Trends of Utilization of Antiepileptic Drugs among Pregnant Women in Manitoba, Canada. A 20-year population study

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THESIS ABSTRACT

Studies from Canada and globally have shown an increase in antiepileptic drug (AEDs) use in the past decade. This could be attributed to the fact that AEDs are being used more for off-label indications or a change in intensity of treatment. Identifying the impact of such increase among vulnerable groups, such as pregnant women, is imperative because pregnant women may have different utilization patterns than the general population. This study examines time-trends of utilization of AED therapies among pregnant women in Manitoba, Canada.

This study is a population-based cohort study using administrative health data from the province of Manitoba. Pregnancies between 1995 and 2018 were included. Four groups of pregnant women were created based on AEDs exposure and epilepsy diagnosis (women with epilepsy exposed to AEDs, women with epilepsy not exposed to AEDs, women without epilepsy exposed to AEDs, women without epilepsy not exposed to AEDs). Epilepsy was defined as ≥1 medical claim or ≥1 hospitalization for epilepsy during the 5 years prior to delivery. Trend analysis for change over time was conducted using linear regression.

Out of 273,492 pregnancies identified, 812 (0.3%) had epilepsy diagnosis and were exposed to AEDs, 963 (0.35%) had an epilepsy diagnosis and were unexposed, 2,742 (1%) were exposed to AEDs and did not have epilepsy diagnosis, and 268,975 (98.35%) were not exposed to AEDs and did not have epilepsy diagnosis. Overall, the number of pregnancies exposed to AEDs increased significantly from 0.56% in 1997 to 2.21% in 2018 ($p<0.0001$). No significant change was observed in the exposure to AEDs among women with epilepsy (from 0.37% in 1997 to 0.36% in 2018, $p=0.24$). In contrast, the percentage of AEDs use among pregnant women without epilepsy increased significantly from 0.19% in 1997 to 1.85% in 2018 ($p<0.0001$).

Over the 20 years of the study, carbamazepine was the most used AED among pregnant women with epilepsy (28.07%), followed by lamotrigine (18.88%), phenytoin (17.08%) and valproic acid (10.79%). At the beginning of the study period, carbamazepine, phenytoin and valproic acid were the most prescribed AEDs among pregnant women with epilepsy. Their use decreased following the increase in the use of second-generation AEDs. By the end of the study

period lamotrigine and levetiracetam became the most used AEDs among pregnant women with epilepsy.

On the other hand, the most prescribed AEDs among women without epilepsy were clonazepam (59.76%) and gabapentin (23.25%). While the use of clonazepam was decreasing throughout the study period, the use of gabapentin was increasing.

There were no major shifts in the use of AEDs observed among women with epilepsy over the 20-year study period. Therefore, concerns about an increased use of AEDs, and reasons for the use, among pregnant women in Manitoba driven by indications other than epilepsy require additional research to better inform prescribers and policymakers.

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DEDICATION

Mom and Dad,

This Thesis is for you.

THESIS PREFACE

This thesis includes five chapters: an introduction, a literature review, methods used for the thesis, a paper intended for publication in peer-reviewed journal, a chapter including the additional results, and a conclusion. The paper includes its own bibliography. A final bibliography for the other chapters is included at the end.

Student contribution: Reviewed existing literature, conducted all analyses, wrote, and submitted a manuscript, wrote and finalized this thesis.

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INTRODUCTION

EPILEPSY

Epilepsy is a chronic neurological disease characterized by unpredictable, unprovoked recurrent seizures that affect a variety of mental and physical functions.[1] About 50 million people have epilepsy worldwide.[1] In Canada, an estimated 139,200 Canadians had epilepsy based on the data of Statistics Canada between 2010 and 2012.[2] People once thought that epileptic individuals were being visited by demons or gods. In 400 B.C., the early physician Hippocrates suggested that epilepsy was a disorder of the brain. The cause of epilepsy is not well known although some causes can be: genetics, brain injuries, central nervous system infections, and neurodegenerative diseases.[3] A person is considered to have epilepsy when two or more unprovoked seizures occur that cannot be explained by a medical condition, such as fever or substance withdrawal occurring more than 24 hours.[4] Epileptic seizures are characterized by an abnormal electrical discharge of the brain neurons.[1,5]

Epilepsy involves many complications beyond seizures. There is a higher risk of social isolation, psychiatric problems, lower education, and financial instability in adult patients with childhood epilepsy. [6] Canada, 18% of patients with epilepsy said that their life was extremely affected due to epilepsy, 25% said they feel embarrassed, and 29% said that their condition interfered with their ability to sleep.[2] Epilepsy affects the ability to find a job, with 40% of Canadians with epilepsy unemployed, and 9% unable to work permanently.[2]

SEIZURE CLASSIFICATIONS:

According to the new classification of seizures by the International League Against Epilepsy (ILAE) 2017, the basic seizure classification divides seizures into focal onset seizures, generalized onset seizures, and unknown onset seizures.[7,8] ILAE defined an expanded seizure classification to be used by clinicians who specialise in diagnosis and treatment of epilepsy.[7] The expanded classification follows the basic classification but with expansion of certain subheadings.[7]

FOCAL ONSET SEIZURES

Previously known as , these seizures begin with a focal onset, which is one hemisphere of the brain.[1,7,8] The level of awareness is used as a parameter to subdivide focal onset seizures. If the awareness is retained, the seizure is called focal aware seizure (previously simple partial seizure).[7] If the patient loses awareness, the seizure will be focal impaired awareness seizure (previously complex partial seizure) these seizures are accompanied by impairment of the patient's ability to maintain normal contact with the surrounding environment. [1,7,8] If the level of awareness is unknown, for example in focal myoclonic seizures, the classification by level of awareness can be removed.

Focal onset seizures are also classified into motor and non-motor according to the presence of movements.[7] Another classification is tonic versus atonic. During a focal atonic seizure, there is a loss of tone in a limb, whereas, during a focal tonic seizure, there is stiffening of a limb or the neck. A focal autonomic seizure influences autonomic functions such as heart rate.

GENERALIZED ONSET SEIZURES

These seizures begin in both cerebral hemispheres simultaneously.[7,8] Awareness is usually impaired in generalized onset seizures, thus they are not classified by the level of awareness.[7] Generalized onset seizures are primarily classified as motor or non-motor.[7] During generalized onset tonic-clonic seizures, the tonic phase comes first, with loss of consciousness and stiffness of all limbs, followed by the clonic phase, characterized by rhythmic jerking of limbs and face.[7,8] The patient's

face becomes blue due to difficulty in breathing. These seizures usually last from 1 to 3 minutes.[7,8] Generalized tonic seizure involves stiffening of all muscles, dilation of the pupils, loss of consciousness, and altered respiratory patterns.[7,8] Generalized clonic seizures involve rapid jerking of the arms and legs that stops in a few minutes.[7,8] Atonic seizures are characterized by loss of muscle control that may cause sudden falls.[7,8] Generalized myoclonic seizure is characterized by irregular bilateral jerking of limbs.[7] Generalized onset typical absence seizure is associated with sudden activity cessation, accompanied with eye fluttering, and head nodding.[7] Status epilepticus is defined as continuous seizure activity for five minutes or more.[9] Status epilepticus is a life-threatening condition that requires immediate treatment to terminate seizures and lower the risk of adverse outcomes.[9]

Unknown onset Seizures

Sometimes the nature of the onset of the seizure is known with less than 80% confidence by the clinician. The level of confidence was chosen to be 80% randomly to match the usual acceptable false-negative error in experiments. If more information become available about the seizure, unknown onset seizures can be reclassified.[7]

Seizures usually evolve and include more brain networks that were not involved at the beginning of the seizure; therefore, these classifications are only used for diagnosis and do not distinguish the propagation pattern.[7]

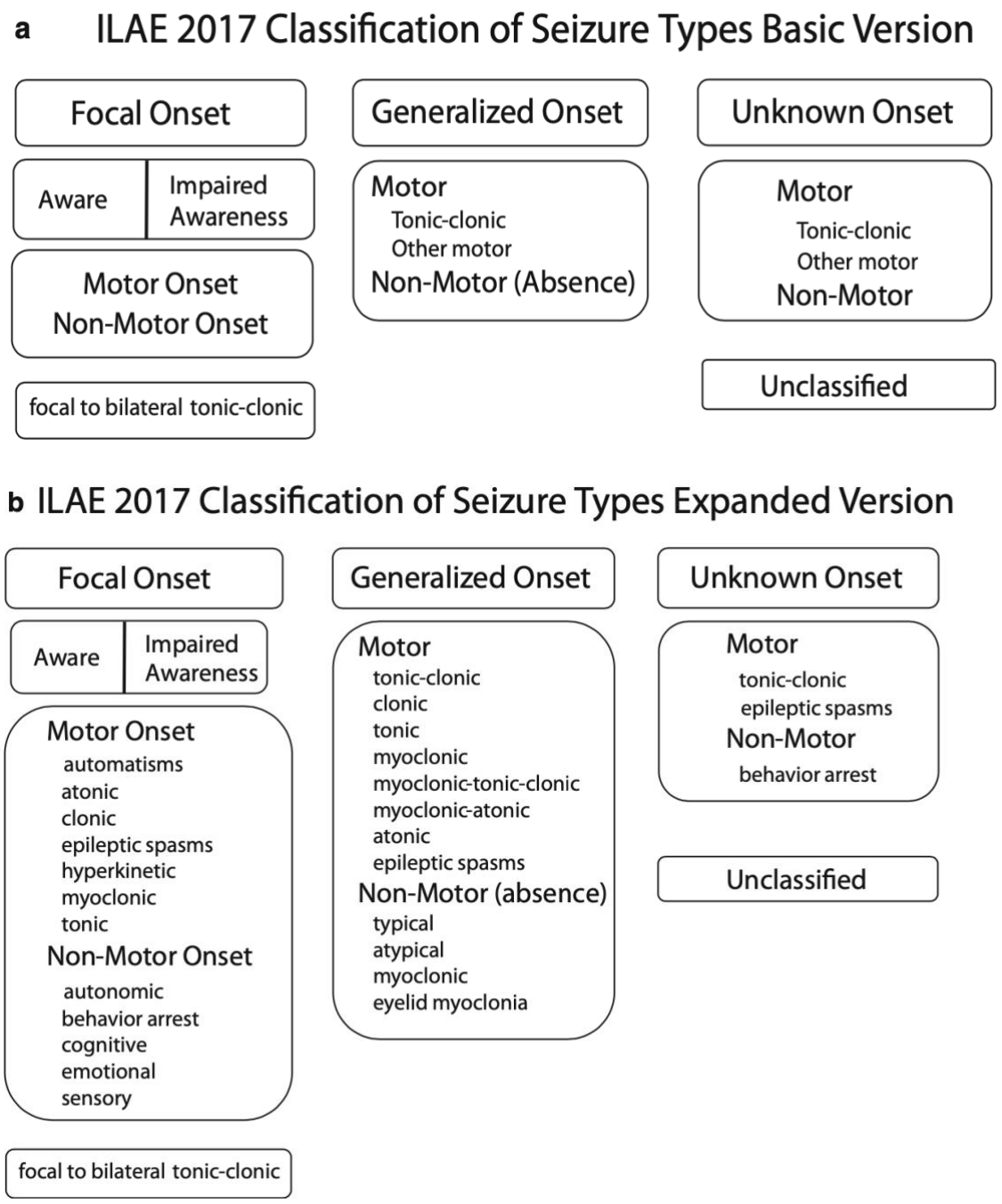

Figure 1 Seizure Classification Adopted from the ILAE 2017

EPILEPSY IN PREGNANCY:

Many AEDs such as carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, and topiramate are enzyme-inducing and may therefore increase the metabolism of oral contraceptives, leading to an increased risk of pregnancy in some patients.[6,10] The estimated prevalence of epilepsy among pregnant women is 0.3% to 0.7%.[11,12] Both epilepsy and AEDs have adverse effects on pregnancy and the fetus, and they can cause undesired neonatal outcomes. However, as the risk of untreated epilepsy during pregnancy is considered worse than fetal exposure to AEDs, the current recommendation is to continue epilepsy treatment during pregnancy to reduce maternal and fetal trauma associated with seizures. Drug target concentrations should be established before conception and maintained during pregnancy to prevent the occurrence or worsening of seizures.[11,13] The AED should be maintained at lowest possible dose without losing its therapeutic benefit, leading to optimum seizure control and minimum fetal exposure to AEDs. [13,14] Combination therapies are generally avoided during pregnancy, because the 2009 American Academy of Neurology / American Epilepsy Society practice parameters concluded that polytherapy contributes to major congenital malformations when compared with monotherapy.[13,14] Although not all polytherapy combinations have the same risk, there are so many combinations to be studied and more data is needed to differentiate the risk of specific polytherapy combinations, taking into consideration different doses and different baseline risk factors. [13,15]

Controlling seizures during pregnancy is extremely important for life-or-death reasons. First, generalized onset tonic-clonic seizures during pregnancy can lead to seizure-related traumas, spontaneous miscarriage, and intrauterine death, due to the increase in blood pressure and electrolyte changes during the seizure.[16,17] Generalized onset tonic-clonic seizures are also associated with maternal and fetal hypoxia.[17] Epileptic seizures during pregnancy are associated with 1.36-fold increase in the risk of low birth weight, 1.63-fold increase in the risk of preterm delivery and 1.37-fold increase in the risk of small for gestational age, when compared with women without epilepsy.[18] An estimated 1:1000 women die during or shortly after pregnancy, mainly from Sudden Unexpected Death due to Epilepsy (SUDEP).[19]

ANTI-EPILEPTIC DRUGS:

FIRST GENERATION AEDS:

VALPROIC ACID (VPA) (DEPAKENE)

VPA was approved by the United States Food and Drug Administration (FDA) in 1978 as an antiepileptic drug.[20] VPA prevents seizures by increasing the level of the inhibitory neuron transmitter gamma-aminobutyric acid (GABA) in the brain. The mechanism by which VPA increases GABA brain levels may be due to the inhibition of GABA catabolism (GABA transaminase) or stimulation of GABA synthesis (glutamic acid dehydrogenase) or both.[1,21]

VPA is a first line drug for the treatment of generalized onset tonic-clonic seizures in adults and children. It can be used as monotherapy or as adjunctive treatment in complex focal onset seizures, and simple and generalized onset typical absence seizures.[1,22] Currently, VPA is being indicated for migraine prophylaxis, and it is widely used in the treatment of migraine headaches and schizophrenia.[20,23] VPA is marketed in 250 mg capsules and sodium valproate syrup containing 266 mg of sodium valproate per 5 mL. VPA is hepatically metabolized, its half-life is 7-13 hours, and it is excreted renally.[1] Gastrointestinal disturbances are the most common adverse effect of VPA occurring in 10-50% of patients. Sedation is reported in up to 50% of patients whether taken alone or in combination with other AEDs. Alopecia is also reported as one of the major adverse effects.[1]

A case-control study by Jentink *et al*. (2010) found an association between valproic acid exposure and increased risk for spina bifida (odds ratio [OR]=12.7), atrial septal defect (OR 2.5), cleft palate (OR 5.2), hypospadias (OR 4.8), polydactyly (OR 2.2), and craniosynostosis (OR 6.8).[24] A review of major congenital malformations in the children of pregnant women with epilepsy exposed to AEDs by Tomson et al. shows that the highest prevalence of major congenital malformations is associated with the exposure to VPA.[25] The risk of both anatomical and behavioral teratogenic effect of VPA is dose-dependent, with an increased risk at doses higher than 500mg/day.[23,25,26]

CARBAMAZEPINE (CBZ): (TEGRETOL)

CBZ was approved by the United States FDA in 1968. CBZ reduces polysynaptic responses and blocks post-tetanic initiation. It acts by blocking voltage-gated sodium channels leading to the prevention of repetitive and sustained firing of action potential.[1,27] CBZ is a first line drug for the treatment of focal onset seizures with complex symptomatology. It is also indicated for the treatment of generalized onset tonic-clonic seizures. It is not effective in generalized onset typical absence seizures. It is also used as an analgesic for trigeminal neuralgia.[1,22,23,28]

In utero exposure to carbamazepine is associated with increased risk of orofacial cleft.[21,23] In a review, cardiac malformations were the most frequent major congenital malformations in the children of pregnant women with epilepsy exposed to carbamazepine (prevalence = 1.57%).[25] However, when compared with other frontline AEDs, carbamazepine has significantly lower teratogenic potential.[23,25,29]

PHENYTOIN (PHT) (DILANTIN)

Phenytoin has been available for more than a century now.[1] Its main mechanism of action is blocking the sodium influx through sodium channels leading to prevention of spread of seizure activity through the motor cortex.[1] However, several central mechanisms are also affected by phenytoin. For example, enhancing GABA neurotransmission, blocking calcium influx, and activation of the sodium pumps.[1,27,30] Phenytoin is a first-line drug for the treatment of focal onset seizures. It is also indicated for controlling generalized onset tonic-clonic seizures, and for the prevention and treatment of seizures occurring during or following neurosurgery.[1,22]

Phenytoin is a known teratogen, as it causes Fetal Hydantoin Syndrome (FHS), which is characterized by hypoplasia and irregular ossification of the distal phalanges. Infants display facial dysmorphism including: epicanthal folds, hypertelorism, broad flat nasal bridges, an upturned nasal tip, wide prominent lips and, in addition, distal digital hypoplasia, intrauterine growth retardation and mental retardation.[23,31,32]

ETHOSUXIMIDE (ZARONTIN)

Ethosuximide was approved by the United States FDA in 1960. The mechanism of action is not entirely understood, but most likely ethosuximide exerts its effects by partial antagonism of T-type calcium channels of the thalamic neurons. This leads to stabilization of the nerve activity in the brain by decreasing the burst firing of the thalamocortical neurons.[1,33] It is a first line drug for the treatment of generalized onset typical absence seizures.[1,22]

PHENOBARBITAL (PB) (LUMINAL)

Phenobarbital was first used as an antiepileptic drug more than 100 years ago in 1912.[34] It is a non-selective central nervous system depressant. It acts on $GABA_A$ receptors, decreasing the excitability of post-synaptic neurons.[1,34]

It is used for the treatment of generalized onset typical absence seizures.[1,34] PB is no longer generally regarded as a first-line drug for epilepsy in the USA and Europe, having been replaced by newer drugs.[23] Owing to its low cost and effectiveness, it remains a front-line treatment for partial and general tonic–clonic seizures in many other countries.[23]

Evidence on the teratogenic effect of phenobarbital remain to be weak, and further studies with larger sample size is still needed.

