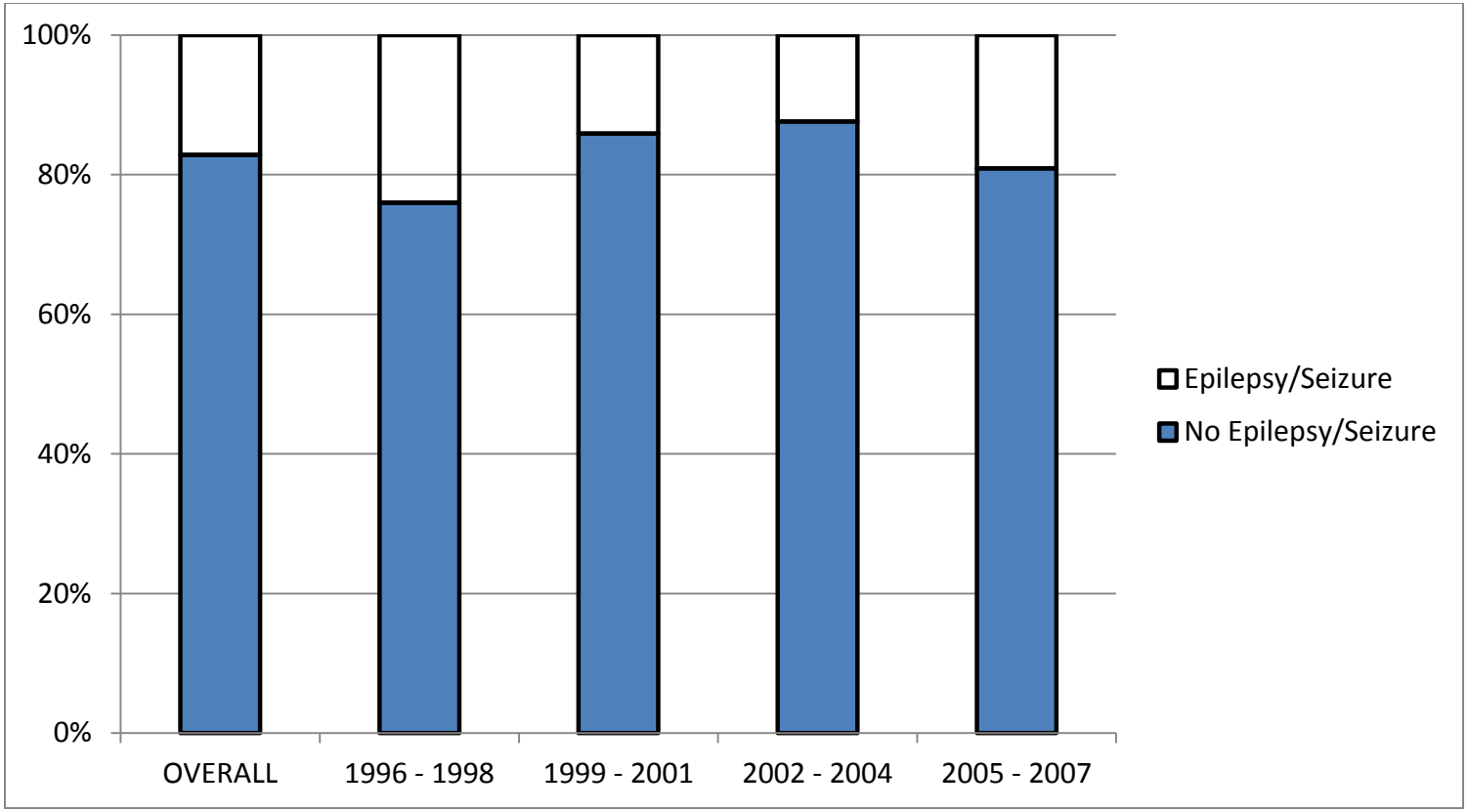


Figure 2. Valproate prescriptions made to all U.S. women aged 15 – 44 years by diagnosis category based on the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007. (Overall 'n' =10,648,000 prescriptions over a 12 year period)

