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Preventing Fetal Valproate Syndrome: Does Practice Reflect FDA Advisement for the Use of Valproate in Women of Childbearing Age?

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PREVENTING FETAL VALPROATE SYNDROME: DOES PRACTICE REFLECT FDA ADVISEMENT FOR THE USE OF VALPROATE IN WOMEN OF CHILDBEARING AGE?

BY

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Until recently, there were very little data on the effects of antiepileptic drug (AED) exposure *in utero*. However, in the past two decades, data from several prospective pregnancy registries have significantly increased the understanding of the critical risks for major congenital malformations associated with several AEDs (Gerard & Meador, 2015). This research examined the risks associated with valproate among women of childbearing age (18-44 years of age) and the risks valproate poses for a child through maternal exposure. The study population came from the 2016-2018 MarketScan® Commercial dataset obtained by the Medical University of South Carolina. In total, there were n=877 women aged 18-44 years of age. There were n=318 women with greater than 3 months prescribed valproate, and there were n=149 women based on 6 month pre-index insurance and 12 months post-index insurance where the data index was the date from which the first valproate prescription was filled. This led to a final cohort size of 149 women. The data was analyzed using measures of central tendency. Tests for differences between those on birth control and those not on birth control were made using Student's t-test for normally distributed data, Wilcoxon-Mann-Whitney for non-normally distributed data, and chi-squared tests for categorical data. Results include 14.5% of the original population being prescribed valproate for 3 or more months, 33.6% being for migraines, followed by 31.5% for bipolar disorder despite research being conducted primarily for those with epilepsy.

In conclusion, the research shows the need for further education on the risks of valproate and women of childbearing age. This is based on the lack of studies focusing on the risks and prescribing patterns outside of the epilepsy community. The research limitations included the length and type of contraceptive use, which the study could not account for as only measurable pregnancy prevention methods were studied. Future research could explore different funding streams as our research focused on commercial payor billing data, which garnered a small sample size.

Table of Contents

List of Figures

List of Tables

CHAPTER 1
INTRODUCTION

Background

Valproate, classified as an anticonvulsant or antiepileptic drug (AED), has several modalities. The pharmaceutical is available as an extended-release formulation in capsule form, as a delayed-release formulation in tablet form, a sprinkle capsule, or syrup (AHFS, 2020). Valproate was first introduced for human use in 1967 in Europe, and its use was licensed in the United Kingdom in 1975. It was not until 1978 that it became clinically available in the United States as an immediate-release formulation and then again in 1983 as alternative formulations (Adab et al., 2004).

The U.S. Food and Drug Administration (FDA) initially approved valproate to treat seizures, but some valproate products are also approved to treat other ailments. Valproate is widely popular for its broad range of anticonvulsant effects and that it also has limited sedative and behavioral outcomes compared to other AEDs (Alsdorf & Wyszynski, 2005). Additionally, it is recognized as one of the most critical AEDs for its wide spectrum effectiveness and is most notable in the acute treatment of bipolar disorder (Alsdorf & Wyszynski, 2005). Valproate products include valproate sodium, divalproex sodium, valproic acid, and other generics (FDA, 2015). As a result, the term *valproate* was be used to encompass the numerous varieties of the drug.

Valproate entered the market as a therapeutic intervention for absence seizures. Since then, its use has expanded to include the treatment of complex and partial seizures, as well as a preventative for migraines in some countries, a treatment for acute mania, and as a mood stabilizer for bipolar disorder (Macfarlane & Greenhalgh, 2018; Wyszynski et al., 2005). Similarly, in 2012, about 1.5 million individuals received valproate on an outpatient basis, to

include 67% for psychiatric and mood disorders, 9% for migraines, and 9% for epilepsy in the United States (Angus-Leppan & Liu, 2018).

Furthermore, valproate is said to cross the placenta and present a higher concentration in the child than in the mother (Alsdorf & Wyszynski, 2005). Additionally, valproate is known to induce apoptosis, a programmed cell death typically occurring in early development to eliminate unwanted cells (NIH, n.d.; Velez-Ruiz & Meador, 2015). Furthermore, valproate is associated with a significant risk increase for teratogenesis, production of malformations in a child, compared to the baseline population rates and other ordinary AEDs for over 30 years of clinical studies (Gerard & Meador, 2015; Jentink et al., 2010).

In a 1983 *Morbidity and Mortality Weekly Report* from the CDC, valproate was stated to be a new cause of congenital malformations (CDC, 1983). The report found a significant association between valproate exposure during the first trimester of pregnancy and spina bifida and concluded that valproate should be considered a human teratogen (CDC, 1983). Since then, many factors are said to contribute to the teratogenic properties. Some of these factors include drug dosage, gestational age of the child at the time of the exposure, and differences in metabolism between the mother and child (Alsdorf & Wyszynski, 2005).

Valproate's teratogenic properties have since been evidenced by clinical studies such as those done by Weston et al. (2016), Christensen et al. (2013), and Eriksson et al. (2005). In addition, national and international pregnancy registries have increasingly identified AEDs' teratogenic properties (Alsdorf & Wyszynski, 2005; Tomson et al., 2011). Furthermore, across several of these human studies, valproate has been the most highly associated with cognitive and behavioral teratogenesis of all AEDs (Gerard & Meador, 2015). In the end, clinical research has identified many risks associated with the drug that include those congenital malformations,

developmental delays, reduced cognitive function, and, most recently, autism (Roullet et al., 2013).

Notably, animal studies have shown that the timing of exposure affects the type of identified malformations. For example, valproate exposure during the first trimester of gestation results in malformations of major organs. By contrast, exposure later in pregnancy results in an increased risk of neurodevelopmental defects when brain cells proliferate and migrate (Alsdorf & Wyszynski, 2005). Animal studies examining valproate have recently shown autistic-like outcomes, including social behavior deficits, increased repetitive behaviors, and communication deficits (Roullet et al., 2013).

Today, an increasing number of pregnant women continue to be exposed to valproate, despite its use during the first trimester being associated with an increased risk of spina bifida (Jentink et al., 2010; Koren, 2006). Adab et al. (2001) say that roughly one-third of all people receiving AEDs were women of childbearing age in 2001. In addition, 1 in 250 pregnancies was exposed to AEDs whereby over one million women with epilepsy in the United States were of childbearing age, and three to five births per 1,000 were to those women in 2015 (Adab et al., 2001). Additionally, it was estimated that 1.5 million individuals were prescribed valproate, in 2012 and roughly 22% of those were women of childbearing age (Angus-Leppan. & Liu, 2018). The total number of children exposed to AEDs, including valproate, however, is likely to be more noteworthy due to their use as treatments for other conditions (Velez-Ruiz & Meador, 2015).

Not long after valproate was introduced for clinical use in epilepsy, emerging cases suggested those increased risk of neural tube defects, including spina bifida (Koren et al., 2006; Jentink et al., 2010). Today, although risk estimations associated with valproate vary, there may

be as much as a two- to three-fold risk increase in congenital malformations among babies born to women with epilepsy on valproate compared to the general population (Adab et al., 2001).

Jentink et al. (2010) found in their review of published cohort studies that there were 14 significant malformations more commonly associated with valproate through various antiepileptic databases. There was a major congenital malformation observed in 118 of 1,565 pregnancies. For these malformations, the risk appeared to be significantly higher with the association of exposure to valproate during the first trimester of pregnancy compared to those with no exposure to antiepileptic drugs during the first trimester (Jentink et al., 2010).

The researchers found significant associations between exposure to valproate monotherapy in the first trimester in six conditions: spina bifida, cleft palate, atrial septal defect, hypospadias, polydactyly, and craniosynostosis. In addition, the researchers found that the risks for five of the conditions were two to seven times higher for exposed children. Specifically, the risk for spina bifida was as much as 16 times higher for exposed children depending on the control group used. Researchers also found an association between limb defects and exposure to valproate compared to other drugs used as an antiepileptic (Jentink et al., 2010).

In 1984, Fetal Valproate Syndrome first started being used to describe the prominent malformations observed in children exposed to valproate *in utero.* This term refers to a collection of minor and major malformations occurring in exposed children, often consisting of facial malformations, including a flat nasal bridge, small upturned nose, and thin upper lip, as well as multiple major malformations and central nervous system dysfunctions (Wyszynski et al., 2005).

Additionally, valproate also causes severe malformations that primarily affect the brain and spinal cord, causing lower intelligence and other cognitive malformations. The low

intellectual ability is seen in 30% to 40% of children born to mothers who took valproate (AHFS, 2020; Sawhney et al., 2019). This exposure to valproate affects a child's development during pregnancy with a significant IQ reduction compared to children exposed to other AEDs. The IQ reductions (8-11 points lower) are considered substantial enough to affect their education and affect them later in life when entering the workforce (Tomson et al., 2015). Children exposed to valproate *in utero* have a delay in achieving developmental milestones, particularly verbal skills. This delay includes communication problems, including talking, poor language skills. Additionally, valproate also can cause coordination problems, including walking and learning problems affecting memory, emotions, and behavior (AHFS, 2020; Gerard & Meador, 2015; Sawhney et al., 2019).

Recently it has been found that children exposed to valproate are more likely to demonstrate poor adaptive skills and a heightened risk for neurodevelopmental disorders, including attention deficit hyperactivity disorder and autism (Gerard & Meador, 2015). Evidence supports this link between cognitive function and the increased risk of autism with valproate exposure (Roullet et al., 2013).

Of all the AEDs available, the use of valproate during childbearing years and pregnancy has raised the most notable concerns (Roullet et al., 2013). FDA warnings related to valproate during pregnancy have emphasized the need for reassessment in its use clinically during these years (Roullet et al., 2013). Hence, despite its known risks, valproate continues to be used in women of childbearing age as several pregnancy registries have established the commonality of valproate to be prescribed (Roullet et al., 2013). Subsequently, valproate has clinical guidelines for practitioners that suggest that it should be avoided during pregnancy. These guidelines

indicate that valproate should be avoided in pregnancy if possible due to the increased risks of congenital malformations (Werler et al., 2011).

This project intends to inform professional practice regarding the number of prescriptions for valproate prescribed to women of childbearing age. Additionally, it looks at how many of those women of childbearing are on pregnancy preventive programs or have a pregnancy given the fetal risks associated with valproate. This research is valuable as a consulting report to physician specialties such as psychiatry, neurology, and obstetrics.

