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The Effects of Co-Prescribing Anti-Epileptic Drugs and Antidepressant Medications among African Americans with Epilepsy at Grady Hospital: A Case-Crossover Study

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Behavioral Sciences and Health Education
2019

The Effects of Co-Prescribing Anti-Epileptic Drugs and Antidepressant Medications among African Americans with Epilepsy at Grady Hospital: A Case-Crossover Study

By

Courtney Lauren Schlusser
MPH Candidate, 2019

Background: People with epilepsy are likely to experience comorbid depression. To treat comorbid epilepsy and depression, patients are co-prescribed anti-epileptic drugs (AEDs) and antidepressants, which increases the risk for drug-drug interactions.

Methods: Data were obtained from medical records of African American adults with an epilepsy diagnosis who sought services at Grady Hospital. 126 patients were included in the analytic data sample who had a seizure event between 2010-2015, were prescribed an AED, and visited Grady Hospital every 90 days. A case-crossover study design was used to assess the effects of the co-prescription of antidepressants with AEDs on seizure activity. Analyses involved two generalized estimating equations (GEE) with different time periods for antidepressant medication use: 3 months and 6 weeks.

Results: Overall, nearly half of the patients were male (48%), and the majority were single (62%) with a mean age of 48 years (SD=16.5). In this sample, there is a low proportion of patients who are prescribed antidepressants (5%). The results of the GEE model suggest that the odds of having a seizure are nearly half for patients who have been co-prescribed an antidepressant with an AED for 6 weeks (OR=0.44; 95%CI: 0.42, 0.45) after adjusting for age, gender, and marital status. The odds of seizure activity further decrease for those who have been co-prescribed the medications for 3 months (OR=0.39; 95%CI: 0.38, 0.40).

Conclusions: Antidepressants, when co-prescribed with AEDs, may have a protective effect on seizure activity. These results present opportunities for future research and interventions to reduce seizure frequency.

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ACKNOWLEDGEMENTS

A number of people were instrumental throughout this study. First of all, thank you to Dr. Rakale Quarrels at the Morehouse School of Medicine and the entire Project UPLIFT study team for the opportunity to contribute to our knowledge of African American people with epilepsy, and for allowing me to use their data.

I also would not have been able to conduct this study without the guidance of my thesis committee. My thesis chair, Dr. Nancy Thompson, provided expertise on the topic of epilepsy and the epidemiologic research process, as well as the guidance on how to apply the learned methodology to my thesis project. Dr. Regine Haardoerfer dedicated her valuable time and knowledge to assist me in the advanced statistical procedures to conduct the longitudinal analyses involved in this study. My pharmacoepidemiology experts, Dr. Timothy Lash and Dr. Edgar Simard contributed their expertise in the field of pharmacoepidemiology, allowing me to create a thesis project rooted in methodological rigor. I feel incredibly lucky to have had such committed, invested, and caring mentors throughout my graduate experience. Thank you, all, for your careful and constructive feedback, and for your continual affirmation throughout this process.

Thank you also to all of my friends, family, and partner, Dan, for your encouragement and support throughout this process. It has been instrumental in giving me the confidence to carry out this thesis project in its entirety. I greatly appreciate your patience during the long hours I have dedicated to this study. Your support of my goals has been invaluable. Finally, thank you to Adaline. I could not have completed this project without you.

TABLE OF CONTENTS

INTRODUCTION

Epilepsy, a disease in which a person is predisposed to recurrent, unprovoked seizures, affects nearly one in sixty-one people in the United States (American Epilepsy Society, 2018). A seizure occurs when electrical signals become abnormal or excessive in brain cells (American Epilepsy Society, 2018). The symptoms of seizures vary in each person with epilepsy. Some common symptoms are loss of awareness, mental confusion, speech impairment, and numbness (American Epilepsy Society, 2018). The incidence of epilepsy is highest among children and older adults (American Epilepsy Society, 2018). The number of adults in the United States with epilepsy has increased from 2.3 million in 2010 to 3 million in 2015 (Centers for Disease Control and Prevention, 2017). Epilepsy can be caused by a variety of factors, including head trauma, stroke, brain tumor, drug effects, genetics, and metabolic disturbances (American Epilepsy Society, 2018).