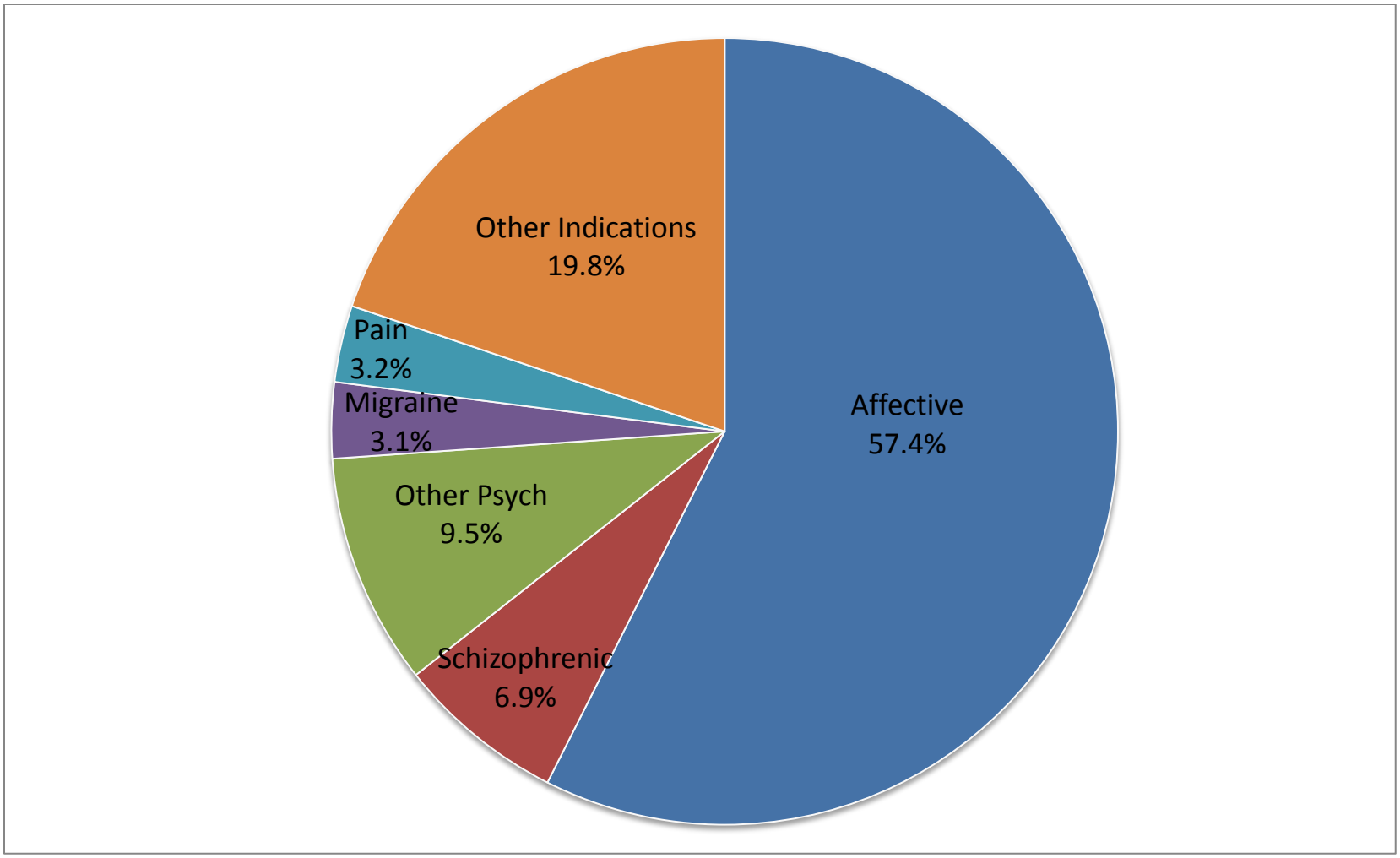


Figure 3. Valproate prescriptions made to U.S. women aged 15 – 44 years without a diagnosis of Epilepsy/Seizure (WWNE) by indication based on the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007 (n = 8,818,000 prescriptions over a 12 year period

SUMMARY, PUBLIC HEALTH IMPLICATIONS, POSSIBLE FUTURE DIRECTIONS

The majority of VPA prescriptions to women of childbearing age in the United States between 1996 and 2007 were for a non-epilepsy/non-seizure diagnosis, of which 74% of these prescriptions were for psychiatric disorders. This suggests that the potential for interventions to reduce birth defects and other adverse outcomes associated with VPA use during pregnancy be targeted towards women receiving VPA for psychiatric indications (11).