Aim

To examine the number of women of childbearing age (18-44) who are prescribed valproate, some of their outcomes, and rates of pregnancy prevention to avoid risks as a result of prenatal valproate exposure.

Under this aim, this project intends to answer the following research questions:

- Question 1: At what rate is valproate being prescribed to women of childbearing age?
- Question 2: What are the most common diagnoses (e.g., bipolar, epilepsy, migraines).
- Question 3: For what age group of women is valproate most commonly prescribed?
- Question 4: How many of those women prescribed valproate were part of a pregnancy prevention program?
- Question 5: Of those women taking valproate, how many later experienced a pregnancy?

Study Importance

As the risks to children of mothers exposed to AEDs have been increasingly understood, the warnings against such medications have been strengthened. Specifically, there has been an increase in healthcare professionals and available patient resources regarding the acceptable use

of valproate (Sawhney et al., 2019). Worldwide there is an agreement that valproate is a serious teratogen. However, there is still no agreement on proper guidelines for women who may become pregnant (Angus-Leppan, & Liu, 2018).

CHAPTER II

LITERATURE REVIEW

Introduction

Until recently, there were very little data on the effects of antiepileptic drug (AED) exposure *in utero*. However, in the past two decades, data from several prospective pregnancy registries have significantly increased the understanding of the critical risks for major congenital malformations associated with several AEDs (Gerard & Meador, 2015). This chapter examines the risks associated with valproate among women of childbearing age and the risks valproate poses for a child through maternal exposure. The chapter primarily looks at valproate in the context of its therapeutic use for epilepsy, as research into its teratogenic properties is limited outside of this field.

Valproate as a Therapeutic

Valproate, classified as an anticonvulsant or AED, has several modalities. The pharmaceutical is available as an extended-release formulation in capsule form, as a delayed-release formulation in tablet form, a sprinkle capsule, or syrup (AHFS, 2020). Valproate was first introduced for human use in 1967 in Europe, and its use was licensed in the United Kingdom in 1975. It was not until 1978 that it became clinically available in the United States as an immediate-release formulation and then again in 1983 as alternative formulations (Adab et al., 2004).

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it is recognized as one of the most critical AEDs for its wide spectrum effectiveness and is most notable in the acute treatment of bipolar disorder (Alsdorf & Wyszynski, 2005). Valproate products include valproate sodium, divalproex sodium, valproic acid, and other generics (FDA, 2015). As a result, the term *valproate* was used to encompass the numerous varieties of the drug.

Valproate is a y-aminobutyric acid (GABA) agonist (Angus-Leppan & Liu, 2018; Wyszynski et al., 2005). Studies show enhanced GABA inhibition and the blockade of NMDA receptors impairs neurogenesis and cell migration, which in turn can lead to cortical dysplasia and reduced brain volume (Velez-Ruiz & Meador, 2015). Furthermore, valproate targets neurotransmitters, ion channels, and second messenger systems in the brain. This neurotransmitter medium in a developing brain plays a significant role in regulating neuronal differentiation and migration (Velez-Ruiz & Meador, 2015).

Drug Uses

Valproate entered the market as a therapeutic intervention for absence seizures. Since then, its use has expanded to include the treatment of complex and partial seizures, as well as a preventative for migraines in some countries, a treatment for acute mania, and as a mood stabilizer for bipolar disorder (Macfarlane & Greenhalgh, 2018; Wyszynski et al., 2005). Similarly, in 2012, about 1.5 million individuals received valproate on an outpatient basis, to include 67% for psychiatric and mood disorders, 9% for migraines, and 9% for epilepsy in the United States (Angus-Leppan & Liu, 2018).

According to Macfarlane and Greenhalgh (2018), the drug's use for epilepsy continues to decline in the United Kingdom as the number of third-generation anticonvulsants increase; its use for bipolar disorder has been growing. Furthermore, this happens mostly among many childbearing age women, which already make up a significant portion of recipients. These data

were like those also seen in Ireland. More alarming, 20% of pregnant women with epilepsy were treated with valproate between 1999 to 2004. Subsequently, a more recent U.K. study revealed that valproate constituted 25% of all AED prescriptions in pregnancy (Macfarlane & Greenhalgh, 2018).

Valproate Transmission

Valproate is said to cross the placenta and present a higher concentration in the child than in the mother (Alsdorf & Wyszynski, 2005). Consequently, valproate is known to induce apoptosis, a programmed cell death typically occurring in early development to eliminate unwanted cells (NIH, n.d.; Velez-Ruiz & Meador, 2015).

Teratogenic Properties

Valproate is associated with a significant risk increase for teratogenesis, production of malformations in a child, compared to the baseline population rates and other ordinary AEDs for over 30 years of clinical studies (Gerard & Meador, 2015; Jentink et al., 2010). In a 1983 *Morbidity and Mortality Weekly Report* from the CDC, valproate was stated to be a new cause of congenital malformations (CDC, 1983). The report found a significant association between valproate exposure during the first trimester of pregnancy and spina bifida and concluded that valproate should be considered a human teratogen (CDC, 1983). Since then, many factors are said to contribute to the teratogenic properties. Some of these factors include drug dosage, gestational age of the child at the time of the exposure, and differences in metabolism between the mother and child (Alsdorf & Wyszynski, 2005).

Valproate's teratogenic properties have since been evidenced by clinical studies such as those done by Weston et al. (2016), Christensen et al. (2013), and Eriksson et al. (2005). In addition, national and international pregnancy registries have increasingly identified AEDs'

teratogenic properties (Alsdorf & Wyszynski, 2005; Tomson et al., 2011). Furthermore, across several of these human studies, valproate has been the most highly associated with cognitive and behavioral teratogenesis of all AEDs (Gerard & Meador, 2015). In the end, clinical research has identified many risks associated with the drug that include those congenital malformations, developmental delays, reduced cognitive function, and, most recently, autism (Roullet et al., 2013).

Dose-Dependent Risks

Although it can be considered generally unsafe for mothers and their developing fetuses, valproate has dose-dependent teratogenic risks (Virta et al., 2018). Although risks are still prevalent, most studies suggest that the chances for major congenital malformations begin to increase significantly at doses of 600 mg a day and become more prominent at doses above 1,000 mg per day (Koren et al., 2006). Many researchers agree that valproate use creates an increased risk for those significant congenital malformations, especially in doses over 1,000 mg per day (Alsdorf & Wyszynski, 2005). Furthermore, apoptosis inducement, as previously discussed, begins to occur at levels below the therapeutic range (Velez-Ruiz & Meador, 2015). The standard therapeutic valproate doses range from 200 mg to 3,600 mg per day (Roullet et al., 2013).

Additionally, a study by Tomson et al. (2011) examined significant congenital malformations of children up to 1 year in age. These data came from the EURAP pregnancy registry and focused on children exposed to four of the most common AEDs, one of which was valproate. The authors aimed to establish the risks of major congenital malformations after monotherapy exposure. This study showed that dose contributed to the risk of congenital disabilities. Analysis showed that an increased dose of valproate was associated with an

increased incidence of congenital malformations. The researchers assessed the pregnancy outcomes according to the dose taken at the time of conception, despite any subsequent dose changes (Tomson et al., 2011).

Subsequently, Mawhinney et al. (2012) used the U.K. Epilepsy and Pregnancy Register to extract data for those pregnancies that were exposed to valproate. They calculated malformation rates and relative risks as a function of the valproate exposure focusing on all pregnancies exposed solely to valproate during the first trimester (Mawhinney et al., 2012). They found a significant dose-response with an almost doubling of the risk for those exposed to more than 1000 mg a day compared to those on less than 1000 mg a day (Mawhinney et al., 2012).

Moreover, a retrospective study of children born to mothers with epilepsy found that doses above 800 mg were associated with 8-15-point lower verbal IQ Valproate exposure was associated with additional education needs (AEN), as 19.7% of the sample had received speech therapy at some point (Adab et al., 2004). Further, Gedzelman & Meador (2012) found that valproate exposure also appears to have a dose-dependent IQ impact, with the effects being more significant on verbal than non-verbal IQ abilities (Gedzelman & Meador, 2012).

Polytherapy Versus Monotherapy

In addition to dose, valproate is also used as either a form of monotherapy or polytherapy, meaning two or more treatments. Research shows that children with prenatal polytherapy exposure have worse cognitive and behavioral outcomes versus those children exposed to monotherapy or unexposed to valproate, whereby there is an increased risk of defects of neurodevelopment when used as a form of polytherapy (Roullet et al., 2013; Velez-Ruiz & Meador, 2015).

In a preliminary retrospective study by Adab et al. (2001), a comparison was drawn between the proportion of school-age children exposed to different drug regimens and those who had AENs with or without physical disability born to mothers with epilepsy. They found that exposure to polytherapy, including valproate, was highly associated with AENs compared to both those who were unexposed and those who were exposed to polytherapy excluding valproate (Adab et al., 2001).

Adab et al. (2001) found that one of the most common monotherapy exposures (37.3%) for school-age children was valproate *in utero*. The polytherapy regimens often vary, but valproate combined with another AED is one of the most common polytherapy forms. Of the women taking AEDs at the time of pregnancy, over two-thirds were on monotherapy, and most of those were on valproate (Adab et al., 2001). Additionally, data for specific drug regimens showed that much of the risks for AENs among those exposed to monotherapy or polytherapy might be accounted for by valproate exposure. Thirty percent of those exposed to valproate monotherapy *in utero* had AENs, compared to 3.2% and 6.5% of those exposed to other AEDs studied (Adab et al., 2001).

Rodent Studies

Behavioral studies of mice and rat offspring are the most used model in human disease research to provide insight into the mechanisms underlying many diseases. They are used to explore the efficacy of drugs and predict patient responses (Justice, 2016). There are reports of valproate teratogenicity in animals since the 1970s and in humans since the 1980s, whereby mouse and rat animal studies have examined anatomical, behavioral, molecular, and physiological outcomes of *in utero* exposure to valproate (Angus-Leppan & Liu, 2018; Roullet et al., 2013).

Notably, these animal studies have shown that the timing of exposure affects the type of identified malformations. For example, valproate exposure during the first trimester of gestation results in malformations of major organs. By contrast, exposure later in pregnancy results in an increased risk of neurodevelopmental defects when brain cells proliferate and migrate (Alsdorf & Wyszynski, 2005). Additionally, animal studies examining valproate have recently shown autistic-like outcomes, including social behavior deficits, increased repetitive behaviors, and communication deficits (Roullet et al., 2013).