Epilepsy is costly, complex, and can lead to early death if not treated properly (Centers for Disease Control and Prevention, 2017). The primary, most effective treatment to control epilepsy is anti-seizure medication, or antiepileptic drugs (AEDs) (American Epilepsy Society, 2018). AEDs do not address the underlying condition of epilepsy but decrease the frequency and severity of seizures while treating their symptoms (Bromfield, 2006). The goal of AEDs is to improve the quality of life of a person with epilepsy, while reducing seizures and adverse drug effects (Bromfield, 2006).

Among people with epilepsy (PWE), comorbid depression and anxiety disorders have been reported in recent epidemiological studies (Kwon & Park, 2014). It is estimated that a range from 9 to 37% of PWE suffer from major depression disorder (MDD), which is a higher proportion than people without epilepsy, which is a prevalence

of 6-19% (Gaitatzis, Trimble, & Sander, 2004; Kwon & Park, 2014). MDD is the most frequently occurring comorbid psychiatric disorder in PWE (Kwon & Park, 2014). It is associated with suicide, suicidal ideation, and stigmatization in PWE (Jones, Hermann, Barry, et al., 2003). Additionally, MDD has been associated with increased adverse events in response to AEDs among PWE, such as poor medication adherence (Kanner, Barry, Gilliam, Hermann, & Meador, 2012). The high prevalence of MDD among PWE is important to recognize because the psychiatric and clinical effects of MDD can impair the quality of life of PWE (Kwon & Park, 2014).

The symptoms of MDD can vary by their temporal relationship with epileptic seizures (Kwon & Park, 2014). Before the seizure occurs, a common symptom of MDD is dysphoric mood (Blanchet & Frommer, 1986). After the seizure, common symptoms include poor frustration tolerance, loss of interest or pleasure, helplessness, irritability, feelings of self-deprecation, feelings of guilt, crying bouts, and hopelessness, which all lead to a decrease in overall quality of life among PWE (Kanner et al., 2004). In addition to poor quality of life, the effects of MDD on PWE include suicidality, stigmatization, and adverse effects of AEDs (Kwon & Park, 2014). Among PWE, the lifetime prevalence of suicidal ideation is higher than the prevalence among people without epilepsy; in particular PWE with MDD had a 32-fold higher risk of completed suicide compared to those without epilepsy with MDD (Kwon & Park, 2013).

Due to the high prevalence and serious effects of MDD among PWE, antidepressant medications are frequently co-prescribed with AEDs (Spina, Pisani & de Leon, 2016). Unfortunately, drug-drug interactions may occur when two or more drugs cause a reaction with each other, resulting in unexpected side effects (U.S. Food and

Drug Administration, 2013). Drug-drug interactions can produce variable effects or no effect on the clinical state of patients. Some possible consequences of drug-drug interactions include changes in the duration or intensity of the desired effect, emergence of a new adverse effect, or worsening of an existing adverse effect (DeVane, 2000). While the drug-drug interactions between AEDs and antidepressants have not been well studied, they are likely to be clinically relevant (Italiano, Spina & de Leon, 2014). Known symptoms and side effects of the co-prescription of AEDs and antidepressants include weight gain, increased seizure activity, insomnia, nausea and vomiting, hypertension and tachycardia, hyperlipidemia, adverse sexual effects, osteoporosis, heart arrhythmias, and liver injury (Italiano et al., 2014). It is essential for clinicians to be aware of the potential drug-drug interactions between AEDs and antidepressants because they could lead to decreased efficacy or enhanced toxicity of one or both of the administered medications (Italiano et al., 2014). Furthermore, the adverse effects of AEDs are among the main reasons for discontinuation of epileptic medications (Kwon & Park, 2014), and PWE with MDD have a higher risk of discontinuing their AEDs compared to PWE without MDD (Kanner et al., 2012). Likewise, adverse effects are a barrier to adherence to antidepressant medication as well (Kwon & Park, 2014).

This study is informed by the PRECEDE-PROCEED planning model and aims to understand the effects on seizure activity of the co-prescription of AEDs and antidepressants among PWE. The PRECEDE-PROCEED model is a theoretical model that aims to promote healthy behaviors and attitudes as a way to prevent illness and improve quality of life. These behaviors are thought to be a participatory process that involves all stakeholders, in this case the PWE co-prescribed AEDs and antidepressants

and their clinicians who are prescribing the medications. PRECEDE and PROCEED are both acronyms. PRECEDE stands for Predisposing, Reinforcing, and Enabling Constructs in Educational/Environmental Diagnosis and Evaluation (Glanz, Rimer, & Viswanath, 2015); this represents the process that leads up to an intervention. PROCEED stands for Policy, Regulatory, and Organizational Constructs in Educational and Environmental Developments, and describes how to proceed with the intervention itself.