Thus far, more attention has been on WWE who receive this medication and their health care, while little attention has been given to women with psychiatric disorders who are also receiving this medication. This oversight may be due to assumptions that people with epilepsy or a seizure disorder use AEDs more. The results of this study have however, demonstrated evidence to the contrary.

The prevalence of AED prescriptions among WWNE has more than tripled between 1996 and 2007. Newer generation AEDs with better therapeutic effects and fewer side effects than the older generation AEDs have been introduced, but their marketing has shifted from use in the management of epilepsy and seizures to other conditions ranging from psychiatric disorders to musculoskeletal disorders (10, 11, 39). For instance, two AEDs, gabapentin and pregabalin (both AEDs), are first line treatments in peripheral neuropathic pain(10) and pregabalin is the first FDA-approved drug for the management fibromyalgia (40). Thus health care providers involved in the management of women of childbearing

age who have indications for any of the antiepileptic medications should exercise caution when prescribing these medications or better still use a safer alternative.

This presents an opportunity for the prevention of AED-related birth defects or other adverse outcomes of AED use by either discontinuing treatment or exploring non-AED options when a pregnancy is planned. Other ways to prevent VPA related congenital malformations is to encourage providers to discuss contraceptive options with female patients without a diagnosis of epilepsy or seizure that are being considered for treatment with VPA. Also increasing awareness among women about the dangers of VPA during pregnancy by emphasizing warning labels on the prescription container so that women can make informed choices about either preventing pregnancy while on VPA or seeking an alternative treatment option from their health care provider.

APPENDICES

Table 2. Number (Frequency) of AED and VPA Prescriptions - Estimated in ten thousands, made to women aged 15 – 44 years, 1996 – 2007

	Overall (95% CI)	**1996 – 1998** (95% CI)	**1999 – 2001** (95% CI)	**2002 – 2004** (95% CI)	**2005 – 2007** (95% CI)
All Women					
- All AEDs	5959.6 (5296.4, 6622.8)	755.5 (609.0, 901.9)	1171.2 (946.1, 1396.4)	1636.0 (1392.6, 1879.3)	2396.9 (1916.9, 2876.9)
- Valproate	1064.8 (914.3, 1215.4)	239.6 (172.1, 307.2)	271.7 (194.0, 349.4)	275.7 (206.1, 345.3)	277.8 (202.1, 353.5)
Women with No Epilepsy (WWNE)					
- All AEDs	5201.7 (4587.8, 5815.6)	609.5 (478.3, 740.6)	1039.0 (830.3, 1247.8)	1453.0 (1225.8, 1680.2)	2100.2 (1666.9, 2533.6)
- Valproate	881.8 (744.4, 1019.2)	182.0 (128.1, 236.0)	233.4 (164.1, 302.6)	241.6 (175.7, 307.6)	224.8 (156.3, 293.3)
Women with Epilepsy/Seizure (WWE)					
- All AEDs	757.9 (645.3, 870.4)	146.0 (100.3, 191.7)	132.2 (90.4, 174.0)	183.0 (132.0, 234.0)	296.6 (220.4, 372.9)
- Valproate	183.0 (134.4, 231.7)	57.6 (23.8, 91.4)	38.3 (14.9, 61.8)	34.1 (17.2, 50.9)	53.0 (28.6, 77.5)

All estimates calculated with analytical weights.