Furthermore, animal studies have suggested that AED-induced apoptosis alters the neurotransmitter environment while impairing synaptogenesis, or the formation of synapses in the nervous system. Moreover, impaired synaptogenesis is one of the mechanisms responsible for cognitive and behavioral teratogenesis (Velez-Ruiz & Meador, 2015).

Valproate and Pregnancy

Today, an increasing number of pregnant women continue to be exposed to valproate, despite its use during the first trimester being associated with an increased risk of spina bifida (Jentink et al., 2010; Koren, 2006). Adab et al. (2001) say that roughly one-third of all people receiving AEDs were women of childbearing age in 2001. In addition, 1 in 250 pregnancies was exposed to AEDs whereby over one million women with epilepsy in the United States were of childbearing age, and three to five births per 1,000 were to those women in 2015 (Adab et al., 2001). Velez-Ruiz & Meador, 2015). Additionally, it was estimated that 1.5 million individuals were prescribed valproate, in 2012 and roughly 22% of those were women of childbearing age (Angus-Leppan. & Liu, 2018). The total number of children exposed to AEDs, including valproate, however, is likely to be more noteworthy due to their use as treatments for other conditions (Velez-Ruiz & Meador, 2015).

Identification of the Risks Associated with Valproate Exposure

Not long after valproate was introduced for clinical use in epilepsy, emerging cases suggested those increased risk of neural tube defects, including spina bifida (Koren et al., 2006; Jentink et al., 2010). Today, although risk estimations associated with valproate vary, there may be as much as a two- to three-fold risk increase in congenital malformations among babies born to women with epilepsy on valproate compared to the general population (Adab et al., 2001).

To determine the risks of major congenital malformations for children exposed to AEDs *in utero*, the U.K. Epilepsy and Pregnancy Register was established (Mawhinney et al., 2012). According to the organization's website, the register began in 1996 for mothers who take one or more AED to prevent seizures. The organization's main objective is to obtain information on the occurrence of significant malformations they then publish. Furthermore, to identify the risks posed by valproate and other AEDs, the EURAP Epilepsy and Pregnancy Registry is an observational cohort study representing physicians from 45 countries, including Europe, Asia, Latin America, and Africa. According to the most recent figures, this registry was established in 1999 and had more than 700 collaborators (EURAP, 2018; Tomson et al., 2011).

Structural Malformations

Valproate has been associated with a number of structural malformations in developing children, including Spina Bifida. A 1982 study established a 20-fold increase in the risk for the occurrence of spina bifida associated with valproate during pregnancy (Wyszynski et al., 2005). A communicative *Morbidity and Mortality Weekly Report* by the CDC (1983) found that two were exposed to valproate among 118 infants with spina bifida. In a group of other malformations, three infants were exposed to valproate. At that time, the CDC estimated that a

pregnant woman in the United States, treated with valproate, would have a 1-2% chance of having a child with spina bifida (CDC, 1983).

To add further evidence of the drug's teratogenicity, the *Morbidity and Mortality Weekly Report* (1983) also referenced a U.K. researcher who concluded that, of infants born to 196 women treated with valproate, nine had spina bifida, and 30 had other structural defects that included cardiovascular defects, orofacial clefts, and abnormalities of the fingers or toes (CDC, 1983). Despite these previous reports, as of 2001, only neural tube defects were explicitly linked with valproate, which had the risk for spina bifida as high as 5% (Adab, Jacoby, Smith, & Chadwick, 2001; Wyszynski et al., 2005).

Likewise, a prospective study looked at the rate of significant malformations identified at birth from mothers who had taken valproate during pregnancy and were enrolled in the North American Antiepileptic Drug Pregnancy Registry, a surveillance registry system for pregnant women exposed to anticonvulsant drugs. For this study, medical records were obtained regarding the mother's medical history and any malformations identified in the child (Wyszynski et al., 2005). The researchers studied 3,441 women enrolled in the pregnancy registry between February 1, 1997, and November 20, 2003. Valproate was taken by 235 of those women for epileptic seizures. In children from this exposed group of women, 16 infants were confirmed as having significant malformations—a four-fold increase in risk for the women taking valproate over other drugs (Wyszynski et al., 2005).

Additionally, Koren et al. (2006) selected controlled cohort studies searching several databases that reported valproate use during the first trimester of pregnancy. They selected studies that had comparison groups of women treated with other antiepileptic drugs, untreated epileptic women, or healthy women that could represent the general population of pregnant

women. After reviewing more than 1,700 exposed infants reported throughout 11 cohort studies, researchers found that women who took valproate during the time in which the embryo develops had more than 2.5 times the risk of having a child with malformations above other AEDs. They also found that using valproate during pregnancy was shown to have a three-fold increase in major congenital malformations compared to the general population not exposed to AEDs (Koren et al., 2006).

Furthermore, Jentink et al. (2010) found in their review of published cohort studies that there were 14 significant malformations more commonly associated with valproate through various antiepileptic databases. There was a major congenital malformation observed in 118 of 1,565 pregnancies. For these malformations, the risk appeared to be significantly higher with the association of exposure to valproate during the first trimester of pregnancy compared to those with no exposure to antiepileptic drugs during the first trimester (Jentink et al., 2010). The researchers then tested this information in a large population-based case-control study. They found significant associations between exposure to valproate monotherapy in the first trimester in six conditions: spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis. They found that the risks for five of the conditions were two to seven times higher for exposed children. Specifically, the risk for spina bifida was as much as 16 times higher for exposed children depending on the control group used. Researchers also found an association between limb defects and exposure to valproate compared to other drugs used as an antiepileptic (Jentink et al., 2010).

Later, Werler et al. (2011) evaluated the use of specific antiepileptic drugs in pregnancy and their relationship with congenital malformations. They used data from the National Birth Defects Prevention Study, one of the largest studies on birth defects in the United States. They

assessed the use of these drugs and the risks posed for neural tube defects, oral clefts, heart defects, hypospadias, a defect in male genitals, and other significant congenital disabilities (CDC, 2019a; Werler et al., 2011). The authors found that increased risks that were drug-specific were observed for valproate. These risks were associated with neural tube defects, oral clefts, heart defects, and hypospadias. For example, mothers exposed to valproate were 9.7 times more likely to have a child with a neural tube defect, 4.4 times more likely to have a child with an oral cleft, 2.0 times more likely to have a heart defect, and 2.4 times more likely to have hypospadias (Werler et al., 2011).

Lastly, Weston et al. (2016) assessed the effects of prenatal exposure to AEDs on the prevalence of congenital malformations using several sources, including the Cochrane Epilepsy Group Specialized Register and Medline. Prospective cohort studies, cohort studies set within pregnancy registries, and randomized controlled trials were used. Fifty studies were included, with 31 contributing to the meta-analysis (Weston et al., 2016). The researchers found that children exposed to valproate had the highest malformation risk levels than other AED. Children exposed to valproate also had a higher risk than both groups of children in the control group versus children exposed to the other AEDs whereby the level of malformation risk was linked to the amount or dose of valproate that the child was exposed to *in utero* (Weston et al., 2016).

Fetal Valproate Syndrome

In 1984, Fetal Valproate Syndrome first started being used to describe the prominent malformations observed in children exposed to valproate *in utero.* This term refers to a collection of minor and major malformations occurring in exposed children, often consisting of facial malformations, including a flat nasal bridge, small upturned nose, and thin upper lip, as well as multiple major malformations and central nervous system dysfunctions (Wyszynski et al., 2005).

Moreover, no test can confirm a diagnosis of Fetal Valproate Syndrome. Other possible causes of the signs and symptomology must be ruled out first. However, Fetal Valproate Syndrome is often suspected in an infant with one or more of the signs and symptoms associated should the mother report having taken valproate during pregnancy (NIH, 2017).

Treatment for Fetal Valproate Syndrome is based on the signs and symptoms present in each child as management often involves a team of medical specialists (NIH, 2017). Moreover, parents of children born with Fetal Valproate Syndrome express grief and anger over delays in recognizing the problem, delays in diagnosis, and inadequate support for those with lifelong disabilities (Angus-Leppan, & Liu, 2018).

Cognitive Malformations

Valproate also causes severe malformations that primarily affect the brain and spinal cord, causing lower intelligence and other cognitive malformations. The low intellectual ability is seen in 30% to 40% of children born to mothers who took valproate (AHFS, 2020; Sawhney et al., 2019).

IQ Reductions

Exposure to valproate affects a child's development during pregnancy with a significant IQ reduction compared to children exposed to other AEDs. The IQ reductions (8-11 points lower) are considered substantial enough to affect their education and affect them later in life when entering the workforce (Tomson et al., 2015).

A meta-analysis of three studies, composed of 67 children exposed to the drug, calculated that fetal valproate exposure was associated with a six-point decrease in full-scale IQ (Gerard & Meador, 2015). Additionally, in a study by Eriksson et al. (2005), the neurological and cognitive

functions of school-aged children aged six and below exposed to valproate *in utero* were examined through a population-based, controlled study that consisted of 28 children. They found that low intelligence prevalence with valproate exposure was 19%, while exceptionally low intelligence was 10% in the valproate exposed children (Eriksson et al., 2005).

Furthermore, an FDA *Drug Safety Communication* (2011) warned the public that a mother's valproate use during pregnancy heightens her risk of having children born with lowered cognitive test scores. Furthermore, the *Drug Safety Communication* (2011) outlined initial cognitive test scores performed on children at age 3 with supportive studies of cognitive tests performed on children ages 5 to 16, with the most extensive research being a prospective cohort study conducted in the United States and the United Kingdom. However, the communication concluded that the long-term effects and whether the impact on cognitive development occurs when the child's exposure does not span the entirety of pregnancy are unknown (FDA, 2011).

Developmental Delays

Children exposed to valproate *in utero* have a delay in achieving developmental milestones, particularly verbal skills. This delay includes communication problems, including talking, poor language skills. Additionally, valproate also can cause coordination problems, including walking and learning problems affecting memory, emotions, and behavior (AHFS, 2020; Gerard & Meador, 2015; Sawhney et al., 2019).