This study is based in the PRECEDE portion of the model, the events that provide the background for intervention development. This study is not based on the PROCEED portion of the model because no intervention has been developed that could be implemented and evaluated. There are five phases of PRECEDE: Social Assessment, Epidemiological Assessment, Behavioral/Environmental Assessment, Educational/Ecological Assessment, and Administrative/Policy Assessment. The current investigation is rooted in an epidemiological assessment and behavioral/environmental assessment of the prescription of antidepressant medications in combination with AEDs. The ultimate purpose of this study is to explore the possible adverse effects and efficacy associated with the co-prescription of AEDs and antidepressants.

The theoretical approach embedded within the PPM provides a useful framework to understand the focused outcome of examining drug-drug interactions resulting from the co-administration of AEDs and antidepressants. Using logistic regression, this study longitudinally examines the effects on seizure activity associated with the co-administration of AEDs and antidepressants among PWE. This study evaluates the hypothesis that PWE who are co-prescribed antidepressants and AEDs have different rates of seizure activity compared to those who are prescribed AEDs alone.

LITERATURE REVIEW

Major Depression Disorder Prevalence in People with Epilepsy

Epilepsy and MDD have a bidirectional relationship in terms of pathophysiology and MDD has a higher prevalence in people with epilepsy compared to the general population in the United States (Kanner et al., 2009; Kwon & Park, 2014). MDD in PWE has a negative impact on the treatment of epilepsy and adversely affects quality of life by inducing fatigue, irritability, aggression, and stress (Kim, Kim, Kim, Yang, & Kwon, 2018). Among PWE, the prevalence of MDD ranges from nine to thirty-seven percent, which is higher than the prevalence of MDD in the general population, seven percent (Kwon & Park, 2014).

The prevalence of MDD in PWE differs significantly between men and women, with a point prevalence of 26% among female PWE and 17% among male PWE (Kim et al., 2018). There is a similar pattern among people without epilepsy, with women having a 2-fold risk of MDD compared to men (Kessler, 2003). There may be several reasons why MDD is more frequent among females than males. The female hormonal environment could be a contributing factor to increased frequency, and females may be more forthcoming in reporting depressive symptoms (Jung, Shin & Kang, 2015; Kim et al., 2018).

Comorbid MDD may negatively impact the treatment outcomes in patients with epilepsy because MDD before the onset of epilepsy is associated with the development of resistance to AEDs (Kim et al., 2018). Adverse events associated with AEDs may also be increased by comorbid MDD (Kim et al., 2018). These adverse events also play a role in medication adherence. The negative effect of MDD on AED adherence leads to poorly

controlled epilepsy and increased risk of sudden unexpected death in epilepsy (Jamal-Omidi, Collins, Fulchiero, Liu, Colon-Zimmermann, Fuentes-Casiano, & Sajatovic, 2018). Additionally, MDD has a reciprocal relationship with the frequency of seizures among PWE (Jamal-Omidi et al., 2018). Specifically, seizure frequency is correlated with depression and anxiety levels, so when depression is reduced through the use of antidepressant medications, seizure frequency is therefore reduced (Dehn, Pfafflin, Bruckner, Lutz, Steinhoff, Mayer, Bien, Nussbeck, and May, 2017). Comorbid MDD also impacts other aspects of epilepsy in PWE, causing increased suicidality and increased perceived stigma (Kwon & Park, 2013).