All prescriptions made to a sample of U.S. women without epilepsy/seizure aged 15 - 44 years based on the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007

Table 3. Prevalence of AED and VPA Prescriptions (per 1,000 patient visits) among women aged 15 – 44 years, 1996 – 2007

	Overall (95% CI)	**1996 – 1998** (95% CI)	**1999 – 2001** (95% CI)	**2002 – 2004** (95% CI)	**2005 – 2007** (95% CI)
All Women					
- All AEDs	25.1 (23.0, 27.3)	12.7 (10.7, 14.7)	20.6 (17.5, 23.7)	27.1 (23.8, 30.4)	39.5 (34.8, 44.3)
- Valproate	4.5 (3.9, 5.0)	4.0 (3.0, 5.0)	4.8 (3.6, 6.0)	4.6 (3.5, 5.7)	4.6 (3.6, 5.6)
Women with No Epilepsy (WWNE)[a]					
- All AEDs	22.0 (20.0, 24.1)	10.3 (8.4, 12.1)	18.3 (15.4, 21.3)	24.2 (21.0, 27.3)	34.9 (30.4, 39.3)
-Valproate	3.7 (3.2, 4.2)	3.1 (2.3, 3.9)	4.1 (3.0, 5.2)	4.0 (3.0, 5.1)	3.8 (2.8, 4.7)
Women with Epilepsy/Seizure (WWE)					
- All AEDs	710.3 (653.4, 767.1)	685.6 (580.3, 790.8)	636.3 (485.6, 787.0)	683.4 (577.0, 790.0)	783.9 (699.6, 868.2)
-Valproate	171.5 (130.4, 212.6)	270.4 (150.3, 390.5)	184.5 (83.3, 285.7)	127.2 (75.4, 179.1)	140.1 (82.4, 197.9)

All proportions calculated with analytical weights.

[a] *WWNE in this table refers to women with no epilepsy who received at least one AED.*