CLONAZEPAM (KLONOPIN)

Clonazepam is a benzodiazepine derivative that was approved in 1976 for the treatment of Lennox-Gastaut syndrome. [1,35] The mechanism of action of clonazepam might be related to enhancing the activity of GABA in the central nervous system.[1]

In addition to its use for the treatment of seizures, clonazepam is one of the most popular benzodiazepine compounds used for the treatment of anxiety.[36] Studies have shown the increased use of clonazepam in some psychiatric indications such as bipolar disorders, mania, and depression.[37,38] It is being used commonly for many other indications including sleep-related disorders, pain management, and other benzodiazepine withdrawal.[36,37,39] Clonazepam might be also used for recreational non-medical purposes due to the euphoric state it causes.[36] A study on

the clonazepam abuse liability developed by the French Centres for Evaluation and Information on Pharmaco-dependence (CEIP) by Frauger et. al. shows that the proportion of illegal acquisition was higher with clonazepam when compared with other benzodiazepines.[37] Clonazepam also showed higher abuse and dependence, and highest proportion of users with daily dose twice the recommended dose.[37]

In Quebec, a study by Eguale et. al. concluded that clonazepam was among the drugs most probably to be used for off-label indications with 96% of prescriptions being for off-label use.[40] A study about off-label drug use of psychiatry outpatient department in Ahmedabad, India, by Rana et al. shows that clonazepam was the most frequently used off-label for psychiatric disorders, with 12.4% of off-label prescriptions for clonazepam.[41] This is significantly higher than any other off-label drug, and it was mostly used for depression.[41]

There is limited information on the teratogenicity of clonazepam in humans. In a 32-month study by Lin et al., there was no increase in major congenital malformations observed in births exposed to clonazepam monotherapy.[42] A population-based case-control study about the teratogenic effect of benzodiazepines including clonazepam by Eros et. al, concluded that the treatment with the studied benzodiazepines during pregnancy was not associated with any teratogenic risk although there were limited data on some congenital abnormalities.[43]

An association between the incident exposure to short- and long-acting benzodiazepines and the increased risk of miscarriage was made in a Quebec study by Sheehy et. al.[44] The adjusted odds ratio for spontaneous abortion among benzodiazepine users compared with non-users was OR= 1.81.[44]

SECOND GENERATION AEDS:

During the past few decades, a new generation of AEDs has been introduced to the market.[45] The effectiveness of the new AEDs is not stronger than older ones, but they have less pharmacokinetic drug interactions leading to the ability to create synergistic combinations.[45,46] Moreover, they have less adverse effects when compared with older generation AEDs (including idiosyncratic, teratogenic, and cognitive ones).[46]

Below is a summary of a few second-generation AEDs:

LAMOTRIGINE (LTG): (LAMICTAL)

Lamotrigine has a unique chemical structure similar to phenytoin and carbamazepine, it acts by inhibition of voltage-sensitive sodium channels, resulting in diminished neuronal activity.[1,27,47] Lamotrigine can be used alone or as conjunctive therapy for the treatment of focal onset seizures generalized onset tonic-clonic seizures, and generalized seizures. It is also indicated for extreme mood swings in bipolar disorder in adults.[1,23]

The kinetics of lamotrigine are affected during pregnancy and clearance can increase by three times that of pre-pregnancy, therefore close monitoring of the serum levels of lamotrigine is advised.[11,48] Evidence of lamotrigine teratogenicity remains uncertain, existing evidence suggests that lamotrigine is less teratogenic than valproic acid or phenytoin.[23,25]

GABAPENTIN (GBP): (NEURONTIN)

Gabapentin was introduced in the USA in 1994.[49] γ-aminobutyric acid (GABA) is the major rapid inhibitory neurotransmitter in the human brain. By design, gabapentin was anticipated to mimic the action of GABA and to act by increasing rapid chloride dependent inhibition.[50] But it more likely modulates calcium channel current, and increases the concentration and probably the rate of synthesis of GABA in the brain.[51]

Gabapentin was found to be one of the most used drugs for off-label indications in a Quebec study by Eguale et. al examining the off-label prescribing in primary care.[40] Gabapentin was used almost exclusively off-label; with around 99.2% of the gabapentin prescriptions for off-label indications.[40]

Gabapentin is used as an adjunctive therapy for the treatment of focal onset seizures in children and adults.[1] Gabapentin is widely utilized for non-epileptic uses, such as neuropathic pain including trigeminal neuralgia, HIV-associated neuralgia, diabetic neuropathy, neoplasia, and strokes. It is also used in the treatment of psychiatric disorders, most notably bipolar disorder. Moreover, it can be used in movement disorders including restless leg syndrome.[49]

Studies about the effect of *in-utero* exposure to gabapentin are limited and inconclusive.[23] However, fetal resorption was observed when gabapentin was administered in early or mid-gestation, resulting with congenital malformations.[52]

Pregabalin (PGB): (Lyrica)

Pregabalin is a GABA analog, but it works on voltage-dependent calcium channels.[53] Pregabalin is indicated as an adjunctive therapy in the treatment of partial-onset seizures in adults.[1] It is also used in neuropathic pain and anxiety disorder.[53]

A study by Sonia Hernandez-Diaz et al. concluded that the prevalence of Major Congenital Malformations (MCM) in pregnancies exposed to pregabalin was 5.9 per 100 deliveries, compared to 3.3 per 100 deliveries in unexposed pregnancies.[54] The crude Risk Ratio (RR) of MCMs in pregnancies exposed to pregabalin was 1.80 (95% confidence interval (95% CI) 1.26–2.58).[54]

Topiramate (TPM): (Topamax)

Topiramate was approved in 1996. It is used, in adults and pediatric patients, as a first line agent for primary generalized onset tonic-clonic seizures and absence seizures, and as an alternative treatment in focal onset seizures.[1,22,55] Some suggested mechanisms of action of topiramate include: augmenting the activity of GABA at some types of GABA receptors, blocking the voltage-sensitive sodium channels, weakly antagonizing the excitatory activity of glutamate receptors.[55]

Topiramate may cause metabolic acidosis, renal calculi and hypohidrosis due to its anhydrase inhibitory effects. Topiramate is also associated with weight loss, with obese patients experiencing the greatest loss during continued therapy.[55] Topiramate has a teratogenic effect when used in the

first trimester of pregnancy and may cause MCMs and decreased cognitive functions in exposed children.[23] However, data on the use of topiramate in pregnancy are still limited.[23,55]

OXCARBAZEPINE (OXC): (TRILEPTAL)

Oxcarbazepine is used as adjunctive and monotherapy in adults to control focal onset seizures.[1,56,57] In children between 2 – 16 years, oxcarbazepine is used as adjunctive therapy.[57] The actual mechanism of action is still unknown, but its major active metabolite appear to affect neuronal ion channels.[56, 57]

Oxcarbazepine is better tolerated than carbamazepine, phenytoin, and valproic acid. Acute hyponatremia develops in 2.7% of patients receiving oxcarbazepine. Data on the teratogenic effects of oxcarbazepine in humans is still limited.[56]

TIAGABINE: (GABITRIL)

Tiagabine is a GABA uptake inhibitor; it acts by inhibiting the GABA reuptake into the presynaptic neurons leading to a prolonged effect of GABA.[1,58] It is effective as an adjunctive in the treatment of refractory focal onset seizures.[58]

There is no data that suggest the teratogenic effect of tiagabine when used in pregnancy.[58]

Lacosamide: (Vimpat)

Lacosamide inhibits repetitive firing of action potential by slow inhibition of voltage-gated sodium channels.[59] It is used as adjuntive treatment in patients with refractory focal onset seizures.[1,59]

RUFINAMIDE: (BANZEL)

Rufinamide's chemical structure is unrelated to other marketed AEDs. It is used as adjunctive treatment of partial onset seizures and seizures associated with Lenox-Gastaut syndrome in children and adults.[1,60] The exact mechanism of action is still unknown, but it most probably prolongs the inactive state of the sodium channels.[1,60]

LEVETIRACETAM (LEV): (KEPPRA)

Levetiracetam is approved as adjunctive therapy for partial-onset seizures, primary generalized onset tonic-clonic seizures, and myoclonic seizures.[1,61] Unlike other AEDs, the mechanisms of action of levetiracetam appear to involve neuronal binding to synaptic vesicle protein 2A, inhibiting calcium release from intraneuronal stores, opposing the activity of negative modulators of GABA- and glycin-gated currents and inhibiting excessive synchronized activity between neurons. In addition, levetiracetam inhibits N-type calcium channels.[61] Larger and more recent studies are still needed to identify if there are any teratogenic effects of levetiracetam, as they are still not well identified.[48]

THIRD GENERATION AEDS:

Despite the medical advancements, 30% of patients with epilepsy are still inadequately treated with the first and second generation AEDs.[62] Therefore, in the past decade, >4 third-generation AEDs were approved for refractory focal onset seizures. These drugs are usually used as adjunctive therapy.[62] These drugs include: perampanel, eslicarbazepine and brivaracetam.

Table 1 Antiepileptic drugs classification

First Generation	Carbamazepine Phenytoin Valproate Ethosuximide Phenobarbital
Second Generation	Gabapentin Pregabalin Tiagabine Vigabatrin Felbamate Lacosamide Lamotrigine Levetiracetam Oxcarbazepine Rufinamide Topiramate Zonisamide
Third Generation	Brivaracetam Eslicarbazepine acetate Fluorofelbamate Fosphenytoin Losigamone Remacemide hydrochloride Retigabine Safinamide Selectracetam Stiripentol Ganaxolon Carabersat Carisbamate Soretolide Valrocemide

MANAGEMENT OF EPILEPSY DURING PREGNANCY

RECOMMENDATIONS

The following are some recommendations to be considered while treating epilepsy in pregnant women:[63,10]

- Valproic acid should be avoided in mono and combination therapy during the first trimester to decrease the risk of major congenital malformations (MCMs).
- Polytherapy should be avoided during the first trimester to reduce the risk of MCMs.
- Phenytoin should be avoided to reduce the risk of cleft palate.
- Carbamazepine should be avoided to prevent posterior cleft palate.
- Phenobarbital, phenytoin, and ethosuximide should be avoided to prevent cardiac malformations.
- To reduce the risk of poor cognitive outcomes, valproic acid, phenytoin, and phenobarbital should be avoided.
- Cognition is probably not reduced in the children of women with epilepsy who are not exposed to AEDs. Therefore, counseling with these women preconception is recommended.
- Due to the potential risk of levetiracetam, the use of safer AEDs in WWE of childbearing age should be addressed if possible. [48]

GUIDELINES

Caregivers should balance the risk versus benefit of using AEDs during pregnancy. Before conception, prescribers must decide if the epilepsy still requires treatment, and if polytherapy can be replaced by monotherapy. [10] The following are recommended strategies for management of epilepsy in pregnancy (according to Expert Opinion on Pharmacotherapy).[11] Ideally, pregnancy must be planned and discussed with the team of caregivers. Prescribers should avoid polytherapy in women with epilepsy who are planning pregnancy, whenever possible. Lamotrigine monotherapy is the first line treatment to be used in all WWE of childbearing age. Carbamazepine has relatively similar rates of MCMs when compared with lamotrigine. Levetiracetam can be

prescribed since it shows an acceptable low rate of MCMs. A strong warning for the use of valproate in WWE of childbearing age was issued by the European Medicines Agency. Folic acid supplements must be given to any sexually active woman with epilepsy of childbearing age to decrease the neural tube malformations.[10] During pregnancy 4 times daily doses may prevent serum level surge and lead to less effects on the fetus.[10] If seizures occur during delivery, benzodiazepines should be given, and Caesarian section should be considered as the patient would not be able to cooperate in a vaginal delivery. AED serum levels must be monitored post-delivery to avoid toxicity due to reversal kinetics.

Due to the constant increase in the number of AEDs and combinations, more studies are still needed, especially for the more recently approved AEDs, to improve the guidelines for treating epilepsy during pregnancy.

EVIDENCE ON THE TRENDS OF UTILIZATION OF ANTIEPILEPTIC DRUGS IN GENERAL POPULATION

Several studies have investigated utilization trends of older AEDs in the general population around the world. The use of AEDs in the general population is increasing internationally. In a study about the use of newer and older AEDs in southern Italy between 2003 and 2005, Alacqua et al. studied the Arianna database which includes more than 300,000 individuals living in the Caserta area.[64] Results showed that the overall one-year prevalence of newer AEDs, with any indication, increased significantly ($p<0.05$), whereas the prevalence of the older generation AEDs remained stable. The rate of incident users of newer AEDs significantly increased from 6.6 per 1000 in 2004 to 8.1 per 1000 in 2005, while the incidence of older AED users did not significantly change. When the analysis was restricted to individuals with epilepsy disorders, the incidence of both groups remained stable. Gabapentin was the most commonly prescribed AED among new users during the study period, 5 times higher incidence when compared to valproic acid in 2004. The incidence of gabapentin decreased significantly from 5.5 per 1000 in 2004 to 4.7 per 1000 in 2005.[64] This decrease may be due to the utilization of pregabalin which was newly marketed during this period.[64]

In total, 3.4% of the whole population received at least one AED prescription during the study period.[64] Among the AED users, 41.4% received older generation AEDs and 68.0% received new generation, hence, 9.5% received at least one prescription of both newer and older AEDs during the study period.[64] Newer AEDs were more likely to be indicated for neuropathic pain than older generation AEDs. Among epileptic patients, users of newer generation AEDs were more likely to be younger females.[64]

In Manitoba, evidence on the increase in the AED use among the general population also exists. In a study by Leong. et al. on the utilization of AEDs in Manitoba during the period between 1998 and 2013, 1.2 million individuals living in Manitoba were included.[65] Individuals were identified to have epilepsy if they had 3 primary care physician claims or one hospitalization coded with a

diagnostic code of International Classification of Diseases, ICD-9-CM 345 (or ICD-10-CA G40/G41, if applicable) within 2 years from the beginning of each quarter. Among individuals with and without a history of epilepsy, those receiving at least one prescription for an AED were identified as the population of AED users. All oral AEDs available in Canada were included in the analysis.[65] To assess trends in AED usage, the prevalence rates were analysed using time series analysis including exponential smoothing models and autoregressive integrated moving average models. AED use increased dramatically in the whole population over the study period, from 8.3 per thousand to 23 per thousand ($p<0.001$). The number of AED users increased from 8,883 (8,017 older AEDs and 322 newer AEDs) to 27,246 (7,617 older AEDs and 17,823 newer AEDs). The use of newer generation AEDs increased by 50-fold during the study period, from 0.3/1000 to 15/1000 ($p<0.001$). Among individuals with epilepsy, the use of older generation AEDs decreased by more than 30% ($p<0.001$), while the use of newer generation AEDs increased by almost 7-fold ($p<0.001$). The use of lamotrigine in individuals with epilepsy increased by 347% ($p<0.001$).[65]

AED users with no epilepsy showed a 210% increase. Moreover, a 55-fold increase in the use of gabapentin among non-epileptic users was observed. The study, however, did not report subgroup analysis for the trends of utilization of AEDs in special populations, such as pregnant women.[65]

Although carbamazepine, valproic acid, topiramate, and pregabalin are the only AEDs that have a Health Canada approved indication for conditions other than epilepsy, this study observed an increase in the use of gabapentin and lamotrigine among individuals without epilepsy. The main reason may be the guidelines that support the off-label use of newer AEDs in conditions as neuropathic pain, migraine prophylaxis, and fibromyalgia.

The study also indicates that more than half AED users in 2013 were using gabapentin, which raises a concern about its use and abuse. Moreover, pregabalin, which is the only AED with Health Canada-approved indication for neuropathic pain, is not covered by health plans in many jurisdictions. This limited access may be the reason for shifting to gabapentin for pain conditions.[65]

The study did not compare the use of AEDs among different groups of users, such as based on the geographic location in Manitoba, or socioeconomic status.[65]

EVIDENCE ON THE UTILIZATION OF AEDS IN PREGNANCY

In the most recently published study about the trends of utilization of AEDs in pregnancy, Cohen et al. studied the databases of five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden), the USA (US Medicaid Analytic eXtra (US MAX) database and US MarketScan), and Australia from 2006 to 2016.[66] Around 5 million pregnancies were investigated in total. The overall use of AED during pregnancies was 15.3 per 1000, the lowest prevalence in Sweden at 6.4 per 1000, and in Australia 12.6 per 1000, while the US MAX database showed the highest prevalence at 34.5 per 1000. Knowing that the US MAX includes claims from 46 states and District of Colombia for publicly insured patients, and there is a mandatory coverage for low income families and individuals with disability.[66] The highest prevalence was found in women <24 years or >40 years. The trend of use of AEDs in pregnancy showed an increase in all the included countries throughout the study period. In Australia, there was a 22% increase, whereas in Sweden there was a 104% increase. The most commonly used AED was Lamotrigine in the Nordic countries, its use increased by 78% between 2006 and 2012 and continued increasing till 2016. In the US, clonazepam was the most commonly used AED, and its use kept on increasing throughout the study period. In Australia the most commonly used AED was valproate, although the use of valproate was decreasing in the Nordic countries (-21%), the US Max (-18%) and the US MarketScan (-26%), there was no change in the utilization of valproate in Australia throughout the study period.