Epilepsy Treatment

Treatments for epilepsy include surgery, vagus nerve stimulation, ketogenic diet, and deep brain stimulation (Italiano et al., 2014). However, antiepileptic drugs are the most common treatment for epilepsy (Italiano et al., 2014). In addition to the treatment of epilepsy, AEDs are also prescribed for managing other non-epileptic and psychiatric conditions (Johannessen, Larsson, Rytter, & Johannessen, 2009). In general, AEDs are divided into two classes: older generation and new generation compounds (Italiano et al., 2014). Compared to the older generation AEDs, the new generation drugs have a wider therapeutic index, a more favorable tolerability and safety profile, and a lower potential for drug-drug interactions (Italiano et al., 2014). For these reasons, newer AEDs have partially replaced the older compounds in the developed world (Marson, Al-Kharusi, Alwaidh, Appleon, Baker, & Chadwick, 2007). The most commonly prescribed new generation AEDs are lamotrigine, levetiracetam, and oxycarbaxepine; valproate is the

only older generation agent still prescribed as a first-line drug in males and non-fertile females (Italiano et al., 2014; Marson et al., 2007)

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics is a quantitative description of what happens to a medication when it enters the body, including its absorption, distribution, metabolism, and elimination (Bromfield, 2006). Drug absorption is determined by the route of intake, which for AEDs and antidepressants is most commonly through oral administration. Once a drug has been metabolized into the bloodstream, it is distributed throughout the body and begins metabolism. Most AEDs are metabolized in the liver; however, some AEDs undergo no metabolism and are excreted unchanged by the kidney. Most antidepressants are also metabolized into active metabolites via the liver (Telles-Correia, Barbosa, Cortez-Pinto, Campos, Rocha, & Machado, 2017). Most drugs, including most AEDs and antidepressants, are eliminated renally (Bromfield, 2006).

Pharmacodynamics refers to the relationship between drug concentration at the site of action and the resulting effect of the drug (American Society of Health-System Pharmacists, 2018). These effects can include the time course and intensity of therapeutic effects, as well as possible adverse effects of the drug (American Society of Health-System Pharmacists, 2018). The effect of a drug at the site of action is determined by the drug's binding with a specific receptor, which for AEDs and antidepressants are located on neurons within the central nervous system (American Society of Health-System Pharmacists, 2018). The intensity of the effect of AEDs and antidepressants is determined by the concentration of the drug at the site of the receptors within the central nervous system (American Society of Health-System Pharmacists, 2018).

Pharmacokinetics of Antiepileptic Drugs

The principal determinant of the pharmacokinetic properties of most AEDs is enzymatic biotransformation, though some drugs are excreted by the kidneys unchanged. Most AEDs undergo linear enzyme kinetics, which causes changes in daily dose to lead to proportional changes in the serum concentration that is absorbed by the liver. It is essential to understand and apply the pharmacokinetics of AEDs, as the therapeutic ranges help to guide drug administration to control seizures without causing intolerable toxicity. Many AEDs have the potential to be involved in pharmacokinetic drug interactions when they are co-prescribed with other AEDs or other medications. The pharmacokinetic interactions of AEDs tend to involve changes in the rate of biotransformation or in the protein binding of one or both co-prescribed drugs (Browne, 1998).

Pharmacologic Therapies for Major Depression Disorder

There are currently four main classes of antidepressants available to patients with major depressive disorder (Italiano et al., 2014). The four classes include the older, more classic agents such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), and the newer antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). There are also other antidepressants with varying mechanisms of action (Stahl, 2013). Currently, newer antidepressants, particularly SSRIs, have become the most commonly prescribed antidepressants for the management of depressive disorders, due to their improved tolerability and safety profile as compared to older classes of antidepressants (Italiano et al., 2014). Antidepressants, like AEDs, are also widely used for the treatment of other

psychiatric conditions, including anxiety disorders, obsessive-compulsive disorder, eating disorders, and various forms of chronic pain (Stahl, 2013).

Pharmacokinetics of Antidepressants

This study will focus on newer classes of antidepressants, SSRIs and SNRIs, because they are more commonly prescribed than the older classes of antidepressants. Newer antidepressants are diverse in their pharmacokinetic properties. The SSRIs have elimination half-lives of 15-26 hours, with extended half-lives of four to six days. The long half-lives of SSRIs result in a prolonged washout period after the medications are discontinued. Most SSRIs are administered as a single daily dose, though some SSRIs and SNRIs have shorter half-lives of two to five hours and need to be dosed at least twice per day. Due to the safer toxicity profile of newer antidepressants compared to TCAs, the variability in clearance is of less importance to clinicians (DeVane, 1994).