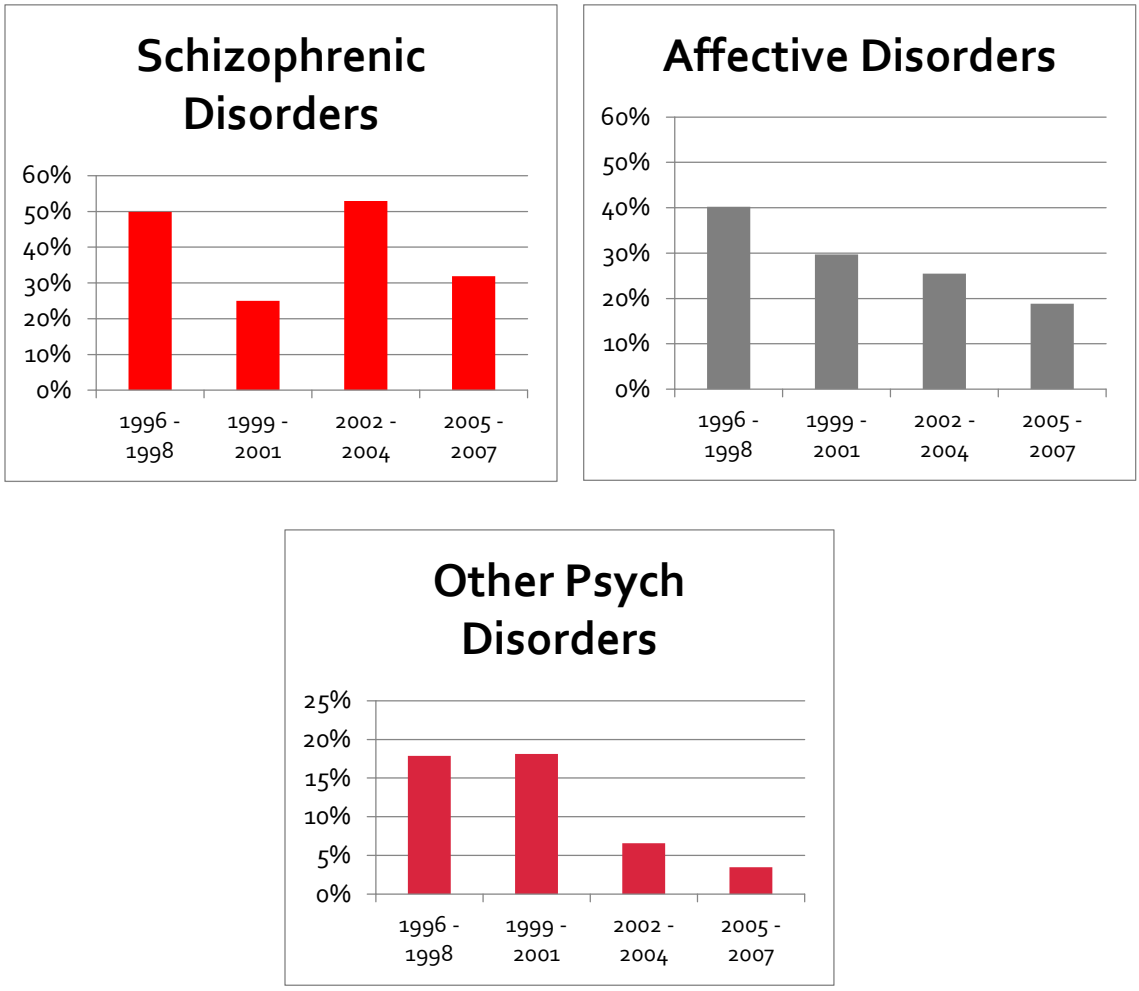


Figure 4. Trends in the proportion of VPA prescriptions for Psychiatric disorders based on the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007