To study the cognitive effects of valproate, Meador et al. (2009) used a cohort consisting of 258 children, 53 of which were exposed to valproate. As part of the Neurodevelopmental Effects of Antiepileptic Drugs study enrolling pregnant women who used AEDs from October 1999 through February 2004 in 25 epilepsy centers in the United States and the United Kingdom, Researchers found the poorest cognitive outcomes for children exposed to valproate. This

included increased developmental delays in children younger than 6 years of age, increased special education needs in children 5 to 18 years of age, and reduced verbal IQ in children 6 to 16 years of age, compared to unexposed children (Meador et al., 2009).

Autism

Recently it has been found that children exposed to valproate are more likely to demonstrate poor adaptive skills and a heightened risk for neurodevelopmental disorders, including attention deficit hyperactivity disorder and autism (Gerard & Meador, 2015). Evidence supports this link between cognitive function and the increased risk of autism with valproate exposure, thereby stressing the importance of understanding how the drug impacts a child's neurodevelopment (Roullet et al., 2013).

Clinical studies show valproate exposure in the first trimester of pregnancy is associated with a higher child incidence of autism. This association is based initially on the increased frequency of autistic symptoms of children diagnosed with Fetal Valproate Syndrome despite the number of studies reporting the prevalence of autism following valproate exposure being limited (Roullet et al., 2013). Supporting this, Christensen et al. (2013) conducted a population-based cohort study evaluating the risk of autism in children exposed to valproate prenatally in Denmark. They found a higher risk of autism spectrum disorder and childhood autism among children of women who used valproate during pregnancy. The risks were also higher than those for children whose mothers were previously valproate users but stopped at least 30 days before conception (Christensen et al., 2013).

History of Guidelines

Of all the AEDs available, the use of valproate during childbearing years and pregnancy has raised the most notable concerns (Roullet et al., 2013). FDA warnings related to valproate

during pregnancy have emphasized the need for reassessment in its use clinically during these years (Roullet et al., 2013). Hence, despite its known risks, valproate continues to be used in women of childbearing age as several pregnancy registries have established the commonality of valproate to be prescribed (Roullet et al., 2013). Subsequently, valproate has clinical guidelines for practitioners that suggest that it should be avoided during pregnancy. These guidelines indicate that valproate should be avoided in pregnancy if possible due to the increased risks of congenital malformations (Werler et al., 2011).

Supporting these claims, according to Jentink et al. (2010), the American Academy of Neurology recommended that valproate also be avoided during pregnancy, if possible. However, it might be challenging to avoid valproate provided reasonable seizure control (Jentink et al., 2010). Additionally, building on those previous dose-dependence claims, doses of more than 1,000 mg per day should be avoided entirely when there is a likelihood of pregnancy (Mawer et al., 2002).

Moreover, the FDA warned that women of childbearing age deciding to take valproate should use adequate birth control precautions while taking the medications. The FDA also advised healthcare professionals to inform women of childbearing age of the increased risks associated with this drug. They should also continue to counsel women that valproate carries an increased risk of major malformations when used during pregnancy (FDA, 2011).

More recently, the FDA released a drug safety communication advising healthcare professionals and women that pregnant women should not take valproate to prevent migraine headaches. This was based on recent studies that suggest that these medications can cause decreased IQ scores in children whose mothers took the drugs while pregnant (FDA, 2013).

Most recently, the AHFS Patient Medication Information in the United States concluded that women of childbearing age not using effective birth control methods or pregnant women must not take valproate for migraine headache prevention, and pregnant women should only take valproate to treat seizures or bipolar disorder if other medications have not successfully controlled the symptoms or other drugs cannot be used. If valproate is being used, one must use effective birth control throughout treatment (AHFS, 2020).

Additionally, in the United Kingdom, a national alert was issued in 2018. The U.K. Medicines and Healthcare Products Regulatory Agency advised that valproate was not recommended in women of childbearing age unless other treatments have been ineffective at managing the symptoms or cannot be tolerated. When alternatives are not possible, there should also be a pregnancy prevention program in place. This strengthened regulation and included new advisement for the use of valproate in pregnancy for bipolar disorder. The advisement is that, should a woman with bipolar disorder become pregnant, the valproate treatment must be discontinued or changed to a treatment alternative (Sawhney et al., 2019). This new guidance required that practitioners be obligated to identify all women within their practice receiving valproate and arrange a prompt review of their contraceptive measures. They were also required to be referred to a specialist to have annual reviews (Sawhney et al., 2019).

Some additional imposed rulings addressing the defects are as follows (Angus-Leppan & Liu, 2018; Macfarlane & Greenhalgh, 2018; Virta et al., 2018).

- In 2014, the New Zealand Medicines and Medical Devices Safety Authority said that valproate should not be used in women of childbearing potential unless other treatments are ruled ineffective.

- In 2014, documented teratogenic effects of valproate prompted restrictions in Finland of its use in females of childbearing age.
- In 2016, the UK Royal College of Obstetricians and Gynecologists recommended avoiding prescribing this drug to any childbearing age women.
- In 2016, the United States' stance was that its use might be acceptable should other medications not control the symptoms for which it is prescribed for epilepsy and bipolar. The risk for pregnant women outweighs any possible benefit for migraines.
- In 2017, the French National Agency for the Safety of Medicines and Health Products (ANSM) imposed a nationwide ban against valproate in pregnancy due to the teratogenic risks
- In 2018. the European Medicines Agency's Pharmacovigilance Risk Assessment Committee ruled that valproate must not be used in pregnancy unless there is a pregnancy prevention program in place.

Finally, the FDA indicated that stronger warnings about its use during pregnancy would be added to the drug labels and valproate's pregnancy category for migraine use would be changed from a "D," meaning the potential benefit of the drug in pregnant women may be acceptable despite the potential risks, to an "X," meaning that the risk of use in pregnant women outweighs any possible benefit (FDA, 2013). This is concluding that for use in pregnant women with epilepsy or bipolar, valproate should only be prescribed if other medications are not effective in treating the condition or are otherwise unacceptable for their condition. However, valproate products remain in the pregnancy category "D" for treating epilepsy and manic episodes associated with bipolar disorder (FDA, 2013). Regarding women of childbearing age who are not pregnant, valproate should not be taken for any condition unless the drug is essential

to the management of the woman's medical condition. Non-pregnant women of childbearing age should use effective birth control (FDA, 2013).

The Stance of Advocacy Groups

Consensus is growing to reduce the number of women taking valproate. This momentum comes from patient support groups, healthcare professionals, and the media. Expert advisory groups have limited responses, and regulations have varied. Reactions have ranged from those advocating shared decision making and informed patient choice to barring the use in pregnancy coupled with a pregnancy prevention program in those still taking the drug (Angus-Leppan, & Liu, 2018). Advocacy groups have suggested that the government, industry, and medical responses are too slow (Angus-Leppan, & Liu, 2018).

Some groups even propose a total ban on valproate as the only way to avoid future problems. The fundamental assumption behind those who want the drug banned is that valproate risks are so high for children that informed consent for the drug in pregnant women is not sufficient. A complete ban on the use during pregnancy would imply that a pregnancy prevention program is enforced with any woman of childbearing age who still wishes to take the drug. This would include a negative pregnancy test before starting a treatment or as part of a regular review process (Angus-Leppan, & Liu, 2018). Lastly, many advocacy groups feel that practitioners should inform women of the increased risks of cognitive deficits associated with the use of valproate, especially in early pregnancy, and when avoidable, the drug should not be used for treatment in female patients of childbearing age (Koren et al., 2006; Tomson et al., 2015).

For instance, there are certain epilepsies where alternatives are either few or have been deemed ineffective. In these scenarios, valproate would be appropriate to be prescribed to

females of childbearing age. Discussions should be taken that evaluate the risk-benefit of treatment options (Tomson et al., 2015).

Discussion of Previous Studies' Limitations

According to some researchers, previous studies' findings are limited by small samples of exposed women and often a retrospective study design (Alsdorf & Wyszynski, 2005; Tomson et al., 2011). However, limitations aside, extensive clinical research outlines the health risks associated with *in utero* exposure to valproate (Roullet et al., 2013). The majority of research has demonstrated a consistent association between valproate exposure and development delay, for example (Gerard & Meador, 2015).

Conclusion

Due to the rapid introduction of new drugs, when and how the drugs are prescribed have changed dramatically. There is a need to develop satisfactory methods to examine the risks of both old and new AEDs as data suggests that valproate should not be used as a first-line antiepileptic drug in women of childbearing age since data shows that roughly half of all pregnancies are unplanned (Adab et al., 2001; CDC, 2019b, Meador, 2009).

As the risks to children of mothers exposed to AEDs have been increasingly understood, the warnings against such medications have been strengthened. Specifically, there has been an increase in healthcare professionals and available patient resources regarding the acceptable use of valproate (Sawhney et al., 2019). Worldwide there is an agreement that valproate is a serious teratogen. However, there is still no agreement on proper guidelines for women who may become pregnant (Angus-Leppan, & Liu, 2018).

Given the risk associated with exposure during pregnancy, many advocates feel that valproate should be avoided, whenever possible, for epilepsy in women of childbearing age. When valproate is the most appropriate for treatment, advocacy groups say that the patient should be informed of the risks associated with valproate use during pregnancy, and all treatment alternatives and effective contraception, when relevant, should be ensured for those prescribed valproate (Sawhney, 2019). Furthermore, according to surveys in the United Kingdom, around half of epileptic women are unaware that valproate poses any risks to the child (Angus-Leppan & Liu, 2018; Macfarlane & Greenhalgh, 2018).

CHAPTER III

METHODOLOGY

Specific Aims

This project intends to inform professional practice regarding the number of prescriptions for valproate prescribed to women of childbearing age. Additionally, it looks at how many of those women of childbearing are on pregnancy preventive programs or have a pregnancy given the fetal risks associated with valproate. This research is valuable as a consulting report to physician specialties such as psychiatry, neurology, and obstetrics.

Aim

To examine the number of women of childbearing age (18-44) who are prescribed valproate, some of their outcomes, and rates of pregnancy prevention to avoid risks resulting from prenatal valproate exposure.

Under this aim, this project intends to answer the following research questions:

- Question 1: At what rate is valproate being prescribed to women of childbearing age?
- Question 2: What are the most common diagnoses (e.g., bipolar, epilepsy, migraines).
- Question 3: For what age group of women is valproate most commonly prescribed?
- Question 4: How many of those women prescribed valproate were part of a pregnancy prevention program?
- Question 5: Of those women taking valproate, how many later experienced a pregnancy?