Drug-Drug Interactions between Antiepileptic Drugs and Antidepressants

Due to the high prevalence of MDD among PWE, antidepressants and AEDs are often prescribed together in patients with both disorders (Italiano et al., 2014). Approximately 58% of PWE with comorbid MDD are co-prescribed both medications (Harden & Goldstein, 2002). Considering the frequent co-prescription of AEDs and antidepressants, it is critical for clinicians to be aware of possible drug interactions between the two compounds. The consequences of a drug interaction can be either beneficial or harmful. The interactions could result in increased therapeutic efficacy or in reduced risks of adverse drug reactions, or the drugs could interact to lead to decreased efficacy or enhanced toxicity or one or both of the medications (Italiano et al., 2014).

Drug interactions can be classified into two main categories, pharmacokinetic interactions and pharmacodynamic interactions.

Pharmacokinetic Drug-Drug Interactions

Pharmacokinetic drug interactions consist of changes in the absorption, distribution, metabolism, or excretion of a drug or its metabolite after being co-administered with another drug (Italiano et al., 2014). No clinically relevant drug-drug interaction has been described so far during the absorption phase or at protein binding between AEDs and antidepressants (DeVane, 2002; Spina, 2009). The majority of important pharmacokinetic drug interactions between AEDs and antidepressant medications occur at a metabolic level and it is hypothesized that these occur for two possible reasons: (1) both AEDs and antidepressants are metabolized by the same enzymes, and (2) AEDs act as inhibitors or inducers for other drug metabolizing pathways (Italiano et al., 2014). Some of the newer antidepressants also act as inhibitors for various metabolic pathways, and may impair the elimination or AEDs (Nemeroff, Preskorn, & DeVane, 2007).

As noted, pharmacokinetic drug interactions can occur during the excretion phase, as well. Most AEDs are metabolized through the kidneys, then later excreted by the kidneys (Italiano et al., 2014). Pharmacokinetic drug interactions between AEDs and antidepressants may also involve drug transporters that play roles in the absorption, distribution, and excretion of medications (Lin, 2007).

Pharmacodynamic Drug-Drug Interactions

Pharmacodynamic drug interactions result in a modification of the pharmacological action of a drug by a direct effect on its site of action. These drug

interactions occur without any changes in the plasma concentration within the body and are, therefore, more difficult to recognize and quantify than pharmacokinetic drug interactions. Pharmacodynamic drug interactions can involve beneficial effects or harmful effects (Italiano et al., 2014). The pharmacodynamics of AEDs and antidepressants, when acting alone, are described below.

The pharmacodynamics of AEDs varies for each use (e.g., epilepsy, bipolar disorder, anxiety, pain). As an antiepileptic, AEDs decrease the activity of voltage-dependent sodium channels, decrease the activity of voltage-dependent calcium channels, increase GABA neurotransmission, and decrease glutamatergic neurotransmission. The complex of AEDs binds to a synaptic vesicle protein, which enhances the activity of the slow voltage-gated potassium channels. There are also various safety concerns of the pharmacodynamics of AEDs. Common concerns of AEDs include sedation, cognitive impairment, depression, visual field defects, weight gain, nausea and vomiting, hyponatremia, and coagulation impairment. Some uncommon safety concerns of AED pharmacodynamics include paradoxical seizures, abuse, psychosis, aggressive behavior, encephalopathy, movement disorders, urinary retention, and leukopenia. Rare concerns of AED pharmacodynamics include sudden cardiac death, liver injury, risk for heat stroke, and pancreatitis (Italiano et al., 2014).

The mechanisms of action for antidepressants also vary by the disorders for which they are prescribed, including depression, obsessive compulsive disorder, anxiety, pain, and weight loss (Italiano et al., 2014). The majority of antidepressants act by inhibiting reuptake transporters to elicit the antidepressant response (Stahl, 2013). To treat MDD, antidepressants act as inhibitors of noradrenaline and serotonin transporter, inhibitors of

the serotonin transporter and serotonin receptor antagonists, as well as agonists and antagonists for certain receptors. Similar to AEDs, there are various pharmacodynamic safety concerns associated with antidepressants. Common safety concerns of antidepressants include weight gain, nausea and vomiting, diarrhea, sexual effects, insomnia, hyperlipidemia, osteoporosis, liver injury, and heart arrhythmias. Uncommon safety concerns related to the pharmacodynamics of antidepressants include hyperhidrosis, mydriasis, urinary symptoms, hypotension, hypertension, and decreased seizure threshold. Rare concerns of the pharmacodynamics of antidepressants include psychotic exacerbation, risk for bleeding, serotonin syndrome, neutropenia, and hyponatremia (Italiano et al., 2014).