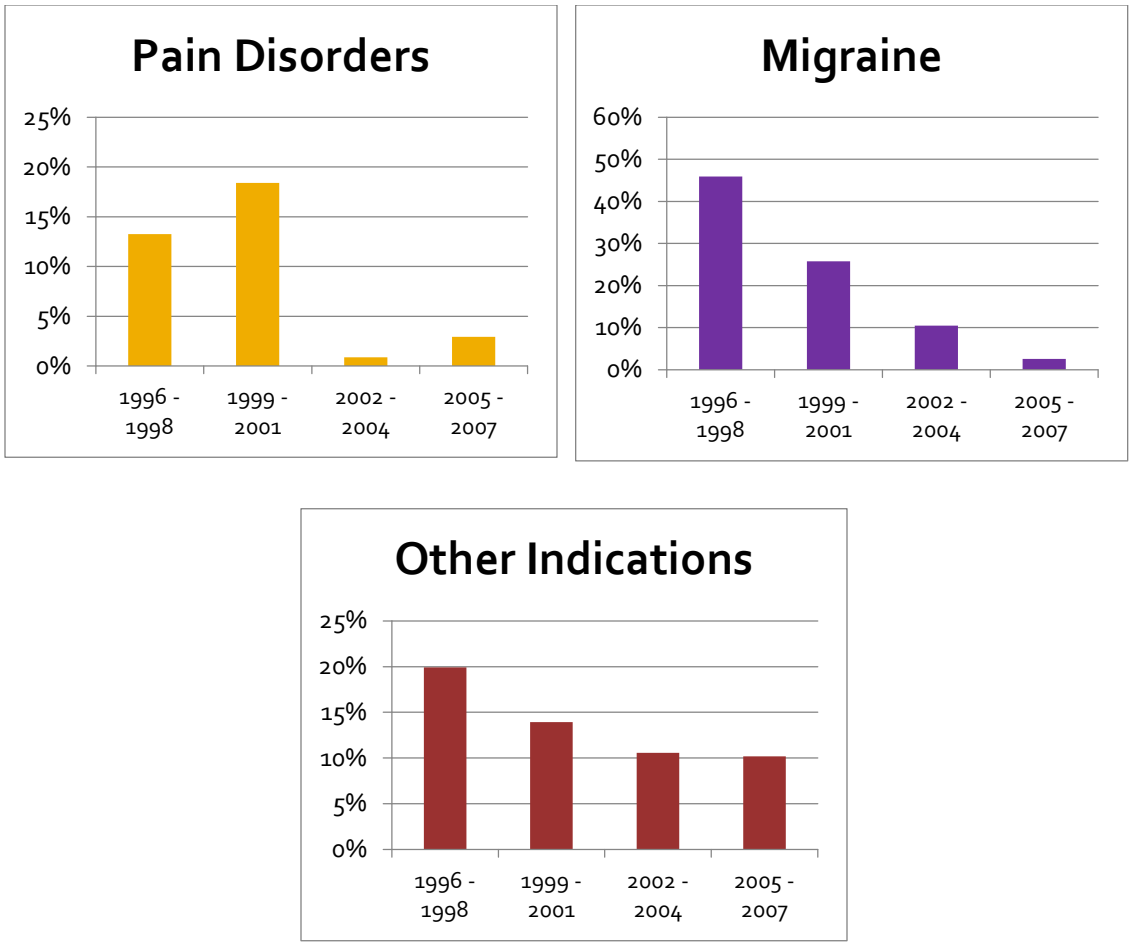


Figure 5. Trends in the proportion of VPA prescriptions for pain and other non-epilepsy disorders based on the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007

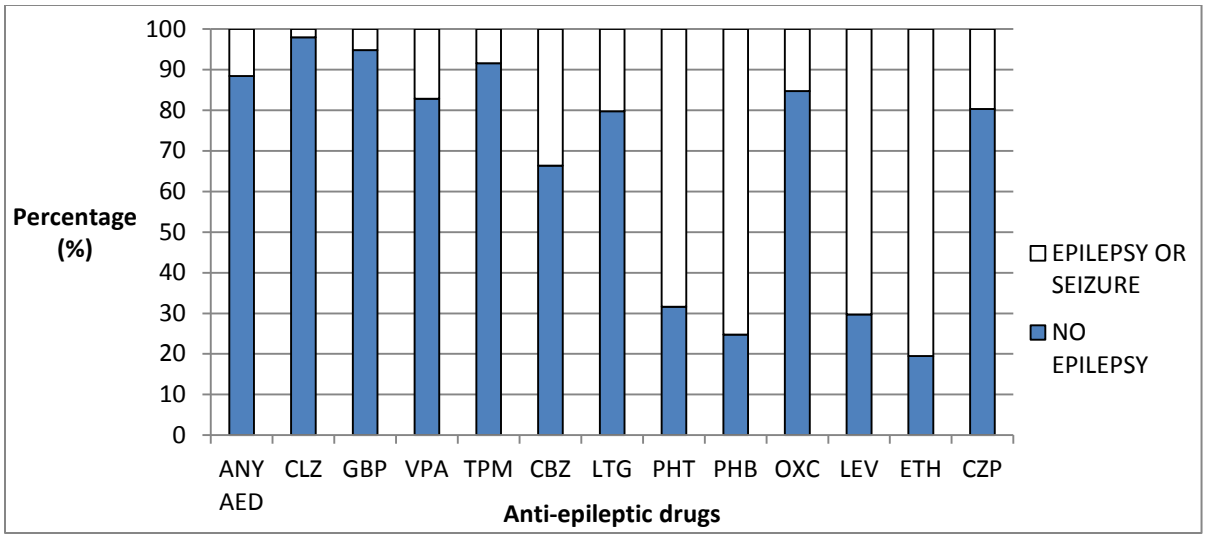
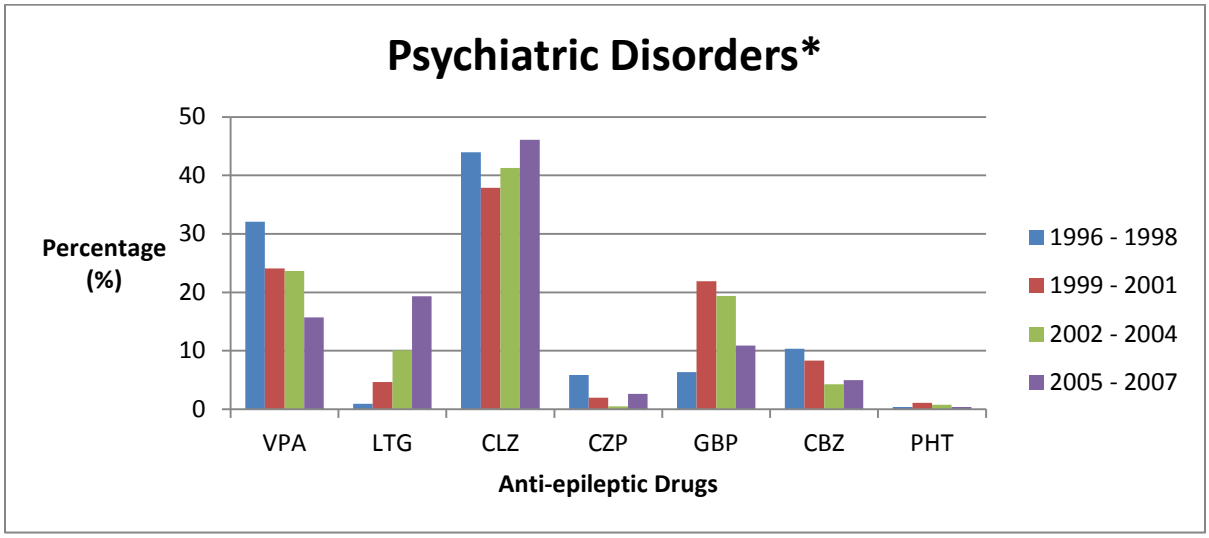