Lamotrigine was the AED with highest continuous utilization throughout pregnancies, and the lowest was valproate.

The study also looked at the utilization of AEDs in each trimester and found out that the use of AEDs was highest before conception and decreased with each trimester (by 27%-70% depending on the country), and then increased after delivery to reach the pre-pregnancy levels 6 months following the birth. Both lamotrigine and carbamazepine showed the most stable levels throughout pregnancy, whereas valproate showed a more obvious decrease during pregnancy.[67]

CANADA

In a Canadian study from Quebec by Kulaga et. al. used the population-based pregnancy databases from 1998 to 2003. The study included all pregnant women between 15 and 45 years of age on the first day of gestation and were continuously insured by the RAMQ drug plan for at least 12 months prior to and during pregnancy. Pregnant epileptic women were defined as the women within the study population who had filled at least one prescription for an AED in the last 12 months prior to gestation and were diagnosed with epilepsy (ICD-9 codes: 3450.x) in the 60 days preceding or following the dispensation date.

The study showed that most pregnant epileptic women (79.6%) received AED monotherapy, 5.8% received polytherapy, and 14.6% were not exposed to any AED. The most commonly used AED during the period of this study was carbamazepine, whether in monotherapy or polytherapy.

This study, however, did not show the trend of utilization of AEDs in pregnancy over the years of the study period. [68]

UNITED STATES OF AMERICA

Bobo et. al. studied the trends of use of AED among pregnant women in the United States, from 2001 to 2007. The study used data from Medication Exposure in Pregnancy Risk Evaluation (MEPREP). The population for this study included 585,615 liveborn deliveries between January 1, 2001, and December 31, 2007. Women were eligible if they were between 15 and 45 years old on the date of delivery.

Descriptive statistics were used to describe the overall prevalence of AED use, and AED use prevalence according to birth year, therapeutic diagnosis, and gestational period.

The prevalence of AED use in pregnancy increased from 15.7 per 1000 deliveries in 2001 to 21.9 per 1000 deliveries in 2007. The use of newer generation AEDs increased fivefold during this period, while the prevalence of older AED use remained relatively unchanged. Approximately 77.5% of the exposed population were exposed to older generation AED during pregnancy.

Indication was identified for approximately 80% of the AED exposed deliveries. The most prevalent indications were psychiatric, pain, and epileptic disorders.
The study included the use of AEDs for any indication, showing an increase in the use of AEDs for psychiatric and pain disorders during the study period, and no such increase for epilepsy.
The study is considered out-of-date, as it did not include any of the AEDs approved in the US after 2006. Moreover, the lack of follow up in the US databases used cannot insure the patient adherence to the regimens as prescribed. [69]

In a retrospective cohort study based on Florida Medicaid claims and Florida Birth Vital Statistics, Wen et al. studied the use of AEDs in pregnant women in Florida from 1999 to 2009. The overall number of pregnancies exposed to first generation AED decreased significantly ($p<0.0001$), whereas, the number of pregnancies exposed to second generation AED increased ($p<0.001$). Carbamazepine, phenytoin, and valproate were the most frequently used AEDs in the period between 2002 and 2004, after 2007 levetiracetam and lamotrigine became the 2 most frequently used AEDs. The trend for AED use in polytherapy did not significantly change during the study period, 62% in 2000 and 63% in 2009 ($p=0.71$). The number of users with epilepsy also did not significantly change ($p=0.75$). The study did not report the changes in utilization of AED in different trimesters of the pregnancies. Moreover, the study depends on the claim data and therefore sample size and power are restricted. The study period ended in 2009, which means it did not study the utilization of the newer AEDs in the market. [70]

EUROPE

A cohort study in Sweden between 1996 and 2013 by Margulis et al. used nationwide Swedish register data. The study reported on the five most commonly used AEDs during the study period: carbamazepine, valproic acid, pregabalin, levetiracetam, and lamotrigine. All pregnant women exposed to these AEDs were included regardless of the indications.
The results showed an overall increase in the use of AEDs in the Swedish pregnant women during the study period. Carbamazepine use decreased from 63% of exposed pregnancies in 1996 to 13%

in 2013. 85% of carbamazepine-exposed pregnancies had epilepsy indication. Valproic acid exposure also decreased from 18% in 1996 to 8% in 2013, and it was more commonly used in mothers with epilepsy. Levetiracetam first appeared in the study cohort in 2002 and became the fourth most commonly used AED during pregnancy in Sweden by the end of the study period, with 10% of exposed pregnancies in 2013. 99% of pregnant women exposed to levetiracetam during pregnancy were diagnosed with epilepsy, and 59% of them were on polytherapy. Although pregabalin first appeared in the study period in 2006, it was the third most commonly used AED in 2013 with 16% of exposed pregnancies. Pregabalin users were special compared to the other AEDs users: they were younger, less educated, more likely to be obese or smokers, and they were more likely to live away from the father. Pregabalin in 69% of exposed pregnancies is used for chronic pain indication. Lamotrigine had the most dramatic increase over the study period from 6% in 1996 to 47% in 2013. 69% of the exposed pregnancies were for women with epilepsy, 20% of them were on polytherapy.[71]

Hurault-Delarue et. al. used the electronic health databases of over one million pregnancies from three European countries between 2007 and 2016 (Italy, France, and the United Kingdom). The results showed that the prevalence of AED prescribing during pregnancy varied between regions, with lamotrigine being among the most prescribed AED in all regions. AED prescribing increased with age in all countries. In the UK, the prevalence of AED prescribing increased over the study period, mainly due to the increase in Pregabalin and Gabapentin prescribing. In France, a general decline in the prescribing of AEDs was noticed during the study period, from 7.4 per thousand in 2007 to 5.4 per thousand in 2015. This is mainly due to the reduction in clonazepam prescribing. In Italy, the prescribing was stable throughout the study period, with a slight reduction in valproate prescribing. Indications were not available in the electronic health care databases, and indications were only known for France and the UK, with epilepsy being the most common indication at 65.9% of the pregnant women exposed to AED in France and 61.8% of in the UK. Moreover, the databases included a small percentage of the general population, and women included in the study may not be considered representative of the general population. [72]

An earlier related study by Charlton et. al. examined the AED prescribing before, during and after pregnancy using seven population-based databases in Europe from 2004 to 2010. The prescribing prevalence of AEDs decreased during pregnancy and returned to pre-pregnancy levels 6 months after delivery. Lamotrigine was the most commonly used in all regions. The use of topiramate, gabapentin, and pregabalin decreased during pregnancy, while the use of lamotrigine and levetiracetam increased. In Denmark, Norway, and the UK, lamotrigine is clearly the drug of choice while in Netherlands and Italy older AEDs are more popular. The regional differences in prescribing patterns suggest difference in the interpretation of scientific evidence. [73]

ASIA

Two Register studies, Vajda et. al. used The Australian Register of Antiepileptic drugs in Pregnancy from 1999 to 2008 and Kinney et. al. used the UK and Ireland Epilepsy and Pregnancy Register (UKIEPR) from 1996 to 2016, both showing similar results. There was no significant change in the polytherapy prescribing rate. However, there was a statistically significant decrease in the proportion of all pregnancies exposed to first generation AEDs (valproic acid, carbamazepine, and phenetoin) and a significant increase in the proportion exposed to newer generation AEDs (lamotregine, topiramate, and levetiracetam). There was also a statistically significant decrease of Valproic acid daily dose over time, and a statistically significant slight increase of phenytoin daily dose over time. Knowing that recruitment of pregnant women in the register is entirely voluntary, findings drawn from these studies may not be representative of the entire population of pregnant women with epilepsy. [74,75]

In a prospective cohort study to investigate AED prescription in pregnancies with epilepsy in Taiwan between 2004 and 2015, Yeh et al. used the Taiwanese Registry of Epilepsy and Pregnancy. Pregnant women had to complete questionnaires until delivery or termination of pregnancy. 69%

of these women received AED monotherapy and 25.7% received polytherapy. Second generation AEDs were the most utilized with 44.5%, whereas first generation were at 32.9% of prescriptions and 17.2% were combination of first and second generation. Over the study period, the polytherapy trend decreased from 40% in 2004 to 20% in 2015 whereas the trend of monotherapy increased steadily from 50% in 2004 to 80% in 2015. First generation AED utilization in pregnancy decreased from 73.3% in 2004 to 8.3% in 2015. [76]

LITERATURE GAP:

All the studies mentioned above show an increase in the utilization of AEDs in the general population and among pregnant women in the past few decades. However, none of the above-mentioned studies have data on the most recently marketed third-generation AEDs. Moreover, most of the studies were conducted among populations outside Canada, where findings may not be generalizable to Canadians.

In Manitoba and Canada, evidence is still needed to inform decision makers on the recently introduced drugs (2nd and 3rd generation AED) in the Canadian context is also necessary. Results from multiple Canadian provinces are needed to allow comparison of the quality of treatment and access to care among different Canadian provinces, as well as between Canada and other countries.

RESEARCH PROJECT

OBJECTIVE

Our **objective** is to examine time-trends of utilization of AED therapies among pregnant women in Manitoba, Canada.

METHODS

DATABASES AND COHORT DEFINITION

A population-based cohort study was conducted in the province of Manitoba, Canada. We constructed a cohort of all pregnant women in Manitoba from April 1, 1995, to March 31, 2019 using the administrative databases from the Manitoba Research Data Repository at the Manitoba Centre for Health Policy (MCHP), University of Manitoba. The Database Repository is a secure data-rich environment containing person-level health information on the entire population of Manitoba. All records in the Repository are de-identified; however, records are linkable at the individual and family levels using a scrambled health number attached to each record. The Repository data are updated annually.

For the current study, we used linked databases including: (1) Drug Program Information Network (DPIN), which includes drug name, brand name, and dispensation date and captures the dispensation of all prescription drugs by pharmacies in Manitoba regardless of the insurance coverage type (1995/96 – 2018/19), (2) Hospital Discharge Abstracts, which includes records of all patients' hospital admissions with summaries for demographic data (1992/93 – 2018/19), (3) Medical Services Database, which includes physician claims was used to identify diagnosis codes using the International Classification of Diseases (ICD-9 and ICD-10) (1992/93 – 2018/19), and (4)The Hospital Newborn to Mother Link, which serves to match the baby's birth hospital record with the mother's obstetrical delivery record. All datasets were linked together by using a

scrambled personal health identification number that is unique for each pregnancy (1995/96 – 2018/19).

STUDY POPULATION

We identified all pregnancies for women living in Manitoba between 1995 and 2018. A woman was defined as having epilepsy if she has 1 or more medical claims or 1 or more hospitalization for epilepsy during the 5 years prior to delivery (ICD-9 345 or ICD-10 G40/G41). Four groups of pregnant women were created: (1) exposed pregnant women with epilepsy, (2) exposed pregnant women without epilepsy, (3) unexposed pregnant women with epilepsy and (4) unexposed pregnant women without epilepsy.

Since we need to look 5 years back to check for epilepsy diagnosis in the mothers, women who did not have five-year coverage by Manitoba Health were excluded. Children born before April 1, 1997, were also excluded because Hospital Abstracts and Medical Claims data goes back to 1992.

Area of residence was defined as urban for women living in Winnipeg or Brandon or rural for women living in all other areas in the province. Income quintiles were used to determine the socioeconomic status of women. Income quintile measures the neighborhood socioeconomic status and divides the population to five income groups from lowest income to highest income (approximately 20% of the population in each group).[77]

Table 2 Definitions of medical conditions

Medical Condition	Definition
Hypertension	Anyone with at least one hospital diagnosis for hypertension (ICD-9-CM: 401-405 OR ICD-10-CA: I10-I13, I15) in one year, or at least two ambulatory visit diagnoses (ICD-9-CM codes: 401-405) in one year, or at least two dispensations for hypertension medication (as described in the 2019 RHA Indicators Atlas).
Diabetes	Individuals with one of the following in 3-year period: one or more hospitalizations with a diagnosis of diabetes (ICD-9-CM code 250; ICD-10-CA codes E10-E14), or two or more physician visits with a diagnosis of diabetes (ICD-9-CM codes as above), or one or more prescriptions for medications to treat diabetes (Anatomical Therapeutic Chemical code ATC code A10).
prenatal mood and/or anxiety disorder (e.g., anxiety and/or depression)	A woman was considered to have prenatal mood and/or anxiety disorder (e.g. anxiety and/or depression) if in the 1 year prior to conception (or hospital discharge in case of a stillbirth) she had: one or more hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD-9-CM codes 296.2-296.8, 300.4, 309, 311; ICD-10-CA codes F31, F32, F33, F34.1,

	F38.0, F38.1, F41.2, F43.1, F43.2, F43.8,F53.0, F93.0) OR one or more physician visits with a diagnosis for depressive disorder, affective psychoses, or adjustment reaction (ICD-9-CM codes 296, 309 or 311) OR one or more hospitalizations with a diagnosis for anxiety disorders (ICD-9-CM code 300; ICD-10-CA codes F32.0, F34.1, F40, F41, F42, F44, F45.0, F451, F452, F48, F68.0, F99) or one or more hospitalizations with a diagnosis for anxiety states, phobic disorders, or obsessive-compulsive disorders (ICD-9-CM codes 300.0, 300.2, 300.3; ICD-10-CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42) OR two or more physician visits with a diagnosis for anxiety disorders (ICD-9-CM code 300).
Pain disorders	Diagnosis of Pain (ICD-9 code 338; ICD-10 R52), or Migraine and Headaches (ICD-9 346 784; ICD-10 G43 R51) during the 1 year before conception.
Personality disorder	A woman was considered to have personality disorder if she had one or more hospitalization with a diagnosis for personality disorders (ICD-9-CM code: 301; or ICD-10-CA codes: F21, F34.0, F60, F61, F62, F68.1, F68.8 or F69) or one or more physician visits with a diagnosis for personality disorders using ICD-9-CM code 301 in the 1 year prior to conception.

Schizophrenia	Any women with one or more hospitalization with a diagnosis for schizophrenia (ICD-9-CM code: 295 (schizophrenic disorders), or ICD-10-CA codes: F20 (schizophrenia), F21 (schizotypal disorder), F23.2 (acute schizophrenia-like psychotic disorder), F25 (schizoaffective disorders), or one or more physician visits with a diagnosis for schizophrenia using ICD-9-CM code 295 in the 1 year prior to conception.

EXPOSURE DEFINITION

AED utilization was identified using the Anatomical Therapeutic Chemical (ATC) codes. Exposure to a prescribed AED was defined as having at least one prescription filled during the exposure window of interest or a prescription filled before the beginning of the exposure window, but with a duration overlapping the exposure window.

EXPOSURE WINDOWS TO AEDS

- First trimester exposure: the time from the first day of gestation until the 14th week of gestation.
- Second trimester exposure: the time between the 15th week and the 25th completed week of gestation.
- Third trimester exposure: the time between the 26th week and the end of the pregnancy.
- Anytime during pregnancy: the time between the first day of gestation and the end of the pregnancy.

The period of pregnancies covered will extend from 1995 to 2018, which overlaps with the introduction of several new-generation AEDs into the market.

THERAPIES

AEDs examined were identified using prescription drug data and the ATC classification codes, specifically all drugs coded as N03A for "antiepileptics", which include phenobarbital, primidone, phenytoin, ethosuximide, mesuximide, clonazepam, carbamazepine, oxcarbazepine, valproic acid, vigabatrin, lamotrigine, topiramate, gabapentin, levetiracetam, pregabalin, and lacosamide.