Specific Pharmacokinetic Drug-Drug Interactions between Antiepileptic Drugs and Antidepressants

The new generation AEDs may induce antidepressant metabolism because they are powerful inducers of various drug-metabolizing enzymes (Italiano et al., 2014). When co-prescribed with antidepressants, enzyme-inducing AEDs are associated with a decrease in concentration of the antidepressants (Spina & Perucca, 2002). Some newer antidepressants, including SSRIs, have been found to decrease the concentration of AEDs when co-administered (Greb, Buscher, Dierdorf, Koster, Wolf, & Mellows, 1989). Compared to the new generation AEDs, older generation AEDs are less likely to cause drug interactions (Italiano et al., 2014).

While some AEDs may cause changes in the concentration levels of antidepressants, there is also evidence that antidepressants can affect the concentration levels of certain AEDs. The concurrent use of newer antidepressants, SSRIs and SNRIs,

and AEDs has resulted in significant increases in the concentration levels of the AED metabolites, leading to toxicity (Jalil, 1992). One explanation for this drug interaction is that antidepressants impair the elimination of AEDs, causing the concentrations to increase to toxic levels (Italiano et al., 2014).

Specific Pharmacodynamic Drug-Drug Interactions between Antiepileptic Drugs and Antidepressants

There is limited literature that supports the theory that the co-administration of AEDs and antidepressants may increase efficacy, resulting in synergistic effects for the treatment of MDD and epilepsy. Some studies have shown that AEDs have beneficial effects in treatment-resistant MDD, specifically major depression disorder, in that they reduce irritability or agitation (Vigo & Baldessarini, 2009).

There is also limited literature to support the theory that AEDs and antidepressants result in decreased efficacy when they are co-administered. In patients with bipolar disorder, the combination of AEDs and antidepressants has resulted in a decrease in the mood-stabilizing properties of antidepressants (Kohler, Gaus, & Bschor, 2014). MDD has been a commonly reported adverse effect of AEDs, so it is pharmacologically reasonable to assume that some AEDs have the ability to decrease, or even eliminate, the antidepressant effects in patients co-prescribed AEDs and antidepressants for the treatment of MDD (Italiano et al., 2014). Some studies have also found that the co-administration of AEDs and older antidepressants, mainly TCAs, results in a decreased seizure threshold and has even been associated with seizures in patients without a medical history of epilepsy (Koster, Grohmann, Engel, Nitsche,

Ruther, & Degner, 2013). For this reason, TCAs should not be co-prescribed to PWE with poor seizure control, as they can decrease the efficacy of AEDs.

Health Disparities

Recently, there has been attention on the health disparities surrounding epilepsy and epilepsy care. The incidence of epilepsy has been shown to be higher in African Americans, compared to Caucasians, and mortality from epilepsy is significantly higher among non-Caucasians in the United States (Chandra, Bharucha, & Schoenberg, 2003; Hussain, Haut, Lipton, Derby, Markowitz, & Shinnar, 2006). While the disease, itself, may be the cause of these health disparities, socioeconomic factors, such as decreased financial resources, contribute to poor epilepsy care (Paschal, Ablah, Wetta-Hall, Molgaard, & Liow, 2005). Another important health disparity lies in the area of medication adherence. African Americans with epilepsy have been shown to have more resistance to using prescription drugs, as well as having poorer medication adherence, when compared to Caucasians (Bautista & Jain, 2011; Horne & Weinman, 1999).

There are also important sociodemographic health disparities surrounding patients with epilepsy in terms of frequency of care visits, as well as where patients receive care (Begley, Basu, Reynolds, Lairson, Dubinsky, Newmark, & Shih, 2009). With respect to hospital care, a study by the U.S. Centers for Disease Control and Prevention indicated that the rate of hospitalization for minority race/ethnic groups was higher than whites, however the rate of specialist and regular physician visits was significantly lower (CDC, 1995). This difference in the standards of epilepsy care means that African Americans are more likely to be diagnosed in an emergency room and other nonspecialized settings,

which increases their chances of receiving suboptimal care (Begley et al., 2009; Hope, Zeber, Kressin, Bokhour, VanCott, Cramer, & Pugh, 2009)

Theoretical Model

The PRECEDE-PROCEED model (PPM) of health program planning provides a framework for health program planning and evaluation aimed at behavior change (Ashwell & Barclay, 2009). The PPM framework uses a series of diagnostic steps for health program planning (phases 1-3) that lead to implementation and evaluation (phases 4-8). **Figure 1** is a diagram representing the general theory behind the PPM. This study will focus on the first three phases, specifically phase 3, to describe health program planning, and it will inform future studies for implementation and evaluation.