Figure 6. Distribution of specific AED prescriptions by diagnosis category made to all U.S women aged 15 - 44 years based on the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007



** Includes Schizophrenic, affective and other psychiatric diagnoses groups.*

Figure 7 Distribution and trends in AED prescriptions for Psychiatric disorders based on the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007

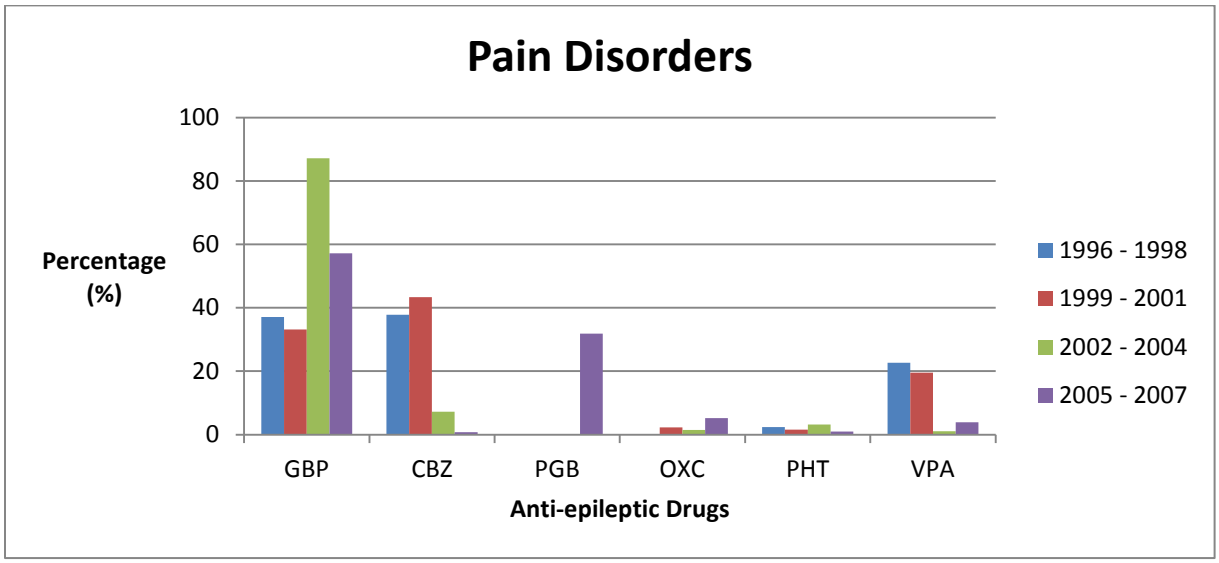


Figure 8. Distribution and trends in AED prescriptions for Pain disorders based on the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007