Study Design

This study is a retrospective cohort study, the researcher followed the sample overtime through billing data using a billing ID, focusing on incidence rates based on the specified

research questions as part of an epidemiological case study design. The research sets to prove no causal relationship but merely describe the distribution between the defined variables.

Population and Sample

The study sample is women of childbearing age, 18 to 44 years of age, based on the CDC indicator definition for reproductive health (CDC, 2015). Inclusion data includes women between the ages of 18 and 44 and those with three or more months of valproate prescription fills. Excluded women were those not between the ages of 18 and 44 and those who had less than three (3) months of valproate prescribed to them.

- *At what rate is valproate being prescribed to women of childbearing age?*

Mawhinney et al. (2012) excluded women from their study women who were missing data on drug dose and administration. Since this study is not concerned with dosage, there was no exclusion.

- *What are the most common prescribing diagnoses (e.g., bipolar, epilepsy, migraines)?*

Inclusion criteria included the three-common diagnosis (bipolar, epilepsy, and migraines). Exclusion criteria were women with those outside these diagnoses.

- *For what age group of women is valproate most prescribed?*
- *How many of those women prescribed valproate were part of a pregnancy prevention program?*

Inclusion criteria included those women who have a billing code of Z30-Z30.9 within their billing history. Exclusion criteria consisted of any women who do not have a billing code within their billing data.

- *How many of those women prescribed valproate were not part of a pregnancy prevention program?*

Inclusion criteria included those women who did not have a billing code of Z30-Z30.9 within their billing history. Exclusion criteria consisted of any women with the billing codes of Z30 to Z30.9 billing code within their billing data.

- *Of those women taking valproate, how many went on to experience pregnancy?*

Inclusion criteria included all pregnancies (Z33). Mawer et al. (2002) had no exclusions in their study but instead included every pregnancy known by women attending the clinic. Since we are not concerned with the viability of the pregnancies, all records were included. There were no exclusions.

The study population comes from the 2016-2018 MarketScan® Commercial dataset obtained by the Medical University of South Carolina. This dataset is a compiled set of 119 million privately insured individuals' billing records. The data are de-identified and examined by the IRB at MUSC and deemed non-human subjects.

Database

According to the White Paper for IBM MarketScan Research Databases for Health Services Researchers (2019),

> The IBM MarketScan® Commercial Database consists of medical and drug data from employers and health plans. It contains data for several million individuals annually, encompassing employees, their spouses, and dependents covered by employer-sponsored private health insurance in the United States. These include PPOs and exclusive provider

> organizations (EPOs), POS plans, indemnity plans, HMOs, and consumer-directed health plans (CDHPs).

This data is of value to the research because, as the White Paper (2019) continues,

> Medical claims are linked to outpatient prescription drug claims and person-level enrollment information. The MarketScan Commercial Database may offer a distinct advantage over other databases for research on medication use. As these data are primarily sourced from employers, claims for mail-order prescriptions and specialty pharmacies are also included.

Definition of Variables

The control variable is birth control, whether oral pills, intrauterine devices, transdermal patches, or other identifiable methods. The researcher used the searchable ICD-10-CM grouping code of Z30 through Z30.9 for contraceptive management.

In the study, the researcher followed a subset of women prescribed valproate using the women's billing data looking for searchable valproate NDC groupings of 71930-057-12 (oral). Additionally, the researcher used the searchable ICD 10 group billing code of Z33 for pregnancy, the DSM code of Z37.*x* for delivery, and the ICD 10 codes for bipolar F31.9.*x*, epilepsy G40.*x*, and migraines G43.*x*.

Table 1. ICD-10-CM codes

Description	Codes
Contraception Management	Z30 – Z30.9
Pregnancy	Z32-Z32.3
Delivery Outcome (i.e. births)	Z37- Z37.9
Bipolar	F31.9
Epilepsy	G40
Migraine	G43

Table 2. Study NDCs

Description	Route	Codes
DIVALPROEX SODIUM	ORAL	0074-3826
DIVALPROEX SODIUM	ORAL	0074-6114
DIVALPROEX SODIUM	ORAL	0074-6212
DIVALPROEX SODIUM	ORAL	0074-6214
DIVALPROEX SODIUM	ORAL	0074-6215
DIVALPROEX SODIUM	ORAL	0074-7126
DIVALPROEX SODIUM	ORAL	0378-0472
DIVALPROEX SODIUM	ORAL	0378-0473
DIVALPROEX SODIUM	ORAL	0615-7949
DIVALPROEX SODIUM	ORAL	0615-7950
DIVALPROEX SODIUM	ORAL	0615-7956
DIVALPROEX SODIUM	ORAL	0615-8237

DIVALPROEX SODIUM	ORAL	0615-8242
DIVALPROEX SODIUM	ORAL	0615-8326
DIVALPROEX SODIUM	ORAL	0615-8327
DIVALPROEX SODIUM	ORAL	0615-8328
DIVALPROEX SODIUM	ORAL	0615-8329
DIVALPROEX SODIUM	ORAL	0615-8330
DIVALPROEX SODIUM	ORAL	0781-2243
DIVALPROEX SODIUM	ORAL	0832-7122
DIVALPROEX SODIUM	ORAL	0832-7123
DIVALPROEX SODIUM	ORAL	0832-7124
DIVALPROEX SODIUM	ORAL	0904-6363
DIVALPROEX SODIUM	ORAL	0904-6364
DIVALPROEX SODIUM	ORAL	0904-6615
DIVALPROEX SODIUM	ORAL	0904-6860
DIVALPROEX SODIUM	ORAL	0904-6861
DIVALPROEX SODIUM	ORAL	10370-510
DIVALPROEX SODIUM	ORAL	10370-511
DIVALPROEX SODIUM	ORAL	16714-484
DIVALPROEX SODIUM	ORAL	16714-485
DIVALPROEX SODIUM	ORAL	17856-0109
DIVALPROEX SODIUM	ORAL	27241-115
DIVALPROEX SODIUM	ORAL	29300-138
DIVALPROEX SODIUM	ORAL	29300-139

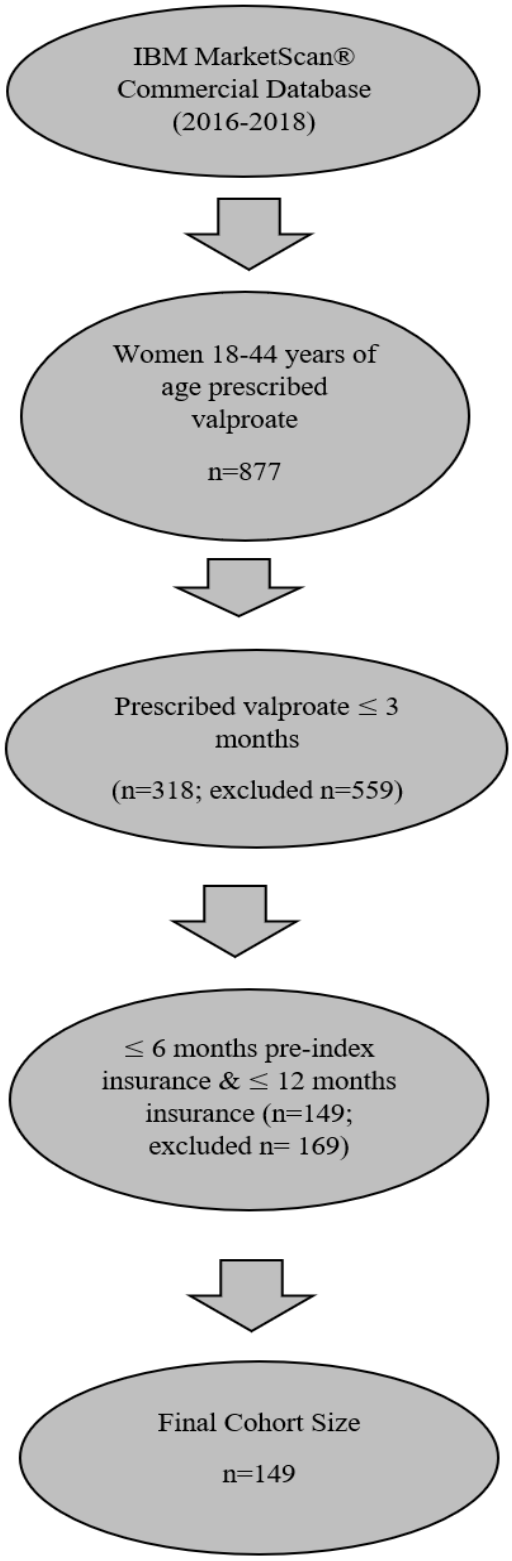
DIVALPROEX SODIUM	ORAL	29300-140
DIVALPROEX SODIUM	ORAL	43063-295
DIVALPROEX SODIUM	ORAL	43353-547
DIVALPROEX SODIUM	ORAL	48433-125
DIVALPROEX SODIUM	ORAL	48433-126
DIVALPROEX SODIUM	ORAL	50090-2007
DIVALPROEX SODIUM	ORAL	50090-3416
DIVALPROEX SODIUM	ORAL	50090-3616
DIVALPROEX SODIUM	ORAL	50090-4187
DIVALPROEX SODIUM	ORAL	50090-4409
DIVALPROEX SODIUM	ORAL	50090-4737
DIVALPROEX SODIUM	ORAL	50090-4861
DIVALPROEX SODIUM	ORAL	50268-258
DIVALPROEX SODIUM	ORAL	51079-766
DIVALPROEX SODIUM	ORAL	51079-767
DIVALPROEX SODIUM	ORAL	51655-365
DIVALPROEX SODIUM	ORAL	55111-529
DIVALPROEX SODIUM	ORAL	55111-530
DIVALPROEX SODIUM	ORAL	55111-531
DIVALPROEX SODIUM	ORAL	55111-532
DIVALPROEX SODIUM	ORAL	55111-533
DIVALPROEX SODIUM	ORAL	55111-534
DIVALPROEX SODIUM	ORAL	55154-4679