Table 3 Included AEDs and their ATC codes

ATC code	**Antiepileptic Drug**
N03	ANTIEPILEPTICS
N03AB	Hydantoin derivatives
N03AB01	ethotoin
N03AB02	phenytoin
N03AB02	phenytoin
N03AB03	amino(diphenylhydantoin) valeric acid
N03AB04	mephenytoin
N03AB05	fosphenytoin
N03AB52	phenytoin, combinations
N03AB54	mephenytoin, combinations
N03AC	Oxazolidine derivatives
N03AC01	paramethadione
N03AC02	trimethadione
N03AC03	ethadione
N03AD	Succinimide derivatives
N03AD01	ethosuximide
N03AD02	phensuximide
N03AD03	mesuximide
N03AD51	ethosuximide, combinations

N03AE	Benzodiazepine derivatives
N03AE01	clonazepam
N03AE01	clonazepam
N03AF	Carboxamide derivatives
N03AF01	carbamazepine
N03AF01	carbamazepine
N03AF02	oxcarbazepine
N03AF03	rufinamide
N03AF04	eslicarbazepine
N03AG	Fatty acid derivatives
N03AG01	valproic acid
N03AG01	valproic acid
N03AG01	valproic acid
N03AG02	valpromide
N03AG03	aminobutyric acid
N03AG03	aminobutyric acid
N03AG04	vigabatrin
N03AG05	progabide
N03AG06	tiagabine
N03AX	Other antiepileptics
N03AX03	sultiame
N03AX07	phenacemide
N03AX09	lamotrigine
N03AX10	felbamate
N03AX11	topiramate
N03AX12	gabapentin

N03AX13	pheneturide
N03AX14	levetiracetam
N03AX14	levetiracetam
N03AX15	zonisamide
N03AX16	pregabalin
N03AX17	stiripentol
N03AX18	lacosamide
N03AX18	lacosamide
N03AX19	carisbamate
N03AX21	retigabine
N03AX22	perampanel
N03AX23	brivaracetam
N03AX23	brivaracetam
N03AX24	cannabidiol
N03AX30	beclamide
N03AA	Barbiturates and derivatives
N03AA01	methylphenobarbital
N03AA02	phenobarbital
N03AA02	phenobarbital
N03AA03	primidone
N03AA04	barbexaclone
N03AA30	metharbital

Statistical Analysis

The characteristics and comorbidities of women were evaluated using descriptive statistics. The use of AEDs during the whole pregnancy and each trimester was estimated using Anatomical Therapeutic Chemical (ATC) codes. The annual trend of use of AED was evaluated for the total population, and for women with epilepsy and women without epilepsy. Linear regression was used to model the trends of utilization of AEDs in each of the four groups of pregnant women. Models were built with data from 1997 to 2018 for statistical stability as some medications were only available starting 1997. We evaluated the use of AED classes (old and new generation) and specific AEDs annually. Since the linear regression showed that the increase in utilization of AED among pregnant women in Manitoba was driven mainly by the utilization among pregnant women without epilepsy, we divided the time trend analysis into women with epilepsy and women without epilepsy. A p-value ≤ 0.05 was considered statistically significant. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

ABSTRACT

Trends of Utilization of Antiepileptic Drugs in Pregnancy in Manitoba, Canada: A 20-year utilization study

Background: Studies from Canada and globally have shown an increase in antiepileptic drugs (AEDs) use in the past decade. AEDs are being used more for off-label indications. Identifying the impact of such increase among vulnerable groups, such as pregnant women, is imperative.

Objective: To examine time-trends of utilization of AED therapies among pregnant women in Manitoba, Canada.

Methods: We conducted a population-based cohort study using administrative health databases from Manitoba. Pregnancies between 1995 and 2018 were included. Utilization was identified by Anatomical Therapeutic Chemical codes. Four groups of pregnant women were created based on AED exposure and epilepsy diagnosis. A woman was considered to have epilepsy if she has 1 or more medical claims or 1 or more hospitalization for epilepsy during the 5 years prior to delivery. Trend analysis was conducted using linear regression.

Results: Out of 273,492 pregnancies identified, 1775 (0.65%) had epilepsy. Among pregnancies with epilepsy, 812 (45.75%) were exposed to AEDs. And 2742 (1% of the total population) were exposed to AEDs and did not have epilepsy diagnosis. Overall, the number of pregnancies exposed to AEDs increased significantly from 0.56% in 1997 to 2.21% in 2018 ($p<0.0001$). No significant change was observed in the exposure to AEDs among women with epilepsy (from 0.37% in 1997 to 0.36% in 2018, $p=0.24$. Whereas the percentage of AEDs use among pregnant women without epilepsy increased significantly from 0.19% in 1997 to 1.85% in 2018 ($p<0.0001$). In the total cohort of pregnancies, 1439 (0.53%) were exposed during the whole pregnancy, 1369 (0.5%) were exposed in the first trimester, 63 (0.02%) were exposed in the second trimester, and 184 (0.07%) were exposed in the third trimester. Clonazepam was the most commonly used

AED during the study period (1953 users, 0.71%), followed by gabapentin (785 users, 0.29%) and carbamazepine (449 users, 0.16%).

Conclusion: No major shifts in the use of AEDs were observed among women with epilepsy. Concerns about an increased use of AEDs, and reasons for the use, among pregnant women in Manitoba driven by indications other than epilepsy require additional research, to understand the reasons for use, potential substitution, and policy implications.

MANUSCRIPT

Trends of Utilization of Antiepileptic Drugs in Pregnancy in Manitoba, Canada

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INTRODUCTION

The estimated prevalence of epilepsy among pregnant women ranges between 0.3% and 0.7%.[1,2] Both epilepsy and antiepileptic drugs (AEDs) are associated with potential adverse effects on pregnancy and the developing fetus.[1,3] Pharmacological management with AEDs during pregnancy should be maintained at lowest possible dose without losing their therapeutic benefit, leading to optimum seizure control and minimal fetal exposure.[3,4]

Worldwide, several studies have reported an increase in the use of AEDs for epilepsy and other indications, during pregnancy.[5–14] In a recently published study, Cohen *et al.* reported the utilization trends of AEDs in pregnancy in five Nordic countries, USA and Australia between 2006 and 2016.[13] A significant increase in the use of AEDs during pregnancy was found in all countries throughout the study period.[13] In Canada, a study from the province of Québec by Kulaga *et al.* found the majority of pregnant women with epilepsy (79.6%) received AED monotherapy, 5.8% received polytherapy, and 14.6% with no AED exposure.[12]

In Manitoba, evidence of an increase in the AED use among the general population exists.[15] A study by Leong et al. showed that AED use increased significantly, from 8.3 per thousand to 23 per thousand between 1998 and 2013.[15] The study showed a 210% increase in AED users with no epilepsy, and 55-fold increase in the use of gabapentin among users without epilepsy.[15] The study, however, did not report subgroup analysis for the trends of utilization of AEDs in special populations, such as pregnant women.[15] In the current study, we aim to examine the trends of utilization of AEDs in pregnant women, and identify the changes in AED prescriptions composition among pregnant women with epilepsy in Manitoba, Canada between 1995 and 2019.

METHODS

Data Sources and design

A retrospective population-based cohort study was conducted using data from the province of Manitoba, Canada. We constructed a cohort of all pregnant women in Manitoba from April 1, 1995, to March 31, 2019 using the administrative databases from the Manitoba Research Data Repository at the Manitoba Centre for Health Policy (MCHP), University of Manitoba. The Database Repository is a secure data-rich environment containing person-level health information on the entire population of Manitoba. All records in the Repository are de-identified; however, records are linkable at the individual and family levels using a scrambled health number attached to each record. The Repository data are updated annually.

For the current study, we used linked databases including: (1) Drug Program Information Network (DPIN), which includes drug name, brand name, and dispensation date and captures the dispensation of all prescription drugs by pharmacies in Manitoba regardless of the insurance coverage type (1995/96 – 2018/19), (2) Hospital Discharge Abstracts, which includes records of all patients' hospital admissions with summaries for demographic data (1992/93 – 2018/19), (3) Medical Services Database, which includes physician claims was used to identify diagnosis codes using the International Classification of Diseases (ICD-9 and ICD-10) (1992/93 – 2018/19), and (4)The Hospital Newborn to Mother Link, which serves to match the baby's birth hospital record with the mother's obstetrical delivery record. All datasets were linked together by using a scrambled personal health identification number that is unique for each pregnancy (1995/96 – 2018/19).

Study population

We identified all pregnancies for women living in Manitoba between 1995 and 2018. A woman was considered to have epilepsy if she has 1 or more medical claims or 1 or more hospitalization for epilepsy during the 5 years prior to delivery (ICD-9 345 or ICD-10 G40/G41).[16,17,15] Four groups of pregnant women were created: (1) exposed pregnant women with epilepsy, (2) exposed

pregnant women without epilepsy, (3) unexposed pregnant women with epilepsy and (4) unexposed pregnant women without epilepsy. Women who did not have five-year coverage or whose children were born before April 1, 1997, were excluded as they would lack five years of follow-up. Area of residence was defined as urban for women living in Winnipeg or Brandon or rural for women living in all other areas of the province. Income quintiles were used to determine the socioeconomic status of women. Income quintile measures neighborhood socioeconomic status and divides the population to five income groups from lowest income to highest income (approximately 20% of the population in each group).

Exposure definition

AED utilization was identified using the Anatomical Therapeutic Chemical (ATC) codes. The exposure windows were: first trimester (1st day of gestation - the 14th week), second trimester (15th week – 25th week), third trimester (26th week – end of pregnancy), and anytime during pregnancy (1st day of gestation – end of pregnancy). Exposure to a prescribed AED was defined as having at least one prescription filled during the exposure window of interest or a prescription filled before the beginning of the exposure window but with a duration overlapping the exposure window. AEDs examined were identified using prescription drug data and ATC codes, specifically all drugs coded as N03A for antiepileptics which include phenobarbital, primidone, phenytoin, ethosuximide, mesuximide, clonazepam, carbamazepine, oxcarbazepine, valproic acid, vigabatrin, lamotrigine, topiramate, gabapentin, levetiracetam, pregabalin, and lacosamide.

Statistical Analysis

The characteristics and comorbidities of women were evaluated using descriptive statistics. The use of AEDs during the whole pregnancy and each trimester was estimated. The annual trend of use of AED was evaluated for the total population, and for women with epilepsy and women without epilepsy. Linear regression was used to model the trends of utilization of AEDs in each group of pregnant women. Models were built with data from 1997 to 2018 for statistical stability as some medications were only available as of 1997. We evaluated the use of AED classes (old and new generation) and specific AEDs annually. A p-value ≤ 0.05 was considered statistically

significant. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Ethical approval

This study was approved by the Health Research Ethics Board (HREB) at the University of Manitoba and Manitoba Health Information Privacy Committee (HIPC).

RESULTS

Table 4M Characteristics of the study population

		Exposed pregnant women with epilepsy	**Exposed Pregnant women without epilepsy**	**Unexposed Pregnant women with epilepsy**	**Unexposed Pregnant women without epilepsy**
Total number, N (%)		812 (0.3%)	2,742 (1%)	963 (0.35%)	268,975 (98.35%)
Mean age (SD)		27.9 (±5.5)	29.2 (±5.6)	26.6 (±6)	28.1 (±5.8)
SES	Low	254 (31.28%)	1193 (43.51%)	301 (31.26%)	70812 (26.33%)
	Med-Lo	214 (26.35%)	561 (20.46%)	203 (21.08%)	56928 (21.16%)
	Medium	153(18.84%)	434 (15.83%)	196(20.35%)	49153 (18.27%)
	Med-Hi	110 (13.55%)	286 (10.43%)	166 (17.24%)	49483 (18.40%)
	High	75 (9.24%)	258 (9.41%)	95 (9.87%)	41820 (15.55%)
Area of Residence	Rural	357 (43.97%)	1029 (37.52%)	387 (40.18%)	125655 (46.71%)
	Urban	449 (55.29%)	1703 (62.10%)	574 (59.60%)	142541 (52.99%)
Hypertension, N (%)		27 (3.33%)	227 (8.28%)	34 (3.53%)	4212 (1.53%)
Diabetes, N (%)		26 (3.2%)	212 (7.73%)	34 (3.53%)	7684 (2.86%)
Mood and anxiety disorders, N (%)		189 (23.28%)	1788 (65.21%)	208 (21.60%)	27481 (10.22%)
Schizophrenia, N (%)		10 (1.23%)	90 (3.28%)	5 (0.52%)	583 (0.22%)

Personality Disorder, N (%)	34 (4.19%)	270 (9.85%)	38 (3.95%)	2638 (0.98%)
Pain, N (%)	86 (10.59%)	557 (20.31%)	122 (12.67%)	14932 (5.55%)
Stillborn, N (%)	5 (0.62%)	28 (1.02%)	8 (0.83%)	8 (0.83%)
Singleton, N (%)	788 (97.04%)	2666 (97.23%)	945 (98.13%)	262111 (97.45%)
Multiple births, N (%)	24 (2.96%)	76 (2.77%)	18 (1.87%)	6864 (2.55%)

Out of 273,492 pregnancies, mean age of 28 years, 0.3% (n=812) were in women with epilepsy exposed to AEDs, 0.35% (n= 963) were pregnancies of women with epilepsy unexposed to AED, and 1% (n=2742) were women without epilepsy but exposed to AEDs (Table 1). Among women with epilepsy, 31.3 % (n= 254) of the exposed pregnancies and 31.26% (n=301) of the unexposed pregnancies were in the lowest income quintile. Whereas, in women without epilepsy, 43.5% (n=1193) of exposed pregnant women were in the lowest income quintile compared to 26.3% (n=70812) in unexposed pregnant women (Table 1). Exposed pregnant women without epilepsy had higher rates of comorbidities compared to other groups. Among pregnant women without epilepsy, 65.21% were diagnosed with anxiety and 20.31% were diagnosed with pain compared to 10.22% and 5.55% respectively in unexposed pregnant women without epilepsy (Table 1).

Trimester analysis

Trimester analysis showed 0.53% (n=1439) of women were exposed throughout their pregnancy, 0.5% (n= 1369) were exposed only in the first trimester, 0.02% (n= 63) were exposed only during the second trimester, and 0.07% (n= 184) were exposed only during the third trimester. Among women with epilepsy, 33.58% were exposed throughout the pregnancy. Detailed analysis of exposures by trimester is presented in supplementary figures 1, 2, and 3.

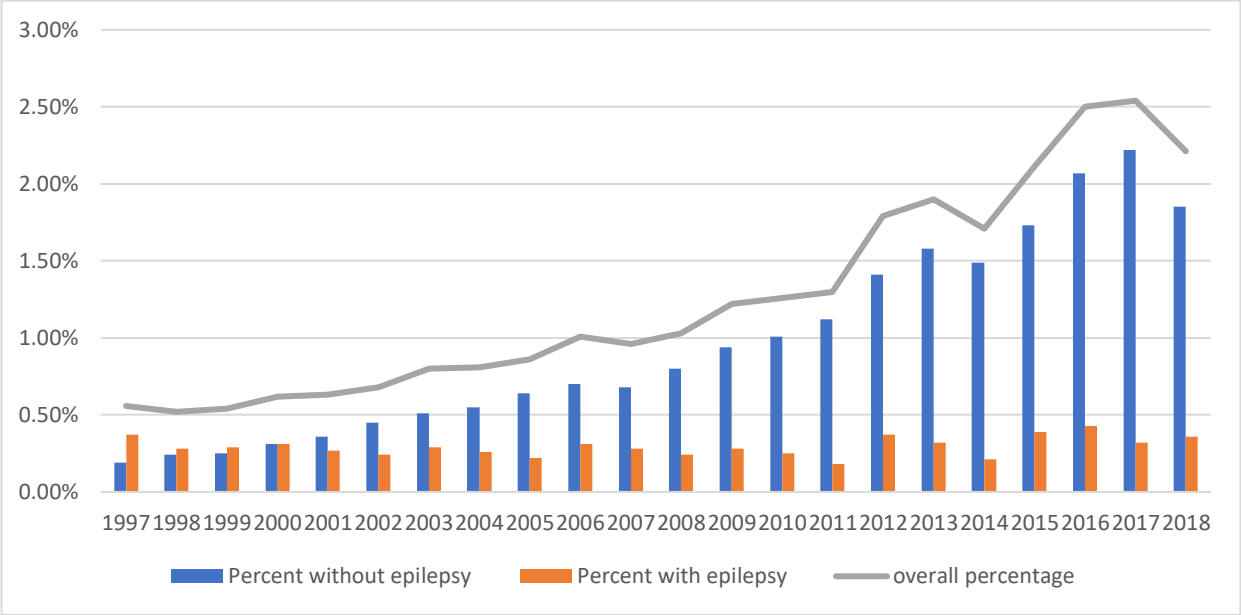


Figure 2M Annual Trend of utilization of AED among all pregnant women and among pregnant women with and without epilepsy

The number of pregnancies exposed to AEDs increased significantly from 0.56% in 1997 to 2.21% in 2018 ($p<0.0001$) (Figure 1). There was no significant change in the percentage of pregnant women with epilepsy exposed to AEDs from 0.37% in 1997 to 0.36% in 2018 ($p=0.2354$). Whereas the percentage of AED-exposures among pregnant women without epilepsy increased significantly (0.19% in 1997 to 1.85% in 2018, $p<0.0001$) (Figure 1).