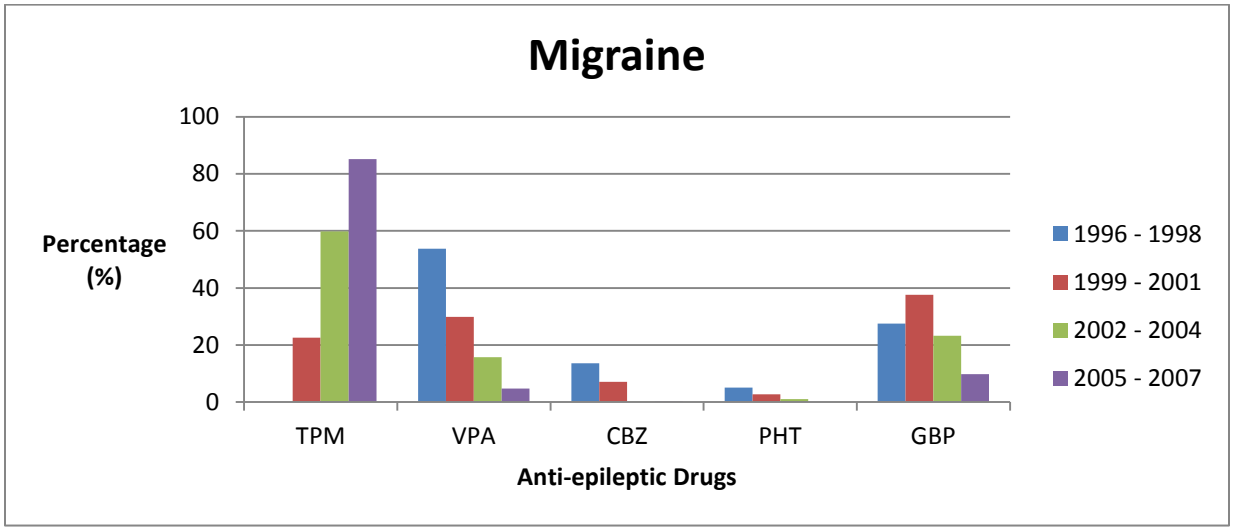


Figure 9. Distribution and trends in AED prescriptions for Migraine based on the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007

Table 4. Codes used for Anti-epileptic Drugs

NCHS [a] Codes											
AED	**G [b]**	***Original Entries***									
CBZ	50880	01063	05680	11549	30730	98114					
CLZ	51270	06980	60790	06990							
CZP	51280	70470	02129	03125	06993	31945	05139				
ETH	52130	11898	35150								
FBM	56415	93221	93341								
FOS	59701	01023	97005	97162							
GBP	57102	94099	94114								
LTG	57220	95181	97136								
LEV	70160	00184	02037								
MPB	53355	18765	18550								
OXC	70128	01216	00076								
PHB	54395	23845	23870	23905	18015	03570	28290	28755			
PHT	54470	03013	03207	09585	09195	09885	09890	24045	93049		
PRM	54795	25055	20135	25060	29450						
TGB	59830	01319	98116								
TPM	59744	97049	98131								
VPA	56145	01264	02099	51927	03012	08835	08836	08902	33573	93249	94081
ZNS	70225	01008	01275								
VGB	70476	02162	06078								
PGB	70999	05097	00084	71000							

[a] National Center for Health Statistics

[b] Generic Code

Drug Names and Abbreviations

Carbamazepine	CBZ	Tiagabine	TGB
Clonazepam	CLZ	Topiramate	TPM
Clorazepate	CZP	Valproate	VPA
Ethosuximide	ETH	Zonisamide	ZNS
Felbamate	FBM	Vigabatrin	VGB
Fosphenytoin	FOS	Pregabalin	PGB
Gabapentin	GBP		
Lamotrigine	LTG		
Levetiracetam	LEV		
Mephobarbital	MPB		
Oxcarbazepine	OXC		
Phenobarbital	PHB		
Phenytoin	PHT		
Primidone	PRM		