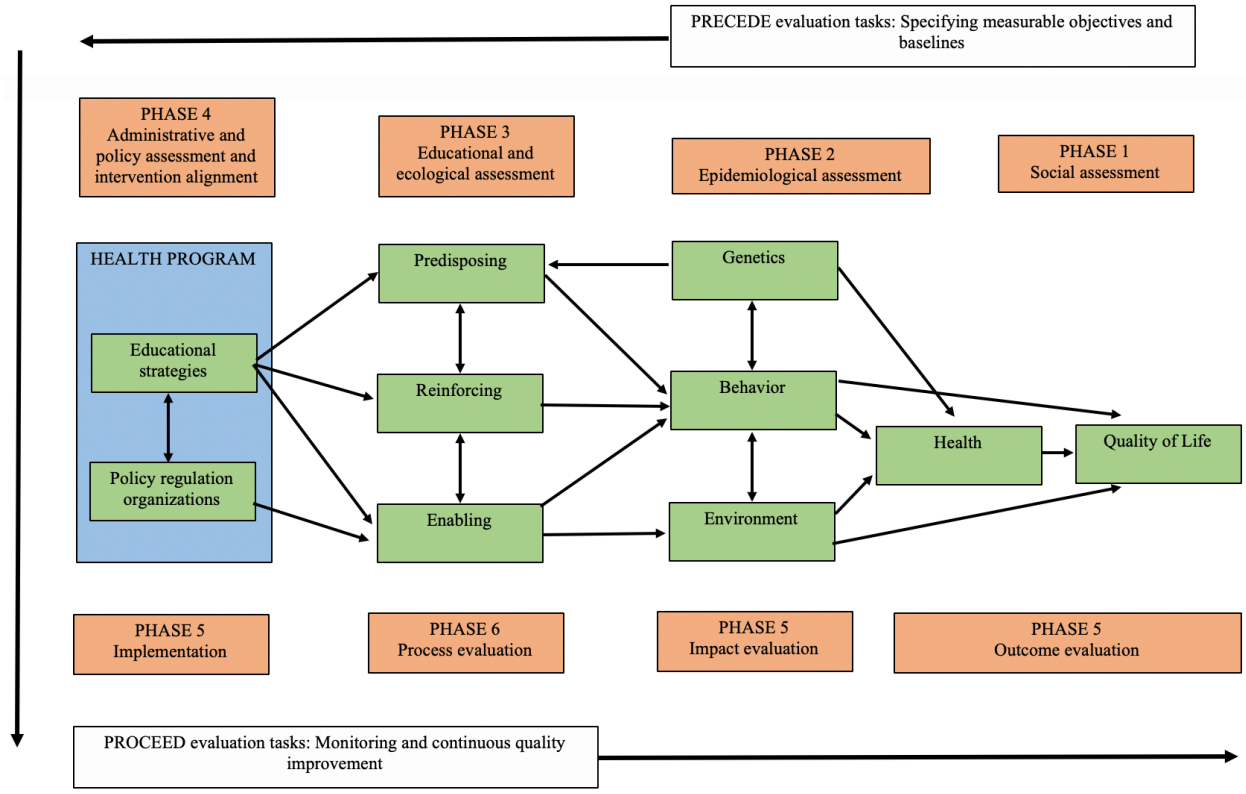

Figure 1. A generic representation of the PRECEDE-PROCEED model, as described by L. Green and M. Kreuter. (2005).

Phase 1 of the PPM is a social assessment of the issue, which relates to quality of life and health outcomes of the drug-drug interactions between AEDs and antidepressants. As noted earlier, PWE experience high rates of MDD, which is a quality of life concern (Ettinger, Good, Manjunath, Faught, & Bancroft, 2014; Loring, Meador, & Lee, 2004). Symptoms of MDD and worrying about having a seizure are the most important factors affecting quality of life among PWE (Loring et al., 2014). Additionally, PWE with MDD have reported increased seizure activity (Ettinger et al., 2004). The impact of MDD is also a determinant of AED adherence among PWE, where PWE with MDD are at an increased risk of AED nonadherence (Ettinger et al., 2004).