DIVALPROEX SODIUM	ORAL	55154-4759
DIVALPROEX SODIUM	ORAL	55154-7145
DIVALPROEX SODIUM	ORAL	55154-7640
DIVALPROEX SODIUM	ORAL	57237-047
DIVALPROEX SODIUM	ORAL	57237-048
DIVALPROEX SODIUM	ORAL	57237-106
DIVALPROEX SODIUM	ORAL	58118-0040
DIVALPROEX SODIUM	ORAL	60687-211

VALPROIC ACID	ORAL	0121-0675
VALPROIC ACID	ORAL	0121-1350
VALPROIC ACID	ORAL	0121-4675
VALPROIC ACID	ORAL	0527-5250
VALPROIC ACID	ORAL	0591-4012
VALPROIC ACID	ORAL	0615-8205
VALPROIC ACID	ORAL	0832-0310
VALPROIC ACID	ORAL	17856-0675
VALPROIC ACID	ORAL	17856-4012
VALPROIC ACID	ORAL	42291-844
VALPROIC ACID	ORAL	43353-085
VALPROIC ACID	ORAL	43353-107
VALPROIC ACID	ORAL	43353-279

VALPROIC ACID	ORAL	50383-792
VALPROIC ACID	ORAL	60429-246
VALPROIC ACID	ORAL	60432-621
VALPROIC ACID	ORAL	60687-262
VALPROIC ACID	ORAL	63629-7597
VALPROIC ACID	ORAL	63739-253
VALPROIC ACID	ORAL	67046-807
VALPROIC ACID	ORAL	67046-808
VALPROIC ACID	ORAL	68094-193
VALPROIC ACID	ORAL	68094-701
VALPROIC ACID	ORAL	69452-150
VALPROIC ACID	ORAL	70518-0079
VALPROIC ACID	ORAL	70518-1968
VALPROIC ACID	ORAL	70518-2215
VALPROIC ACID	ORAL	71930-057
VALPROIC ACID	ORAL	72189-010

Figure 1. Study Flowchart



Data Analysis

These data were analyzed using SAS version 9.4 (Cary, NC). Data is described using measures of central tendency (mean, median, mode) and dispersion (standard deviation, quartiles, min, max). The researcher seeks to describe and quantify the number of pregnancies in the dataset among women 18-44 years of age on valproate in this descriptive survey. Differences between those on birth control and those not on birth control were made using student's t-test for normally distributed data, Wilcoxon-Mann-Whitney for non-normally distributed data, and chi-squared tests for categorical data. Statistical significance has been defined *a priori* to be <0.05.

Limitations

Factors that affected my findings included the length of contraceptive use and type of contraceptive use, such as condom use, which the study could not account for. The researcher studied only measurable pregnancy preventions (oral pills, intrauterine devices, transdermal patches) for this research. Filtering this data did not increase the level of control for these factors. Additional limitations include the fact that there is no way to know whether a woman prescribed valproate ingested the oral medication, nor does the researcher match dates to verify events' timing.

CHAPTER IV
ARTICLE MANUSCRIPT

Introduction

Valproate entered the market as a therapeutic intervention for absence seizures. Since then, its use has expanded to include the treatment of complex and partial seizures, a preventative for migraines in some countries, a treatment for acute mania, and a mood stabilizer for bipolar disorder. [1,2] Today, an increasing number of pregnant women continue to be exposed to valproate, despite its use during the first trimester being associated with an increased risk of spina bifida. [3,4] Adab et al.[5] say that roughly one-third of all people receiving Antiepileptic Drugs (AEDs) were women of childbearing age in 2001. In addition, 1 in 250 pregnancies was exposed to AEDs whereby, over one million women with epilepsy in the United States were of childbearing age, and three to five births per 1,000 were to those women in 2015.[5] Additionally, it was estimated that 1.5 million individuals were prescribed valproate, in 2012 and roughly 22% of those were women of childbearing age. [6] The total number of children exposed *in utero* to AEDs, including valproate, however, is likely to be more noteworthy due to their use as treatments for other conditions. [7]

Valproate is associated with a higher risk for teratogenesis, the production of malformations in a child, compared to the baseline population rates and other ordinary AEDs for over 30 years of clinical studies. [8, 3] There are reports of valproate teratogenicity, the capability to cause malformations, in animals since the 1970s. Additionally, teratogenicity has been reported in humans since the 1980s, whereby mouse and rat animal studies have examined anatomical, behavioral, molecular, and physiological outcomes of *in utero* exposure to valproate. [6, 9]

Notably, these animal studies have shown that the timing of exposure affects the type of identified malformations. For example, valproate exposure during the first trimester of gestation results in malformations of major organs. By contrast, exposure later in pregnancy results in an increased risk of neurodevelopmental defects when brain cells proliferate and migrate. [10] Additionally, animal studies examining valproate have recently shown autistic-like outcomes, including social behavior deficits, increased repetitive behaviors, and communication deficits. [9]

Valproate's teratogenic properties have been evidenced by clinical studies done by Weston [11], Christensen [12], and Eriksson [13]. In addition, national and international pregnancy registries have increasingly identified AEDs' teratogenic properties. [10, 14] Furthermore, across several of these human studies, valproate has been the most highly associated with cognitive and behavioral teratogenesis of all AEDs. [8] In the end, clinical research has identified many risks associated with the drug that include those congenital malformations, developmental delays, reduced cognitive function, and, most recently, autism. [9]

A prospective study looked at the rate of significant malformations identified at birth from mothers who had taken valproate during pregnancy and were enrolled in the North American Antiepileptic Drug Pregnancy Registry, a surveillance registry system for pregnant women exposed to anticonvulsant drugs. Medical records were obtained regarding the mother's medical history and any malformations identified in the child for this study. [15] The researchers studied 3,441women enrolled in the pregnancy registry between February 1, 1997, and November 20, 2003. Valproate was taken by 235 of those women for epileptic seizures. In children from this exposed group of women, 16 infants were confirmed as having significant malformations—a four-fold increase in risk for the women taking valproate over other drugs. [15]

Additionally, Koren et al. [16] selected controlled cohort studies searching several databases that reported valproate use during the first trimester of pregnancy. They selected studies that had comparison groups of women treated with other antiepileptic drugs, untreated epileptic women, or healthy women that could represent the general population of pregnant women. After reviewing more than 1,700 exposed infants reported throughout 11 cohort studies, researchers found that women who took valproate during the time in which the embryo develops had more than 2.5 times the risk of having a child with malformations above other AEDs. They also found that using valproate during pregnancy was shown to have a three-fold increase in major congenital malformations compared to the general population not exposed to AEDs. [16]

Furthermore, Jentink et al. [3] found in their review of published cohort studies that there were 14 significant malformations more commonly associated with valproate through various antiepileptic databases. There was a major congenital malformation observed in 118 of 1,565 pregnancies. For these malformations, the risk appeared to be significantly higher with the association of exposure to valproate during the first trimester of pregnancy compared to those with no exposure to antiepileptic drugs during the first trimester. [3] The researchers then tested this information in a large population-based case-control study. They found significant associations between exposure to valproate monotherapy in the first trimester in six conditions: spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis. They found that the risks for five of the conditions were two to seven times higher for exposed children. Specifically, the risk for spina bifida was as much as 16 times higher for exposed children depending on the control group used. Researchers also found an association between limb defects and exposure to valproate compared to other drugs used as an antiepileptic. [3]

Later, Werler [17] evaluated the use of specific antiepileptic drugs in pregnancy and their relationship with congenital malformations. They used data from the National Birth Defects Prevention Study, one of the most extensive studies on birth defects in the United States. They assessed the use of these drugs and the risks posed for neural tube defects, oral clefts, heart defects, hypospadias, a defect in male genitals, and other significant congenital disabilities. [18, 17] The authors found that increased risks that were drug-specific were observed for valproate. These risks were associated with neural tube defects, oral clefts, heart defects, and hypospadias. For example, mothers exposed to valproate were 9.7 times more likely to have a child with a neural tube defect, 4.4 times more likely to have a child with an oral cleft, 2.0 times more likely to have a heart defect, and 2.4 times more likely to have hypospadias. [17]

Lastly, Weston et al. [11] assessed the effects of prenatal exposure to AEDs on the prevalence of congenital malformations using several sources, including the Cochrane Epilepsy Group Specialized Register and Medline. Prospective cohort studies, cohort studies set within pregnancy registries, and randomized controlled trials were used. Fifty studies were included, with 31 contributing to the meta-analysis. [11] The researchers found that children exposed to valproate had the highest malformation risk levels than other AED. Children exposed to valproate also had a higher risk than both groups of children in the control group versus children exposed to the other AEDs. The malformation risk level was linked to the amount or dose of valproate that the child was exposed to in utero. [11]

Methods

This study is a retrospective cohort study. The researcher followed the sample longitudinally through billing data using a billing ID, focusing on incidence rates based on the

specified research questions as part of an epidemiological design. The research set to prove no causal relationship but merely describe the distribution between the defined variables.

The study population came from the 2016-2018 MarketScan® Commercial Claims & Encounters dataset obtained by the Medical University of South Carolina. This dataset was a compiled set of 119 million privately insured individuals' billing records. The data were de-identified and examined by the IRB at MUSC and deemed non-human subjects.

Patients and Settings

The study sample was women of childbearing age, 18 to 44 years old, based on the CDC indicator definition for reproductive health. [19] Inclusion criteria included women with three or more months of valproate prescription fills. Exclusion criteria consisted of those not between 18 and 44 and those who had less than three (3) months of valproate prescribed. Insurance information obtained from the MarketScan® data was 6 months pre-index and 12 months post-index, whereby the data index was the date from which the first valproate prescription was filled.

Aim

To examine the number of women of childbearing age (18-44) who were prescribed valproate, some of their outcomes, and rates of pregnancy prevention to avoid risks resulting from prenatal valproate exposure.

Under the aim, the project intended to answer the following research questions:

1) *At what rate is valproate being prescribed to women of childbearing age?*

Mawhinney [20] excluded women from their study who were missing data on drug dose and administration. Since this study was not concerned with dosage, there were no exclusions

whereby the research examined all billing data for valproate within the pre and post-index of women ages 18-44.

2) *What are the most common prescribing diagnoses (e.g., bipolar, epilepsy, migraines)?*

The research was only interested in the three common diagnoses (bipolar, epilepsy, and migraines) and therefore studied only the DSM-10 billing codes of F31.9 (bipolar), G40-G40.9 (Epilepsy), and G43-G43.9 (migraines).