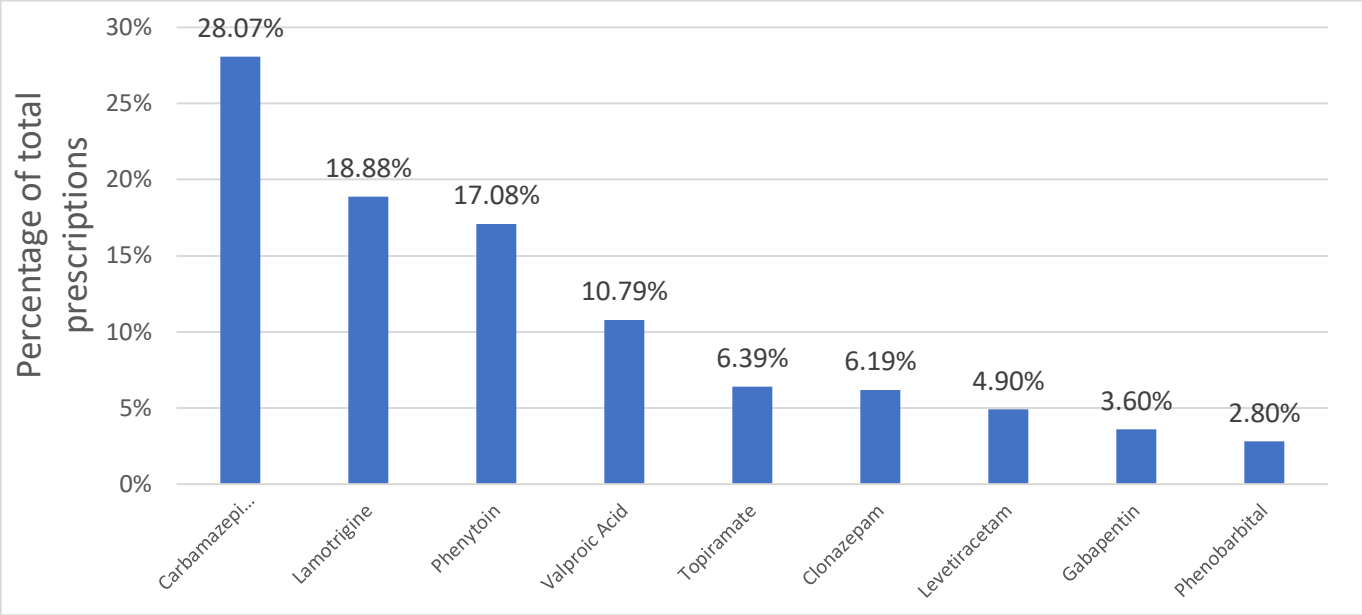


Figure 3M Most used AEDs among pregnant women with epilepsy

Table 5M Percentage of exposed pregnancies to each AED by group

	All Exposed pregnant women	Exposed pregnant women with epilepsy	Exposed pregnant women without epilepsy
Clonazepam	45.88%	6.19%	59.67%
Gabapentin	18.38%	3.6%	23.52%
Carbamazepine	9.33%	28.07%	2.81%
Lamotrigine	7.86%	18.88%	4.03%
Levetiracetam	1.31%	4.9%	suppressed
Valproic Acid	5.46%	10.79%	3.61%
Phenytoin	5.44%	17.08%	1.39%
Topiramate	4.41%	6.39%	3.72%

The most used AED among pregnant women throughout the study period was clonazepam (44.44% of all exposed pregnancies) followed by gabapentin (17.85%) and carbamazepine

(10.22%) (Table 2). Whereas, among pregnant women with epilepsy, carbamazepine (33.86%), lamotrigine (22.77%), phenytoin (17.08%) and valproic acid (13%) were the most used. (Figure 2)

AED annual prescriptions

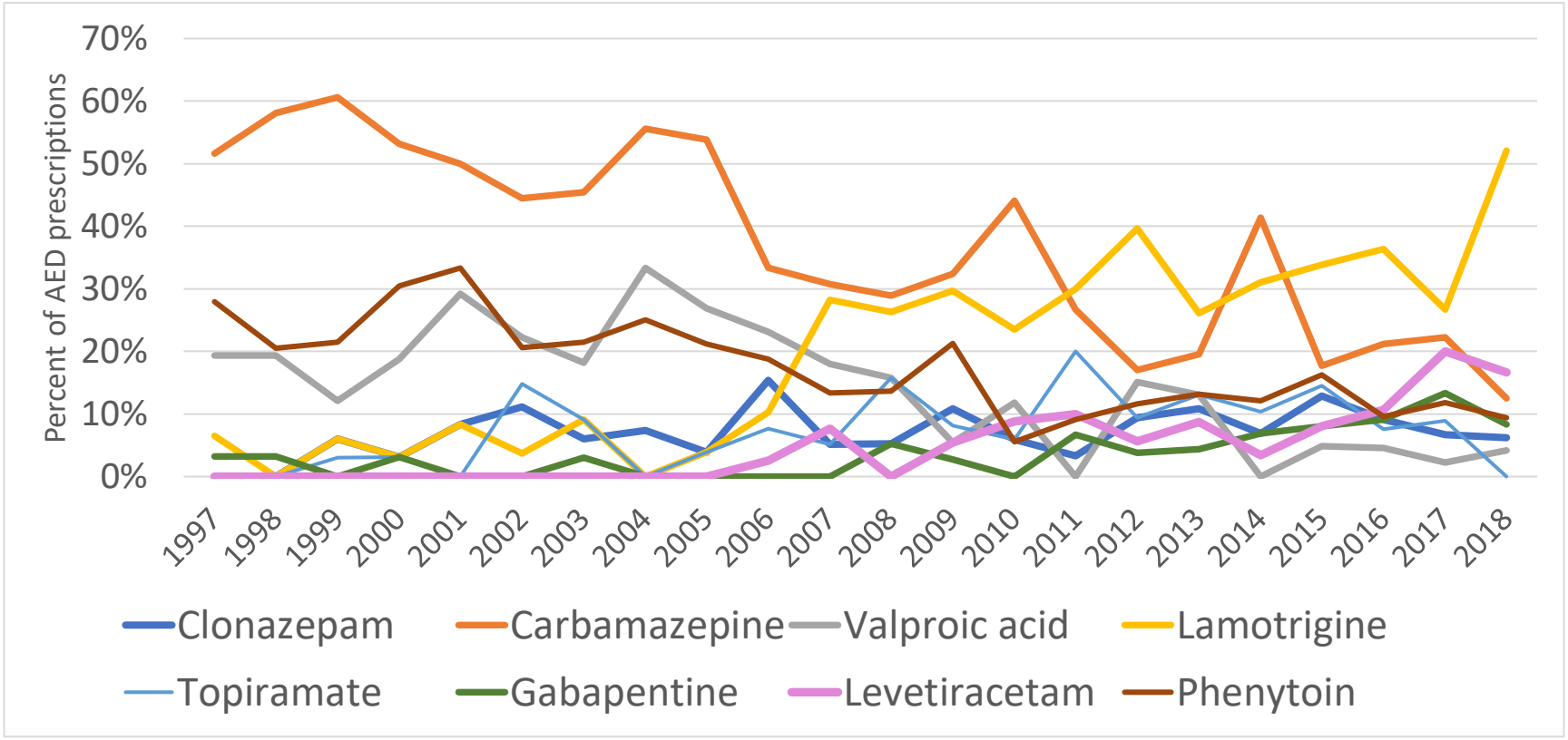


Figure 4M Trends of top AED prescriptions among pregnant women with epilepsy

Carbamazepine was the most prescribed AED for pregnant women with epilepsy with 51% of prescriptions in 1997 and decreased to 12.5% in 2018. Whereas lamotrigine prescriptions increased from 6.45% (1997) to 52% (2018) (Figure 3)

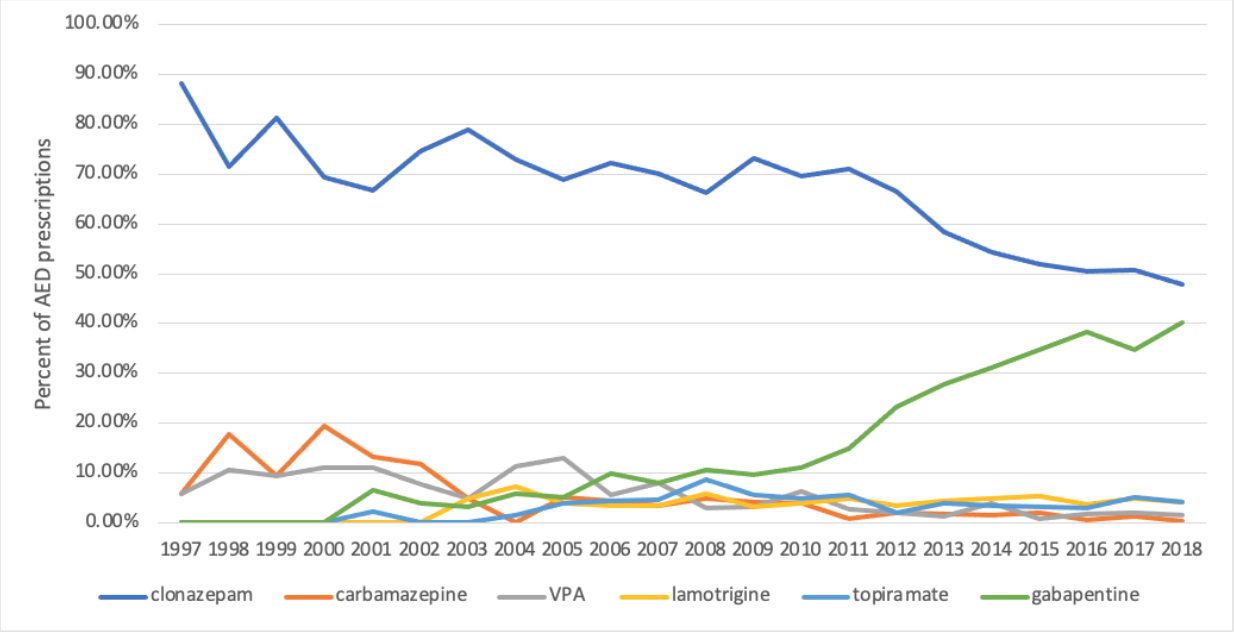


Figure 5M Trends of top AED prescriptions among pregnant women without epilepsy

On the other hand, among women without epilepsy, clonazepam remained the most used AED throughout the study period. However, its utilization decreased from 88.24% in 1997 to 47.97% in 2018. Gabapentin first appeared among women without epilepsy in 2001 and its utilization increased to reach 40.22% of prescriptions in 2018. (Figure 4)

DISCUSSION

In this population-based cohort study, we observed a significant increase in the utilization of AEDs among pregnant women in Manitoba between 1997 and 2018. This increase was attributed mainly to the increased use of clonazepam and gabapentin among women without epilepsy. In general, there was no major shift in the utilization of AEDs among pregnant women with epilepsy over the study. In contrast, a significant increase in the utilization of AEDs among women without epilepsy was observed.

Among women with epilepsy in the US, lamotrigine and levetiracetam were the most commonly used between 2012-2016.[18] We observed similar results in our study during the same period lamotrigine . Our study captures the entire population of Manitoba within 20 years; therefore, carbamazepine was the most commonly used especially before 2007. Our results are concordant with data from Australia, showing carbamazepine and lamotrigine as the most frequently used among pregnant women.[19,20]

Our study showed an increase in lamotrigine prescriptions among pregnant women with epilepsy, and a decrease in valproic acid and carbamazepine use. Similar results were reported in the UK and Ireland, with an increase in lamotrigine and levetiracetam use and a decrease in valproic acid and carbamazepine between 1996 and 2016.[21] Lamotrigine prescriptions increased from 15% of the total AED prescriptions in Uk and Ireland in 2000 to 31% in 2016, at the same time valproic acid prescriptions decreased from 22% in 2000 to less than 5% in 2016.[21]

AEDs are frequently used for indications other than seizure control. For example, valproic acid is indicated for migraine prophylaxis and to treat migraine headaches and schizophrenia.[22,23] It is also used for the treatment of anxiety disorders and sleep-related problems.[22,24,25] Lamotrigine is indicated for extreme mood swings in bipolar disorder in adults.[26,23] Gabapentin is primarily used

to treat neuropathic pain including trigeminal neuralgia, HIV-associated neuralgia, diabetic neuropathy, neoplasia, and strokes.[26,27] It is also used in the treatment of psychiatric disorders, most notably bipolar disorder, and in movement disorders as restless leg syndrome.[26,27] The study results showed that among the subgroup of women without epilepsy, gabapentin use is significantly increasing.

Most exposed pregnant women with epilepsy (33.58%) were exposed throughout the pregnancy period, reflecting optimal management of seizures. Among the women with epilepsy, more than 54% were unexposed to any AED, this could be attributed to the presence of mild/controlled epilepsy, or the accuracy of the epilepsy definition used in our study. We conducted sensitivity analysis using diagnosis codes in 2,5 and 10 years prior to pregnancy case. The 5 years' definition was used to minimize false-negative cases. Among women without epilepsy, the majority were exposed only during the first trimester, which indicates discontinuing AEDs after knowledge of conception.

Strengths and Limitations

The databases used in this study are a major strength in terms of external validity.[28] The MCHP repository includes objectively measured medical records for all Manitoba residents. Our study captured the prescription practices of prescribers in Manitoba during the past 20 years. We were able to link dispensation records to variables like socioeconomic status due to the depth of information in the Manitoba databases. Our study, however, has limitations. First, exposure was derived from dispensing records and not actual intake.[29] Second, we did not have data on the severity of epilepsy cases. Third, we did not describe other indications directly linked to each AED (for example, if gabapentin was prescribed for neuropathic pain or another disorder) as this was out of the scope of the current study. Additional studies examining AEDs indications are warranted.

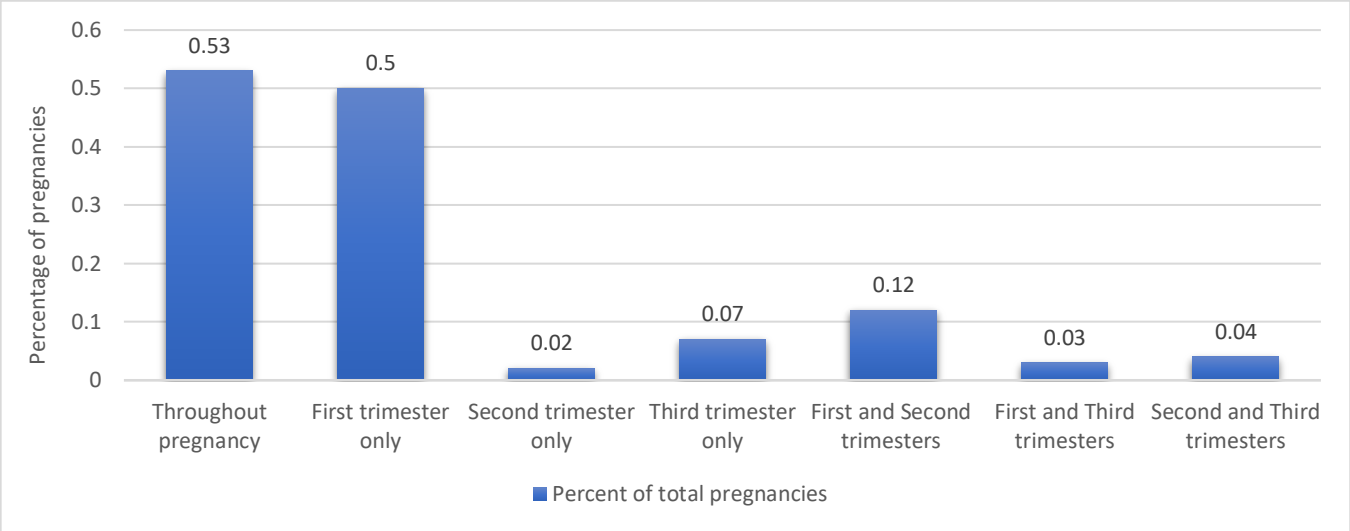
CONCLUSION

Over the study period, no major shifts in the use of AEDs were observed among pregnant women with epilepsy. The reduction in carbamazepine use coupled with the increase in lamotrigine use reflects Manitoba prescribers' adherence to updated guidelines. Consistent with previous reports among the general population of Manitoba, gabapentin is increasingly used among pregnant women, mostly for indications other than epilepsy. Future studies on the utilization and safety of gabapentin and other new-generation AEDs in pregnancy are warranted to inform prescribers and policymakers.