3) *For what age group of women is valproate most prescribed?*

The research examined all billing data pertaining to women 18-44 years of age that fell within the pre and post-index.

4) *How many of those women prescribed valproate were part of a pregnancy prevention program?*

This interest area included whether the women were partaking in a pregnancy prevention program as indicated by the ICD-10 CM codes of Z30-Z30.9 for contraceptive management within their billing history.

5) *Of those women taking valproate, how many later experienced a pregnancy?*

For this area of interest, ICD-10 CM billing codes of Z32-Z32.3 were examined. Mawer [21] had no exclusions in their study but instead included every pregnancy known by women attending the clinic. This study also used this logic. Of those pregnancies, the delivery outcome (i.e., births) was also examined using the ICD-10 billing codes of Z37- Z37.9.

Statistical Analysis

These data were analyzed using SAS version 9.4 (Cary, NC). Data are described using measures of central tendency (mean, median, mode) and dispersion (standard deviation, quartiles, min, max). The research describes and quantifies the number of pregnancies among women 18-44 years of age on valproate in this epidemiological study. Tests for differences between those on birth control and those not on birth control were made using Student's t-test for normally distributed data, Wilcoxon-Mann-Whitney for non-normally distributed data, and chi-squared tests for categorical data. Statistical significance has been defined a priori to be <0.05.

Results

Table 3. Sample Characteristics

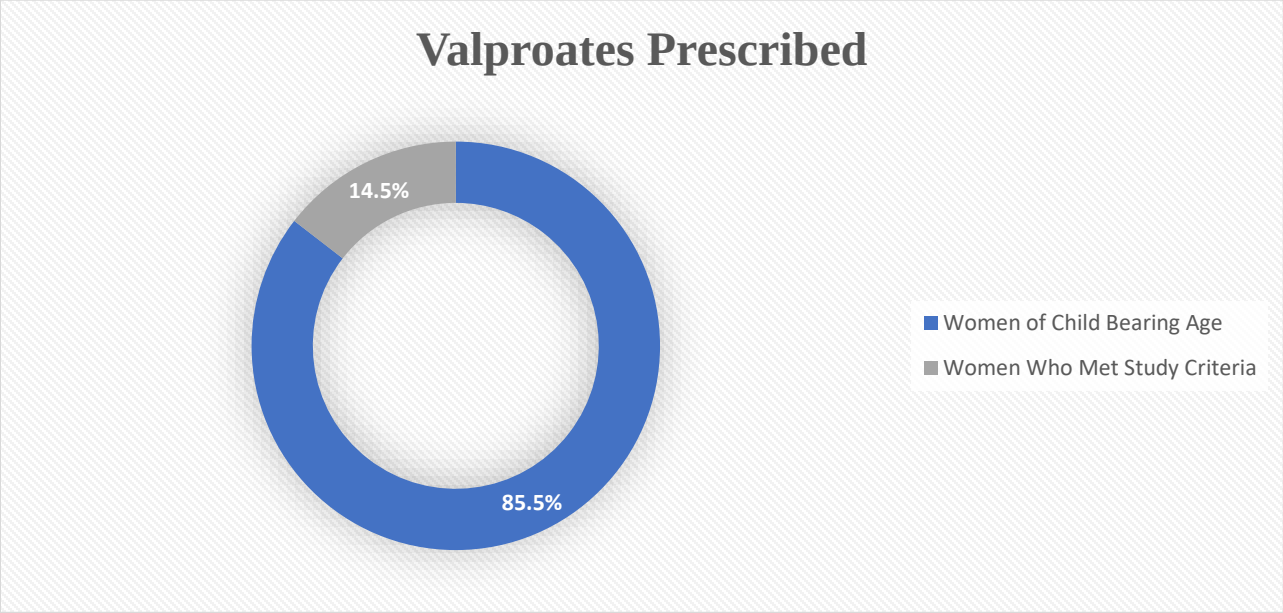
Clinical characteristics	
Charlson comorbidity score	0.0 ± 0.0
Elixhauser conditions	
Alcohol Abuse	2 (1.3)
Blood Loss Anemia	1 (0.7)
COPD	13 (8.7)
Cardiac Arrhythmia	3 (2.0)
Coagulopathy	2 (1.3)
Deficiency Anemia	7 (4.7)
Depression	35 (23.5)

Diabetes, Complicated	2 (1.3)
Diabetes, Uncomplicated	5 (3.4)
Drug Abuse	6 (4.0)
Fluid/Electrolyte Disorder	2 (1.3)
Hypertension, Uncomplicated	14 (9.4)
Hypothyroidism	7 (4.7)
Obesity	13 (8.7)
Other Neurological Disorder	12 (8.1)
Psychoses	4 (2.7)
Pulmonary Circulation Disorder	1 (0.7)
Rheumatoid Arthritis	4 (2.7)
Weight Loss	3 (2.0)
All values expressed as n (%) mean ±s.d., or median [Q1 - Q3]	

The women examined for the study were primarily healthy, with the most notable characteristic being depression with n=23 (23.5%) of the sample. Other characteristics would not be classified as significant.

For research question 1: *At what rate is valproate being prescribed to women of childbearing age*, there were n=877 women aged 18-44 on valproate during 2016-2018. There was n=318 women across 3 years of MarketScan ® data prescribed 3 or more months of the drug. Of the 318 women, n=149 (46.8%) were analyzed for the study based on a 6-month pre-index and 12-month post-index insurance.

Figure 2. Valproates Prescribed

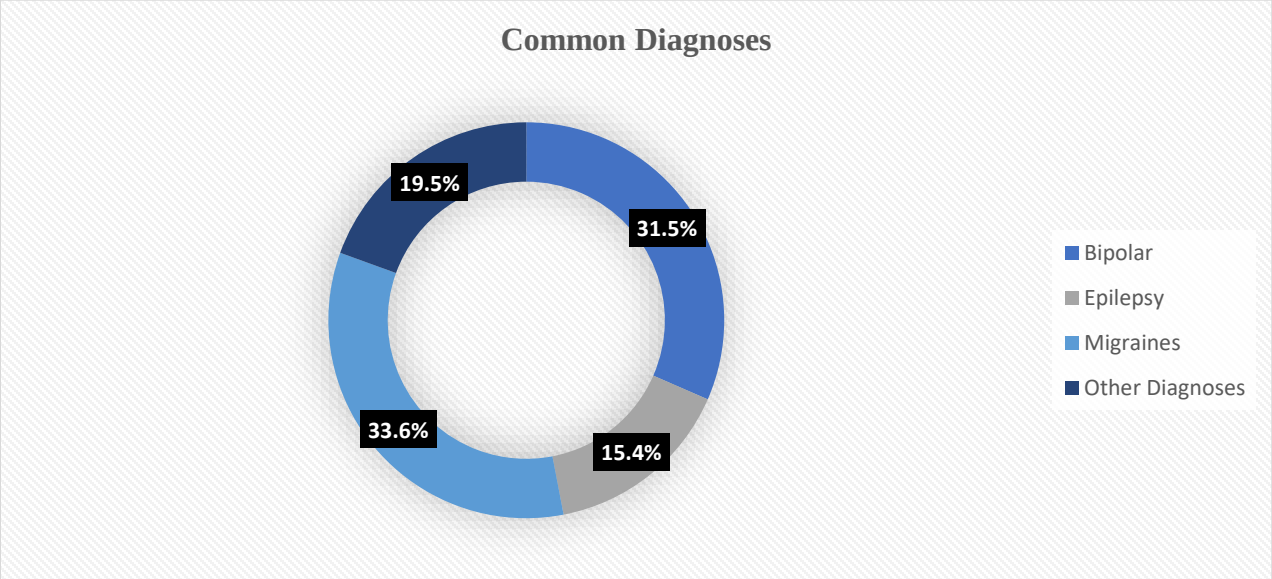


For research question 2: *What are the most common diagnoses (e.g., bipolar, epilepsy, migraines)*, it was found that n=102 (68.4%) of the n=149 women were prescribed valproate for one of the three diagnoses researched- there were no instances of multiple diagnoses within those examined. Of those diagnoses, the most commonly prescribed was as a therapeutic for migraines (n=50) followed by as a therapeutic for bipolar disorder (n=47).

Table 4. Diagnosis

Diagnosis	Frequency (n=102)
Bipolar	47 (31.5)
Epilepsy	23 (15.4)
Migraines	50 (33.6)
All values expressed as n (%)	

Figure 3. Common Diagnoses

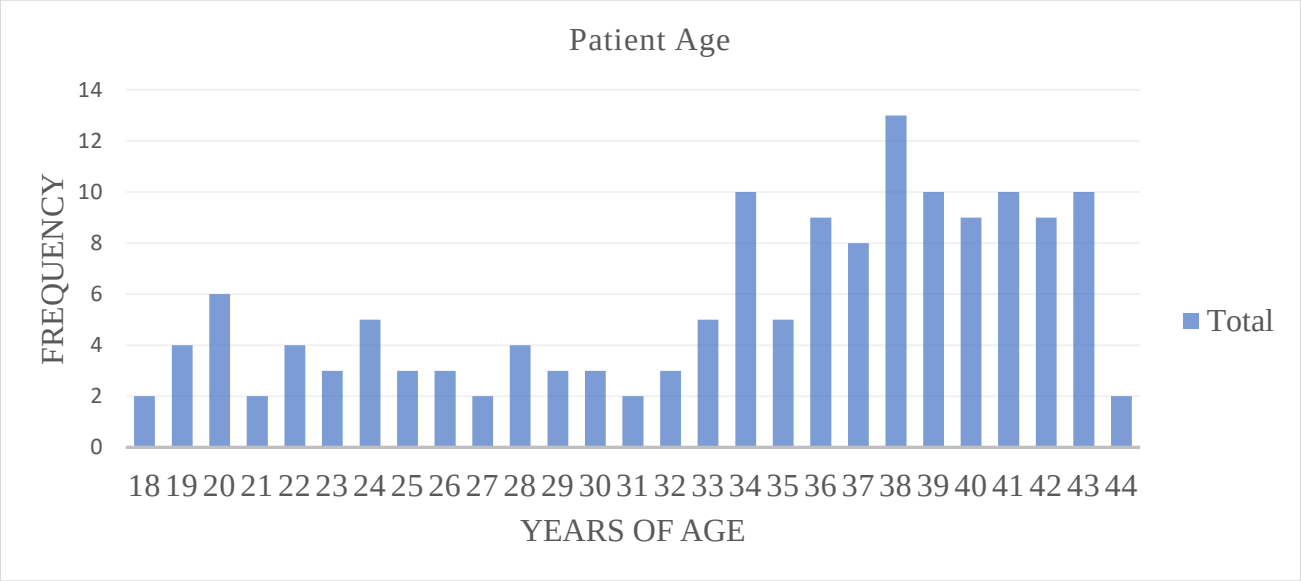


For research question 3: *For what age group of women is valproate most commonly prescribed*, the research showed that the average age for which valproate was prescribed was 34 years of age (standard deviation of 7.4), and the median age was 36 years of age.

Figure 4 Descriptive Statistics: Age of Women Represented in the Research

	Average of Age of	StdDev of Age	Max of Age	Min of Age	Median of Age
Grand Total	33.9	7.4	44	18	36

Figure 5. Patient Age

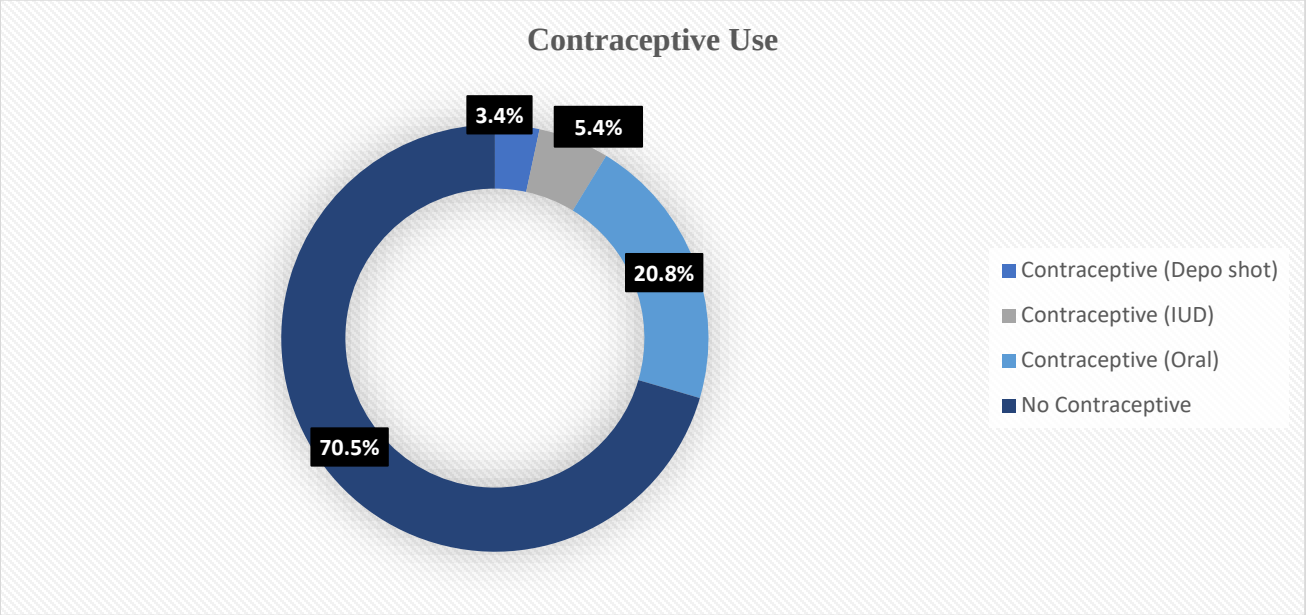


For research question 4: *How many of those women prescribed valproate were part of a pregnancy prevention program*, the research showed that n=43 (28.9%) women were on one of the three forms of birth control investigated, with the most common form being an oral contraceptive (n=31). There was one billing ID that data showed was on both Depo and an IUD within the data set.

Table 5. Contraceptives

Contraceptive (Any)	43 (28.9)
Contraceptive (Depo shot)	5 (3.4)
Contraceptive (IUD)	8 (5.4)
Contraceptive (Oral)	31 (20.8)
All values expressed as n (%)	

Figure 6. Contraceptive Use



For research question 5: *Of those women taking valproate, how many went on to experience pregnancy*, the research showed that of those women taking valproate, n=3 went on to experience a pregnancy while there was n=1 recorded birth out of the n=149 women.

Table 6. Outcomes

Pregnancy	3 (2.0)
Birth	1 (0.7)
All values expressed as n (%)	

Discussion

Of all the AEDs available, the use of valproate during childbearing years and pregnancy has raised the most notable concerns. [9] FDA warnings related to valproate during pregnancy have

emphasized the need for reassessment in its use clinically during these years. [9] Hence, despite its known risks, valproate continues to be used in women of childbearing age as several pregnancy registries have established the commonality of valproate to be prescribed. [9]

Furthermore, a consensus is growing to reduce the number of women taking valproate. This momentum comes from patient support groups and healthcare professionals based on the expert advisory groups' limited responses and variations of regulations regarding the drug's use. There are also mixed reactions among advocates, with reactions ranging from those advocating shared decision making and informed patient choice to those advocating to bar the drug's use in pregnancy unless coupled with a pregnancy prevention program in those still taking the drug. [6]

Moreover, the FDA's most recent guidance declares that valproate should not be administered to women of childbearing age unless other medications have failed to provide adequate symptom relief or are otherwise unacceptable. They continue by saying that in these situations, effective contraception should be used. Ultimately there is no change from their previous guidance in 2013.[22.] Notably, the research showed that 46.8% of the 318 women prescribed valproate were of childbearing age and were prescribed 3 or more months of valproate, whereby n=105 (70. 5%) of the sample were not on 1 of the 3 most common contraceptive methods.

Equally important is a recent study by Tachibana et al.[23], who investigated patterns in psychiatrists' prescriptions of valproate for bipolar female patients of childbearing age in Japan. The reason for doing so was based on the global procedures that state valproate should not be used for women of childbearing age. In this research, 571 psychiatrists responded to the survey, with approximately 70% answering that they frequently or occasionally prescribed valproate for bipolar women of childbearing age.[23] Our study supported this finding, as valproate was most

commonly prescribed for migraines followed by bipolar disorder. This despite research on the effects of the drug being primarily focused on valproate as a therapeutic for epilepsy.

Meanwhile, the reason for the continued prescribing of valproate products is not yet apparent.[24] One possible explanation could be that the risks associated with prescribing valproate have mainly been researched and limited to the epilepsy community, as mentioned previously, with neurologists primarily reading this research. [24] Psychiatric journals, for instance, contain only sporadic articles that may address the issue. Additionally, another main problem is that guidelines lack a set of mandatory and required rules. For example, some guidelines call for discussing the associated risks with those prescribed while paying attention to contraceptive use. In contrast, others mention the guidance that valproate should not be used in women of childbearing age unless other options have proven unsuitable and there is a contraception plan in place. Ultimately, most of those guidelines associated with fetal risks focus solely on treating women with epilepsy with the lack of awareness among psychiatrists and other practitioners.[24]

In conclusion, this research's findings highlight the importance of further education on the risks of valproate and women of childbearing age. This is based on the lack of studies focusing on the risks and prescribing patterns outside of the epilepsy community. Limitations to the research included the length of contraceptive use and type of contraceptive use, such as condom use, which the study could not account for. Ultimately, the researcher studied only measurable pregnancy preventions (oral pills, intrauterine devices, transdermal patches) for this research. Filtering this data did not increase the level of control for these factors. Furthermore, future research could explore different funding streams as our research focused on commercial payor billing data, which garnered a small sample size.

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Appendix

A: Contraceptives Studied

Description	National Drug Code (NDC)
Depo Shot	00009024802, 00009062601, 00009737611, 50090045900, 50090066500, 54868334801, 00009074630, 00009074635, 54569370100, 54569490400, 54569552700, 54868361300, 54868410000, 54868410001, 00009470913, 54569621900, 00548540000, 00548540025, 00548570100, 00703680101, 00703680104, 50090088300, 50090332800, 54569561600, 54569677100, 54868525700, 59762453701, 59762453702, 59762453802, 62756009040, 62756009045, 67457088700, 67457088701, 67457088799, 71205011801, 00548541000, 00548541025, 00548571100
Oral Contraceptive	00046257512, 51862023803, 52544095931, 54868491100, 76388028301, 00555905167, 00555905179, 51862007201, 51862007206, 52544094028, 00378729653, 00555905058, 00555905079, 54569582600, 54868474200, 00603751201, 00603751217, 00603751249, 51285012058, 54868473100, 00555904358, 00555904379, 50090248100, 54868475400, 50102015401, 50102015403, 50102025421, 50102025423, 00052026108, 54868386300, 00378728253, 00378728285, 16714036701, 16714036704, 00254203373, 00254203380, 00254203391, 00603754017, 00603754049, 54569645700,

	68180088211, 68180088213, 68180089111, 68180089113, 68180089171, 68180089173, 00781406615, 70700011384, 70700011385, 16714046401, 16714046404, 65862088728, 65862088788, 54868270100, 00093330416, 00093330428, 52544095428, 53217012728, 54569603200, 50419040901, 50419040903, 54868618300, 54868582800, 50419040701, 50419040703, 00781407515, 68180089411, 68180089413, 52544029831, 52544029841, 00378729953, 00378729985, 00378730053, 50090249400, 50090259400, 54569668800, 54569668900, 59746076342, 59746076343, 60505418301, 60505418303, 68180090211, 68180090213, 68462072029, 68462072084, 68462073329, 68462073384, 71205014428, 00093542328, 00093542358, 00093542362, 54569627200, 54868616200, 50102024021, 50102024023, 59651002928, 59651002988, 00781565615, 70700011484, 70700011485, 54569662200, 68180088611, 68180088613, 68180088671, 68180088673, 00555913167, 00555913179, 05559013179, 54569612800, 54868592200, 00781565815, 70700011584, 70700011585, 52544098228, 52544098231, 54569657600, 50419040201, 50419040203, 54569534900, 54868459000, 50419040501, 50419040503, 54569614400, 51862003603, 52544098131, 54569643400, 59651003028, 59651003085, 54868040400, 54868379000, 00378730653, 00378730753,

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