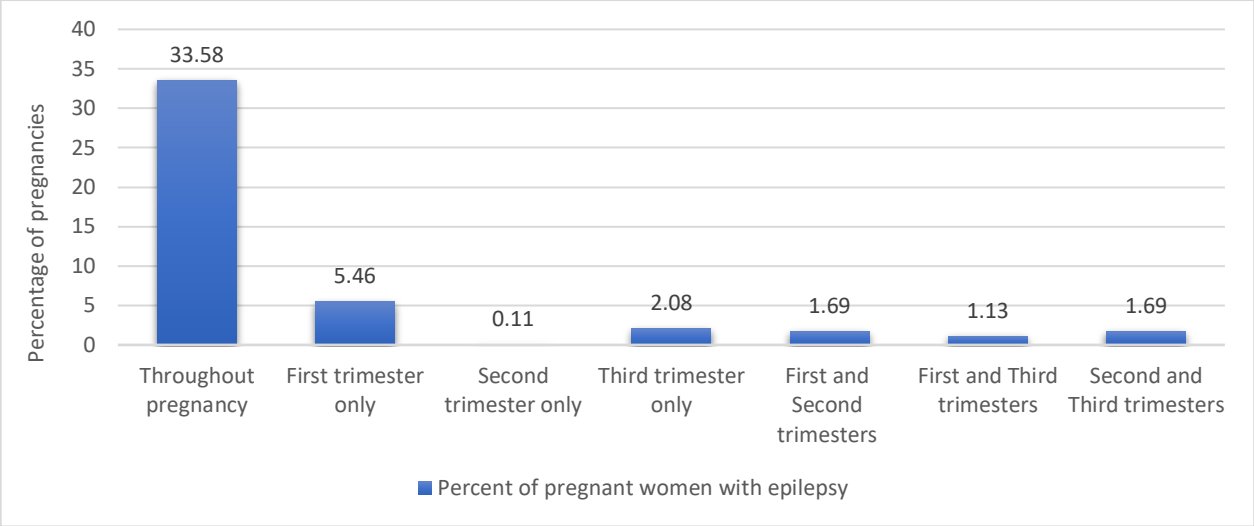
SUPPLEMENTARY

The medical conditions and comorbidities of the four groups were identified using ICD codes from physician claims and hospitalizations. We assessed the prevalence of medical comorbidities including hypertension, diabetes, chronic pain, mood and anxiety disorders, schizophrenia, and personality disorders. Hypertension was defined as anyone with at least one hospital diagnosis for hypertension (ICD-9-CM: 401-405 OR ICD-10-CA: I10-I13, I15) in one year, or at least two ambulatory visit diagnoses (ICD-9-CM codes: 401-405) in one year, or at least two dispensations for hypertension medication (as described in the 2019 RHA Indicators Atlas).[30] Diabetes was defined as individuals with one of the following in 3-year period: one or more hospitalizations with a diagnosis of diabetes (ICD-9-CM code 250; ICD-10-CA codes E10-E14), or two or more physician visits with a diagnosis of diabetes (ICD-9-CM codes as above), or one or more prescriptions for medications to treat diabetes (ATC code A10).[31] A woman was considered to have prenatal mood and/or anxiety disorder (e.g. anxiety and/or depression) if in the 1 year prior to conception (or hospital discharge in case of a stillbirth) she had: one or more hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD-9-CM codes 296.2-296.8, 300.4, 309, 311; ICD-10-CA codes F31, F32, F33, F34.1, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8,F53.0, F93.0) OR one or more physician visits with a diagnosis for depressive disorder, affective psychoses, or adjustment reaction (ICD-9-CM codes 296, 309 or 311) OR one or more hospitalizations with a diagnosis for anxiety disorders (ICD-9-CM code 300; ICD-10-CA codes F32.0, F34.1, F40, F41, F42, F44, F45.0, F451, F452, F48, F68.0, F99) or one or more hospitalizations with a diagnosis for anxiety states, phobic disorders, or obsessive- compulsive disorders (ICD-9-CM codes 300.0, 300.2, 300.3; ICD-10-CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42) OR two or more physician visits with a diagnosis for anxiety disorders (ICD-9-CM code 300).[32] Pain disorders were defined as: diagnosis of pain (ICD-9 code 338; ICD-10 R52), or migraine and headaches (ICD-9 346 784; ICD-10 G43 R51) during the 1 year before conception. A woman was considered to have personality disorder if she had one or more hospitalization with a diagnosis for personality disorders (ICD-9-CM code: 301; or ICD-10-CA codes: F21, F34.0, F60, F61, F62, F68.1, F68.8 or F69) or one or more physician visits with a

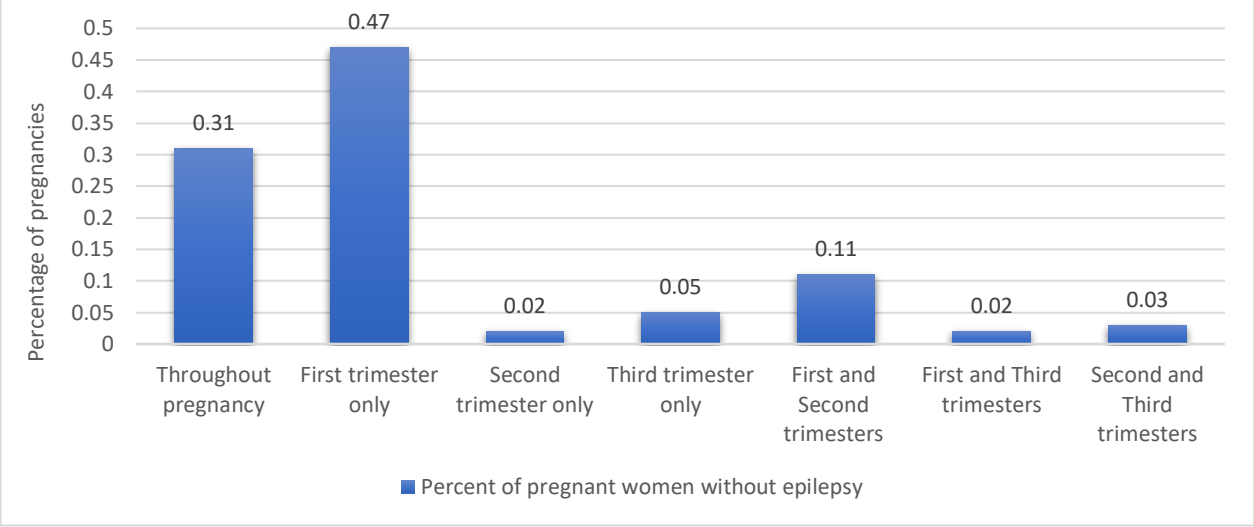
diagnosis for personality disorders using ICD-9-CM code 301 in the 1 year prior to conception. Schizophrenia was defined as any women with one or more hospitalization with a diagnosis for schizophrenia (ICD-9-CM code: 295 (schizophrenic disorders), or ICD-10-CA codes: F20 (schizophrenia), F21 (schizotypal disorder), F23.2 (acute schizophrenia-like psychotic disorder), F25 (schizoaffective disorders), or one or more physician visits with a diagnosis for schizophrenia using ICD-9-CM code 295 in the 1 year prior to conception.



Supplementary Figure 1 Percentage of women exposed to AEDs by trimester



Supplementary Figure 2 Percentage of exposed pregnant women with epilepsy by trimester



Supplementary Figure 3 Percentage of exposed pregnant women without epilepsy by trimester

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Additional Results

Most Commonly used AEDs

Among all pregnancies in the cohort

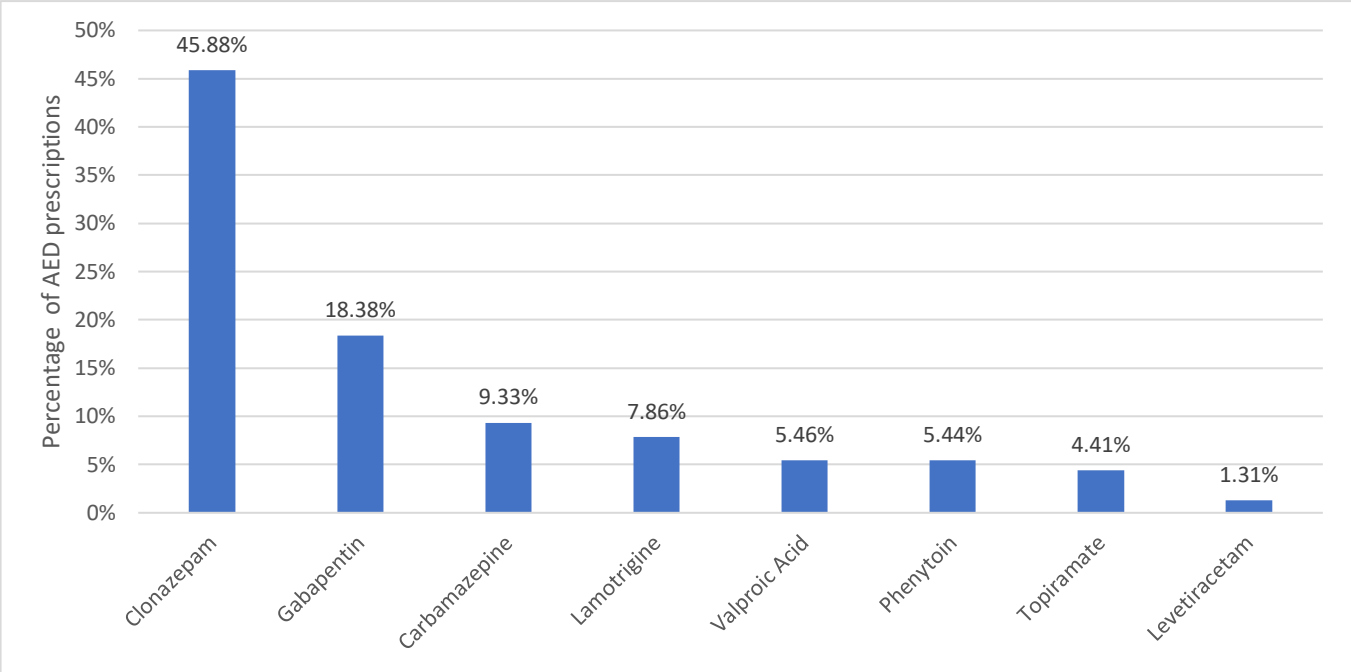

Figure 6 Most commonly used AEDs among all pregnant women in Manitoba 1997-2018

The most used AED among our cohort during the study period was clonazepam with 45.88% of users, followed by gabapentin (18.39%) and carbamazepine (9.33%).

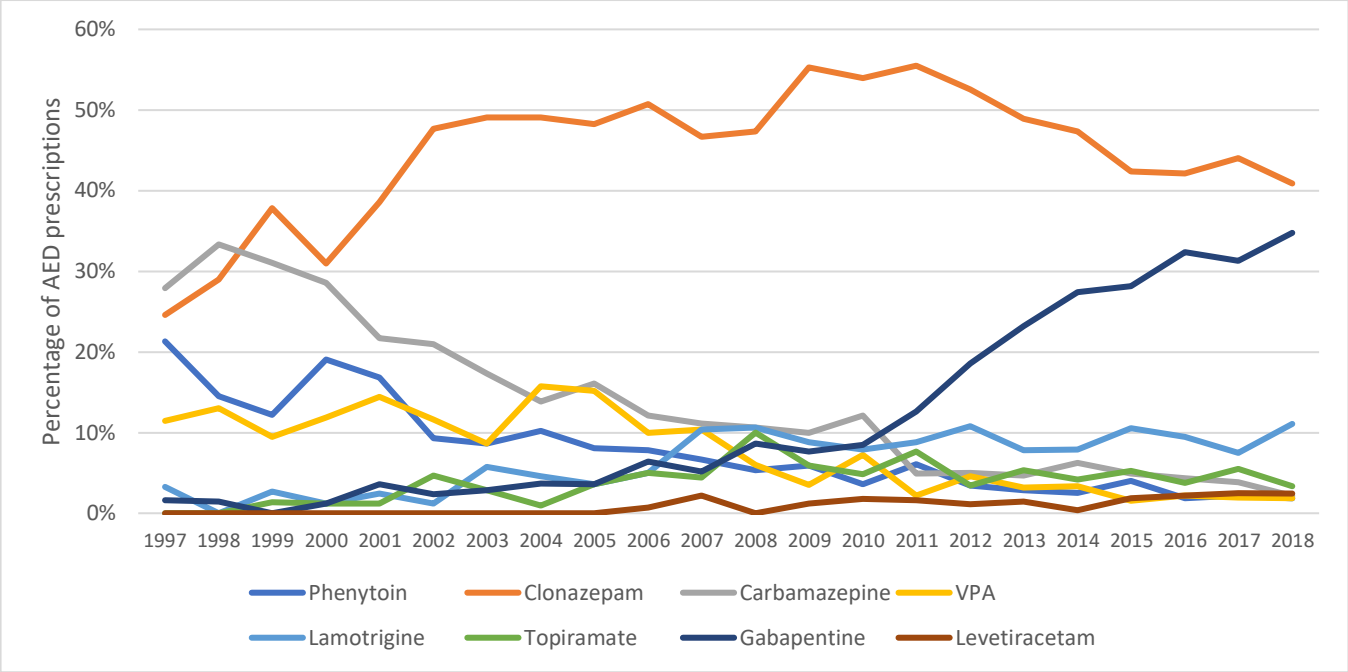

Figure 7 Trends of utilization of AEDs among all pregnancies

Among Women with Epilepsy

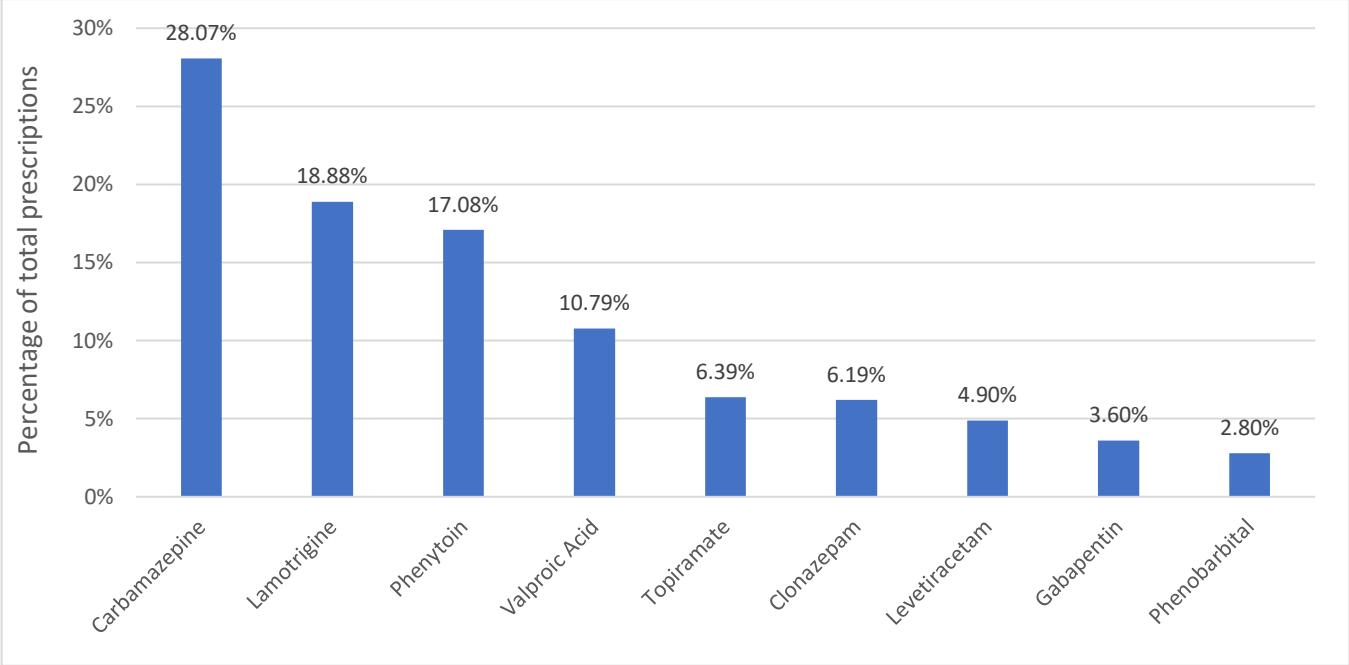

Figure 8 Most commonly used AEDs among pregnant women with epilepsy

The most used AED among pregnant women throughout the study period was clonazepam (44.44% of all exposed pregnancies) followed by gabapentin (17.85%) and carbamazepine (10.22%). Whereas among pregnant women with epilepsy, carbamazepine (33.86%), lamotrigine (22.77%), phenytoin (17.08%) and valproic acid (13%) were the most used.

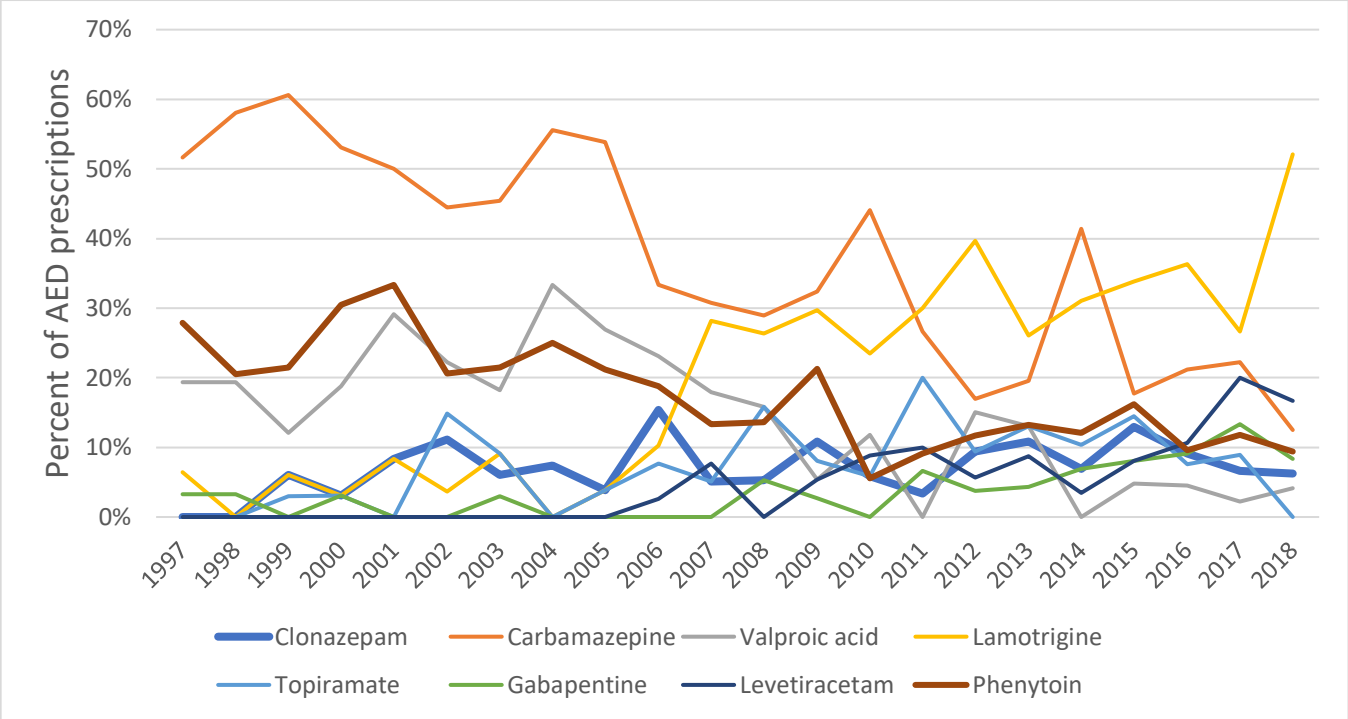

Figure 9 Trends of top AED prescriptions among pregnant women with epilepsy

Carbamazepine was the most commonly prescribed AED for pregnant women with epilepsy at the beginning of the study with 51% of prescriptions in 1997. The utilization of carbamazepine decreased among pregnant women with epilepsy throughout the study period to reach 12.5% of prescriptions in 2018. Whereas lamotrigine prescriptions constituted 6.45% of the prescriptions to pregnant women with epilepsy in 1997 and its utilization increased to become the most frequently used AED among pregnancies with epilepsy by 2018 with 52%. Levetiracetam first appeared in the cohort in 2016 and its use increased to become the second most used AED in 2018 with 15% of AED prescriptions to pregnant women with epilepsy.

Among Women Without Epilepsy

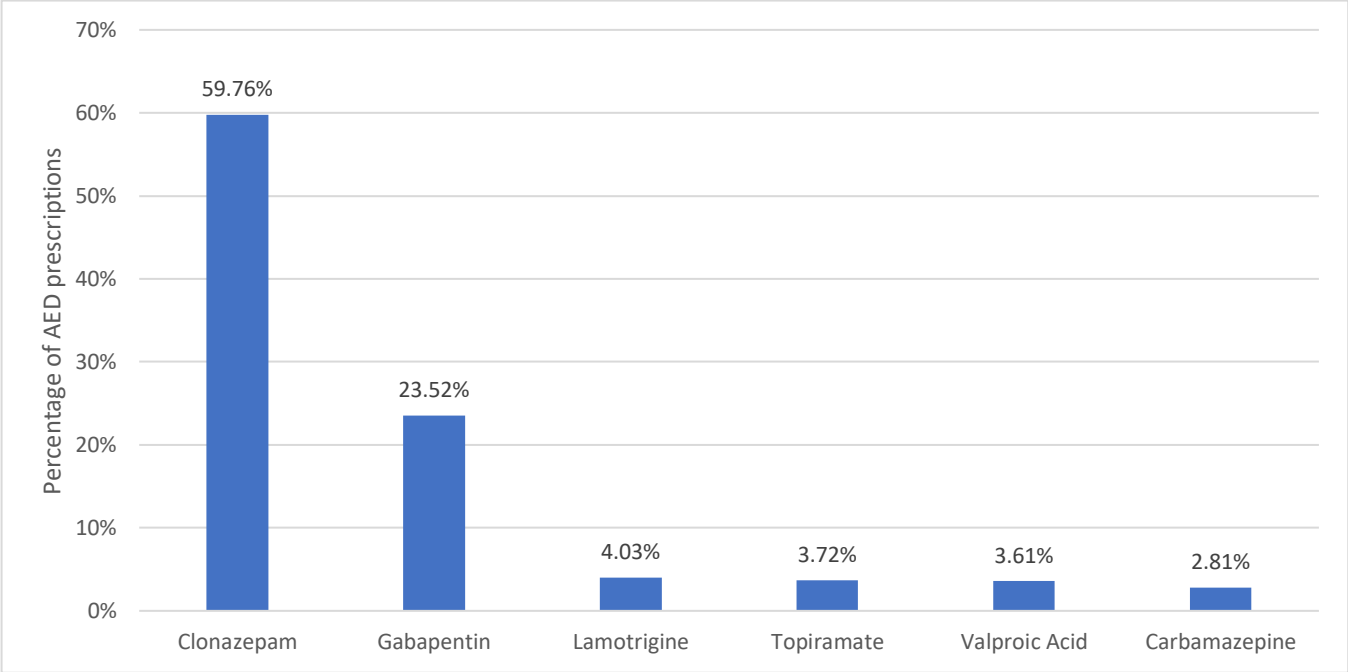

Figure 10 Most used AEDs among pregnant women without epilepsy throughout the study period

The most used AEDs among pregnant women without epilepsy were clonazepam with around 59.76% of prescriptions to pregnancies of women without epilepsy throughout the study period, followed by gabapentin with 23.53%.

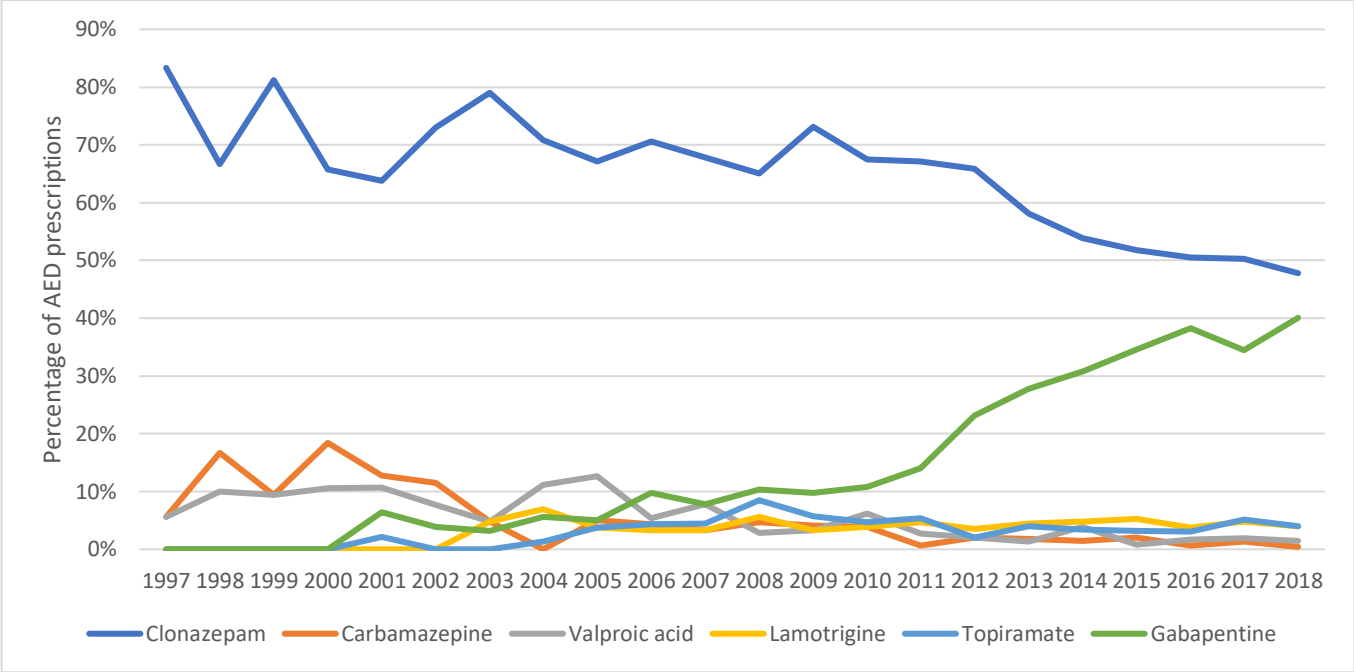

Figure 11 Trends of top AED prescriptions among pregnant women without epilepsy

TRENDS BY DRUG CLASS

First generation AEDs includes phenobarbital, primidone, phenytoin, ethosuximide, clonazepam, carbamazepine, and valproic acid. Second generation includes gabapentin, lamotrigine, topiramate, pregabalin, mesuximide, oxcarbazepine, vigabatrin, levetiracetam, and lacosamide.

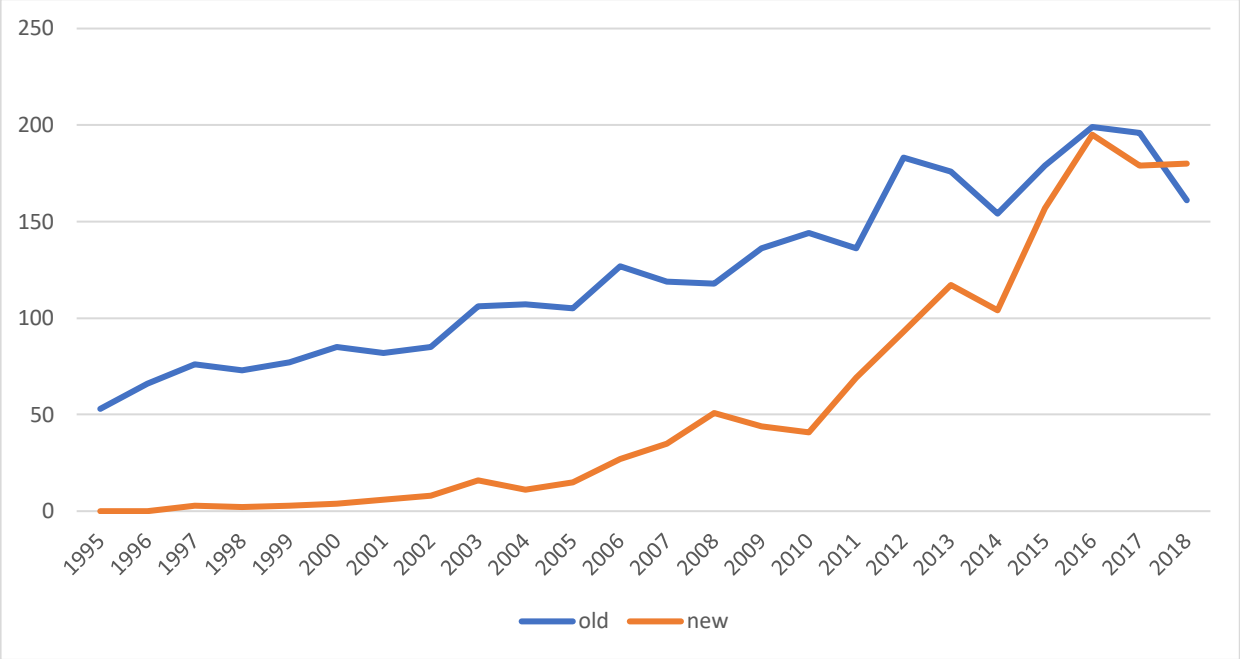

Figure 12 Trends of utilization of AEDs by drug class among the full cohort

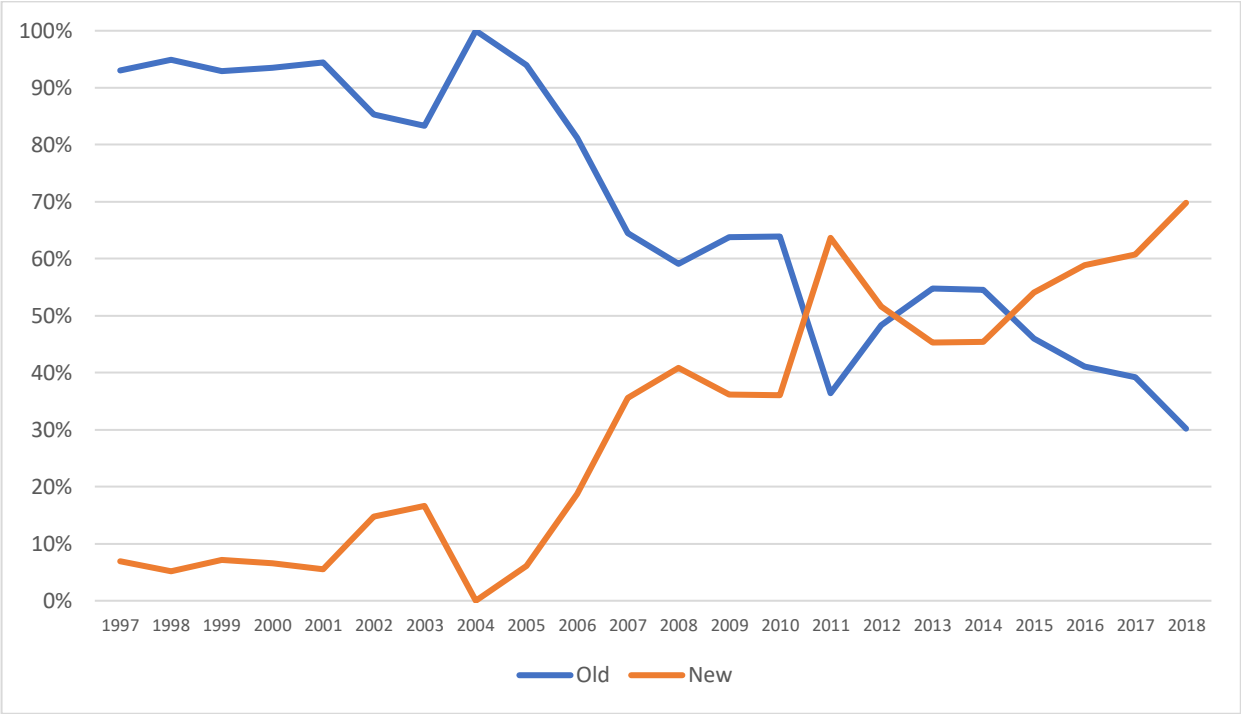

Figure 13 Trends of utilization of AED by class among women with epilepsy

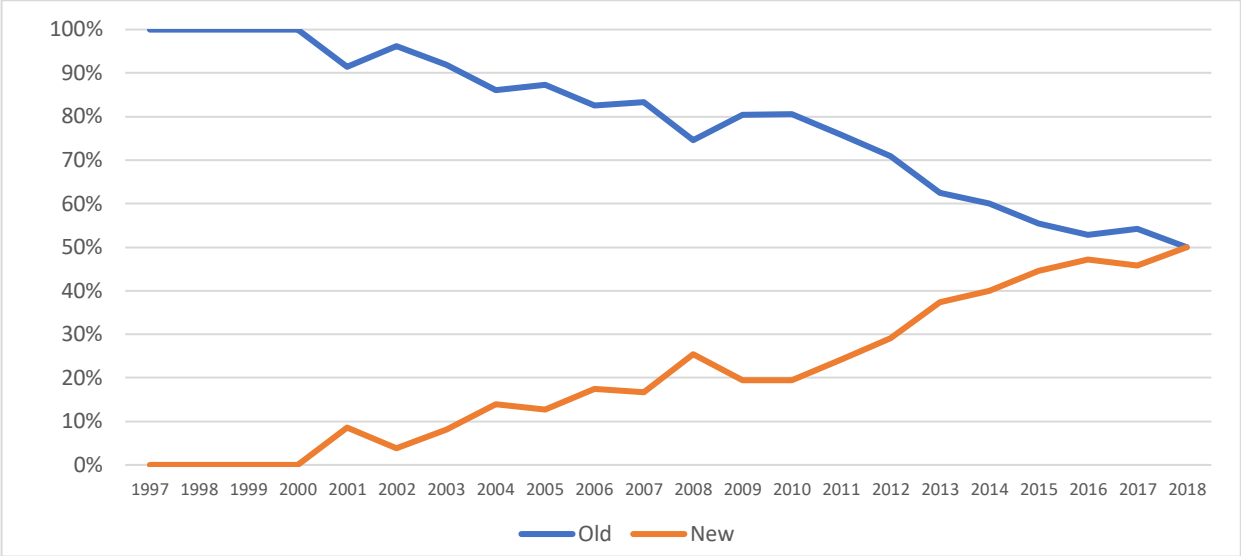

Figure 14 trends of utilization of AED by class among women without epilepsy

TRENDS OF INDICATIONS

The number of pregnancies exposed to AEDs with a diagnosis of anxiety increased 10 times from 17 pregnancies in 1997 to 171 pregnancies in 2018. This increase was significant ($p<0.0001$). Similarly, the number of pregnancies exposed to AEDs with a diagnosis of pain increase 8 times from 9 pregnancies in 1997 to 77 pregnancies in 2018 ($p<0.0001$).

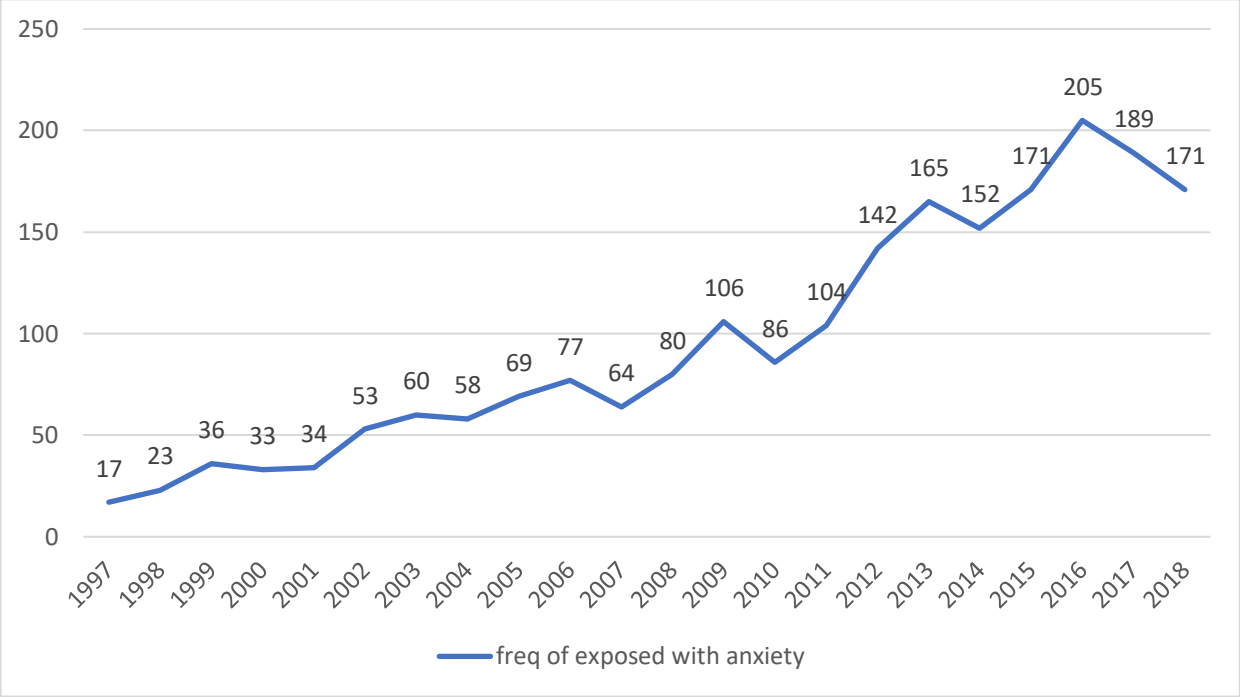

Figure 15 Frequency of exposed pregnant women with anxiety diagnosis by year

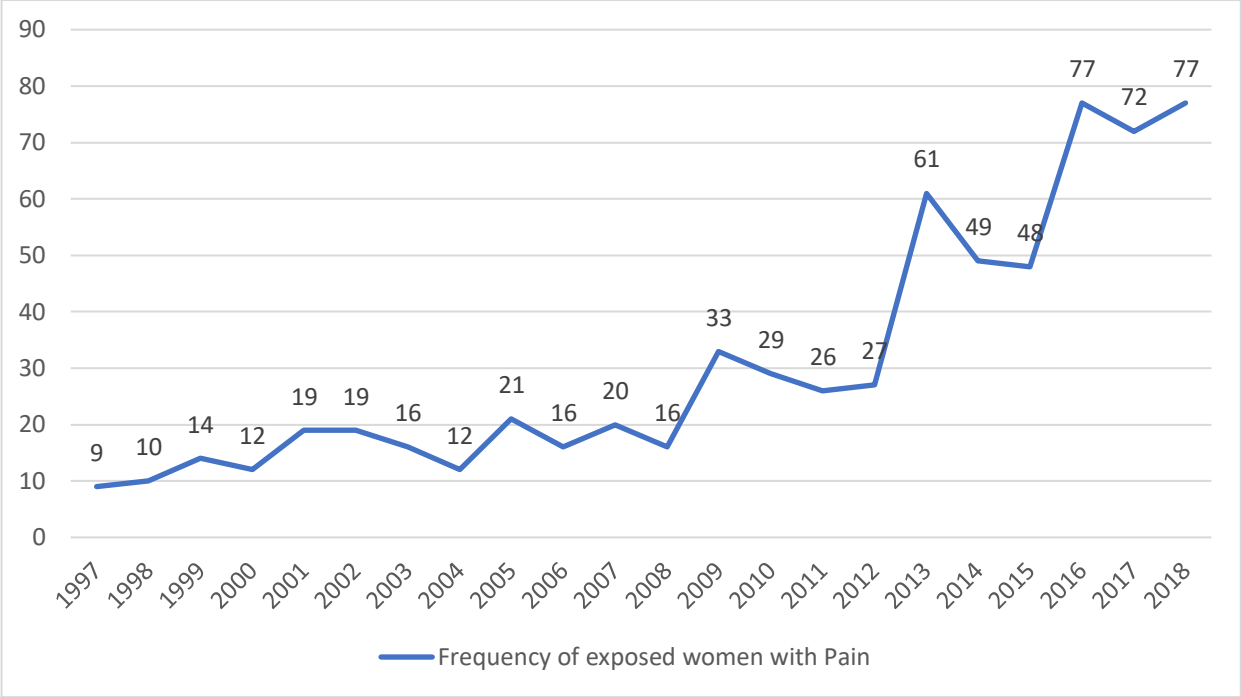

Figure 16 Frequency of exposed pregnant women with pain diagnosis by year

DISCUSSION

In this retrospective cohort study, 273,492 pregnancies were included. Out of these pregnancies, 0.3% (812) had an epilepsy diagnosis and were exposed to AED, whereas 0.35% (963) had an epilepsy diagnosis but were not exposed to AED. Among the pregnant women with epilepsy, more than 50% were unexposed to AEDs, this could be attributed to the presence of mild/controlled epilepsy, or the accuracy of the epilepsy definition used in the study. In our cohort of pregnancies, 1% (2742) were exposed to AED and did not have an epilepsy diagnosis. It is important to select the best reference group in later outcome studies. From this cohort, we can have multiple reference groups that will help answer many research questions.

Among pregnant women exposed to AEDs without epilepsy diagnosis, 45.5% were in the lowest socioeconomic status compared to 26.33% in the unexposed pregnant women without epilepsy. This might be due to the higher prevalence of many of the indications of AEDs among people of the lowest socioeconomic status. A study from Sweden by Mwinyi et. al. shows that women with anxiety had a significantly lower socioeconomic status than men, and that low socioeconomic status and negative impact of reduction of the income were significantly associated with anxiety in women more than men.[78] Other studies show that the prevalence and incidence of migraine are significantly higher among people in the lowest socioeconomic status.[79]

The percentage of women in the lowest socioeconomic status among exposed and unexposed women with epilepsy was similar (31.28% and 31.26% respectively). Many studies have shown a relationship between epilepsy and lower SES.[80] But lower socioeconomic status might be a risk factor for incidence of epilepsy in adults.[81]

Among pregnant women with no epilepsy exposed to AED, 62.1% were from the urban setting, which is higher than the percentage of urban pregnant women unexposed to AED and without epilepsy which was around 53%. This might indicate that the women in the urban areas are more prone to psychological disorders and other indications that can be treated off-label by AEDs. At the same time this might be due to reverse causality, where women who need treatment with AEDs move to the urban setting to be closer to specialized healthcare. On the other hand, pregnant women with epilepsy showed similar percentages for urban living (55.3% in the exposed group and 59.6% in the unexposed group).

Examining the comorbidities in the groups of women, 65.2% of the women exposed to AEDs without epilepsy were diagnosed with anxiety and 20.3% were diagnosed with pain. This can be mainly attributed to the increased practice of the use of AEDs off-label to treat anxiety and pain, especially Clonazepam and gabapentin. The prevalence of other comorbidities is higher among exposed pregnant women without epilepsy when compared with all other groups; 8.28% had hypertension, 7.73% had diabetes, 3.28% had schizophrenia, and 9.85% had personality disorders.

Among women with epilepsy, 33.58% were exposed throughout the pregnancy, demonstrating that most women with epilepsy require continuous treatment throughout their pregnancies to control their seizures. From women with epilepsy, only 5.46% were exposed during first trimester, which means that these women had controlled seizures and prescribers decided to stop their treatments upon conception. Only 0.11% were exposed during second trimester, and 2.08% were exposed during the third trimester, which shows that fewer women with epilepsy start using AEDs in later stages of their pregnancy.

However, among women without epilepsy, the highest percentage was for pregnancies exposed only during the first trimester, which is 0.47% of pregnant women without epilepsy. This indicates that physicians (or women) stop AED prescriptions when they know of the

conception, especially when these pregnancies are unplanned. A lower percentage, 0.31%, were exposed throughout pregnancy, which shows that these women still require continuous treatment with AEDs to control symptoms of diseases other than seizures. Moreover, 0.02% were exposed during second trimester and 0.05% were exposed during the third trimester.

We used linear regression models to study the annual trends of utilization of AEDs among pregnant women in Manitoba, and we observed a significant increase in the utilization of AEDs among pregnant women in Manitoba between 1997 and 2018, attributed mainly to the increased use of clonazepam and gabapentin. In general, there was no major shift in the utilization of AEDs among pregnant women with epilepsy, whereas a significant increase in the utilization of AEDs among women without epilepsy was observed.

In our study, clonazepam was the most used AED among pregnant women in Manitoba during the study period. This may be relayed to the fact that clonazepam is one of the drugs that are most used off-label for psychological indications.[41]

AED polypharmacy, including valproic acid, phenytoin, carbamazepine, phenobarbital, should be avoided while prescribing to pregnant women, when possible, due to their high risk of causing undesired pregnancy outcomes that include major congenital malformations, cleft palate, and cardiac malformations. Prescribers should also avoid valproic acid and phenytoin due to their poor cognitive outcomes.[63] Recently more guidelines are encouraging the use of many AEDs for indications other than seizure control. AEDs like valproic acid and gabapentin are being utilized for the treatment of migraine headaches, and anxiety. [1,20,23] Valproic acid is being used also for sleep related problems.[20,36,82] Gabapentin is used in a wide variety of off-label indications including the treatment of neuropathic pain, trigeminal neuralgia, HIV-associated neuralgia, diabetic neuropathy, neoplasia, and strokes, psychiatric disorders, most notably bipolar disorders,

movement disorders including restless leg syndrome. [1,49] Lamotrigine is indicated for extreme mood swings in bipolar disorder in adults.[1,23]

The trends in our study are comparable with the results reported by Cohen et.al in five Nordic countries, the USA, and Australia from 2006 to 2016.[66] The trend of use of AEDs in pregnancy showed an increase in all countries throughout the study period. In Australia there was a 22% increase, whereas in Sweden there was a 104% increase. Like our results clonazepam was the most commonly used AED in the United States, with a stable increasing trend. While the most commonly used AED was lamotrigine in the Nordic countries and valproate in Australia. The use of valproate among the pregnant women in Manitoba decreased through the study period. Similarly, the use of valproate was decreasing in the Nordic countries and the US.

In Europe, the exposure to AEDs was 3 per 1,000 in Romagna, Italy, 6.8 per 1,000 in France and 7.8 per 1,000 in UK which is less Manitoba where the prevalence was around 13 per 1,000.[72] The most used AED in the 3 European countries were lamotrigine, whereas, in Manitoba, clonazepam is the most used AED. The prevalence of exposure to valproic acid is 28.6% in the 3 European countries compared to in our study 5.78% in Manitoba.[72] Knowing that most guidelines advise strongly against the use of valproic acid during pregnancy, this might indicate that prescribers in Manitoba are better aware of the warnings against the use of valproic acid during pregnancy due to the risk of major congenital malformations.[23,83] Similar to the results in Manitoba, there was an increase in the utilization of AEDs among pregnant women attributed to the increase in the utilization of gabapentin in UK. Whereas a decrease in the utilization of AEDs was noticed in France, and no change was noticed in Italy.

Among women with epilepsy there was no significant increase in the utilization of AEDs. Unlike the full cohort, the most used AED was carbamazepine (28% of prescriptions to women with epilepsy) followed by lamotrigine (18.88%). The trend shows that the use of first-generation AED was decreasing throughout the study period including carbamazepine, phenytoin and valproic acid. On the other hand, second generation AEDs were increasing, lamotrigine became the most used AED among pregnant women with epilepsy in 2018, and levetiracetam became the second most used AED. This is mainly due to the guidelines that encourage the use of lamotrigine and levetiracetam due to their lower risk of causing major congenital malformations.

Similar results were obtained in the study looking at the prescriptions of AEDs among pregnant women with epilepsy in Australia by Vajda et. al.[84] Data from the Australian register of AED in pregnancy showed that lamotrigine and carbamazepine were the most used AEDs between 1999 and 2012.[84] The study also shows that the declining use of first-generation AEDs was compensated by the increasing prescriptions of second generation AEDs (including lamotrigine, topiramate, and levetiracetam).[84]

Studies about the use of AED among women of childbearing age with epilepsy show similar results. The study by Kim et. al. looked at the use of AEDs among women of childbearing age using nationwide commercial databases across the United States. The results showed that the most prescribed AED for incident epilepsy cases between 2009 and 2013 were levetiracetam, lamotrigine, and topiramate which are second generation AEDs. [85]

On the other hand, prescriptions to women without epilepsy were mainly clonazepam and gabapentin. The use of clonazepam was decreasing throughout the study period, paralleled by an increase in gabapentin prescriptions to become almost equal in 2018.

Other studies have shown the increased use of clonazepam in some psychiatric indications such as bipolar disorders, mania, depression, sleep-related disorders, pain management, and other benzodiazepine withdrawal.[36,37,38,39] Clonazepam might be also abused for recreational non-medical purposes due to the euphoric state it causes.[36] In fact, the

proportion of illegal acquisition was higher with clonazepam when compared with other benzodiazepines in the French Centres for Evaluation and Information on Pharmaco-dependence.[36,37]

In Quebec, clonazepam is among the drugs most probably to be used for off-label indications with 96% of prescriptions being for off-label cause.[40] A study about off-label drug use of psychiatry outpatient department in Ahmedabad, India, by Rana et al. shows that clonazepam was used off-label for psychiatric disorders significantly higher than any other off-label drug, and it was mostly used for depression[41]

Gabapentin was found to be one of the most commonly used drugs for off-label indications in a Quebec study by Eguale et. al, where gabapentin was used almost exclusively for off-label indications (99.2%).[40]

STRENGTH AND LIMITATIONS

The MCHP repository includes objectively measured medical records for all Manitoba residents. Our study captured the prescription practices of prescribers in Manitoba during the past 20 years. The data was linked across multiple datasets by using personal health identification numbers (PHIN), for mothers and newborns. This helped us link dispensation records to socioeconomic status and other variables.

This study is the first in a larger project looking at the outcomes of epilepsy and AED treatment regimens in pregnancy in Canada. From the results of this study, we can have multiple reference groups that will help answer many research questions. Using the group of unexposed women will show us the safety of the drug versus no pharmacological treatment and no underlying indication. Using the group of unexposed women with epilepsy will help us know the safety of the AEDs versus no pharmaceutical treatment for epilepsy.[86] The aim is to reach drug and disease separation from which we can identify the safest AED with the best seizure control and the least undesired pregnancy outcomes. Moreover, assessing the exposure during different exposure windows is extremely important in future outcome studies to avoid exposure misclassifications.

Limitations

First, exposure was derived from dispensing records and not actual intake, therefore, the adherence of the patients is assumed. However, women with epilepsy generally tend to adhere to their treatments to avoid seizures.[86] Second, we did not have data on the severity of epilepsy cases. Third, we did not describe other indications directly linked to each AED (for example if gabapentin was prescribed for neuropathic pain or another disorder) as this was out of the scope of the current study. Additional studies examining AEDs indications are warranted. Only medications classified as antiepileptic (ATC code starting with N03) were included in this study. We conducted a sensitivity analysis of using 2,5 and 10 years for the baseline data for epilepsy definition. We used 5 years for the current study to minimize false negative cases. We did not have a gold standard and more studies are needed to validate this definition. In the current study, we did not describe or compare monotherapy versus polytherapy, which was out of the scope of this project. We were not able to identify the specialty of prescribers in this study. We understand that the modern term for "antiepileptic drug" (AED) is "antiseizure medication" (ASM) because these drugs do not affect epileptogenesis but rather, they simply prevent expression of symptoms (seizures). However, for the sake of concordance with the most recent literature we used the term AEDs.

CONCLUSIONS AND FUTURE RESEARCH RECOMMENDATIONS

This population-based study showed an increase in the utilization of AEDs among pregnant women driven by the increase in their utilization among pregnant women without epilepsy. However, the use of AEDs among pregnant women with epilepsy did not change significantly. The prescriptions trend among women with epilepsy showed a decrease in first generation AEDs, including carbamazepine, phenytoin, and valproic acid. This decrease was accompanied by an increase in the prescriptions of second-generation AEDs. By 2018, lamotrigine and levetiracetam were the two most prescribed AEDs among pregnant women with epilepsy. This indicates strong compliance of prescribers to the most recent guidelines for the treatment of epilepsy during pregnancy.

On the other hand, the utilization of AEDs among pregnant women without epilepsy increased more than 10 times. Although clonazepam prescriptions were decreasing throughout the study period, there was an increase in gabapentin prescriptions. This is consistent with previous reports among the general population of Manitoba. Gabapentin is being used mostly for indications other than epilepsy, including pain and anxiety. These results increase the concerns about the safety and efficacy of these agents for off-label indications especially during pregnancy.

<u>RELEVANCE AND SIGNIFICANCE:</u>

This project is part of The Canadian Epilepsy and Mother-Infant health Group *(CAN-EMIG)* project, a novel pan-Canadian initiative. No study has yet provided a detailed investigation of the time-trends and prescribing patterns of AEDs in pregnant women with epilepsy in Canada, especially new-generation AEDs. This study will detail the prescribing patterns in four large Canadian provinces covering a period of 20 years, offering unprecedented data that support policymakers and enable valuable interprovincial comparisons. The study will also identify subgroups of women who are at risk of receiving non-optimal treatments (over or undertreatment).

This study is a part of a bigger project investigating the outcomes of pregnancies of women with epilepsy. Knowing the patterns and trends of epilepsy diagnosis and AED utilization will help in the analysis and interpretation of the outcomes results of the outcomes studies. This study will also help in the evaluation of the quality of the current policies and guidelines. Our study will help in improving the health of the Canadian population by looking at a very critical and understudied disease that can have negative impact on the physical and mental health of many women and children in Canada.

FUTURE DIRECTIONS

We were able to create four groups of pregnant women within this cohort based on AED utilization and epilepsy diagnosis. These groups will help the identification of pregnancy outcomes among users for epilepsy indication and non-epilepsy indications. Ultimately reaching drug-disease separation where we will be able to find the AED with least undesired pregnancy outcomes and most seizure control. This will not only help prescribers in choosing the drugs, but also will assure patients that they are receiving the optimal treatment.

More evidence is needed to assess the utilization of AEDs for off-label indications among pregnant women. There is a need for more research to specify the major indications driving the increase of the off-label use of AEDs especially gabapentin.

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