The second phase of the PPM includes an epidemiological assessment that explores how MDD has been shown to have both a direct effect on quality of life, and an indirect effect, both of which affect adherence to AEDs and antidepressants. MDD is more prevalent in epilepsy in comparison to other chronic medical conditions (Mula & Schmitz, 2009). A large US survey investigated MDD in a large sample of patients with epilepsy, comparing the prevalence rates of MDD with those of patients with asthma and healthy controls (Ettinger et al., 2004). This study demonstrated that symptoms of MDD are significantly more frequent in the epilepsy group, compared to those with asthma and healthy controls (Ettinger et al., 2004). It has also been suggested that, in select patient populations, MDD could be related to the recurrence of seizures (Jacoby, Baker, Steen, Potts, & Chadwick, 1996). It is common practice to co-prescribe AEDs and antidepressants in this population; however, AEDs may have negative effects on mood and behavior, leading to non-adherence of both medications (Mula & Schmitz, 2007; Zullino, Khazaal, Hattenschwiler, Borgeat, & Besson, 2004).

Phase 2 of the PPM also includes a behavioral and environmental assessment of determinants leading to drug-drug interactions of AEDs and antidepressants. An important environmental determinant is the co-prescription of AEDs and antidepressant medication as a solution to the high rates of MDD among PWE (Mula & Schmitz, 2009). The behavioral assessment finds that the side effects of AEDs and antidepressants have been shown to influence non-adherence behavior to both medications (Getnet, Woldeyohannes, Bekana, Mekonen, Fekadu, Menberu, Yimer, Assave, Belete & Belete, 2016; Ho, Jacob, & Tangiisuran, 2017; Murata, Kanbayashi, Shimizu, & Miura, 2012). Furthermore, the patient lack of belief in the benefit of the treatment, as well as the actual efficacy of the drugs, have been shown to relate to adherence to both AEDs and antidepressant medications (Conrad, 1985; Martin-Vazquez, 2016; Osterberg & Blaschke, 2005).

The third phase of the PPM includes the educational assessment. This phase includes causal factors that influence health behavior, which are classified as predisposing, reinforcing, and enabling factors (Green & Kreuter, 2005). This phase will be the main focus of the current study to understand if the co-prescription of AEDs and antidepressant medications predispose PWE to adverse health outcomes. There is a current gap in the literature to examine the adverse health outcomes associated with the co-prescription of AEDs and antidepressant drugs, so little is known about the potential changes in efficacy or side effects to PWE with concurrent MDD. There is also little research that explores the effects of non-adherence in the co-prescription of AEDs and antidepressants. This study will examine the determinants of PWE that are co-prescribed

AEDs and antidepressant medications to explore potential health effects, specifically differential seizure activity, to fill the gap in the literature.

METHODS

Patients

Data were obtained from medical records of African American adults with an epilepsy diagnosis who sought services at a large, urban, public hospital in the southeastern United States between 2010 and 2015. The research protocol was approved by the Emory University Institutional Review Board prior to study initiation (IRB# 00103748). The original dataset consisted of 25,865 patients. The sample (n=126) consisted of African American patients with regular (3-month) physician visits who had a reported seizure in their medical records and were prescribed an AED.

Study Site

The research team obtained the data for this study from Grady Memorial Hospital, in Atlanta, GA. Grady Hospital is the largest hospital in the city of Atlanta, and the fifth-largest public hospital in the United States ("Grady Memorial Hospital," 2017). This hospital serves a large proportion of low-income patients and provides services to those with private insurance, public insurance, and those who are uninsured ("Grady Memorial Hospital," 2017). Grady Hospital is one of the busiest Level I trauma centers in the United States, making it an ideal place for patients experiencing seizures to report.

Sample Size

Of the 25,865 patients in the total dataset, 19,905 patients were excluded from analyses for a lack of seizure event, ICD-9 780.39. From the selection of 5,960 patients with a seizure event, another 2,377 were excluded from the study sample because they were not prescribed any AEDs in their medical records. Next, patients were excluded if they did not have physician visits every three months. The final sample of patients

included in the analyses was 126 patients. **Figure 4** is Consort flow diagram explaining the process of analytic sample selection (Falci & Marques, 2015).

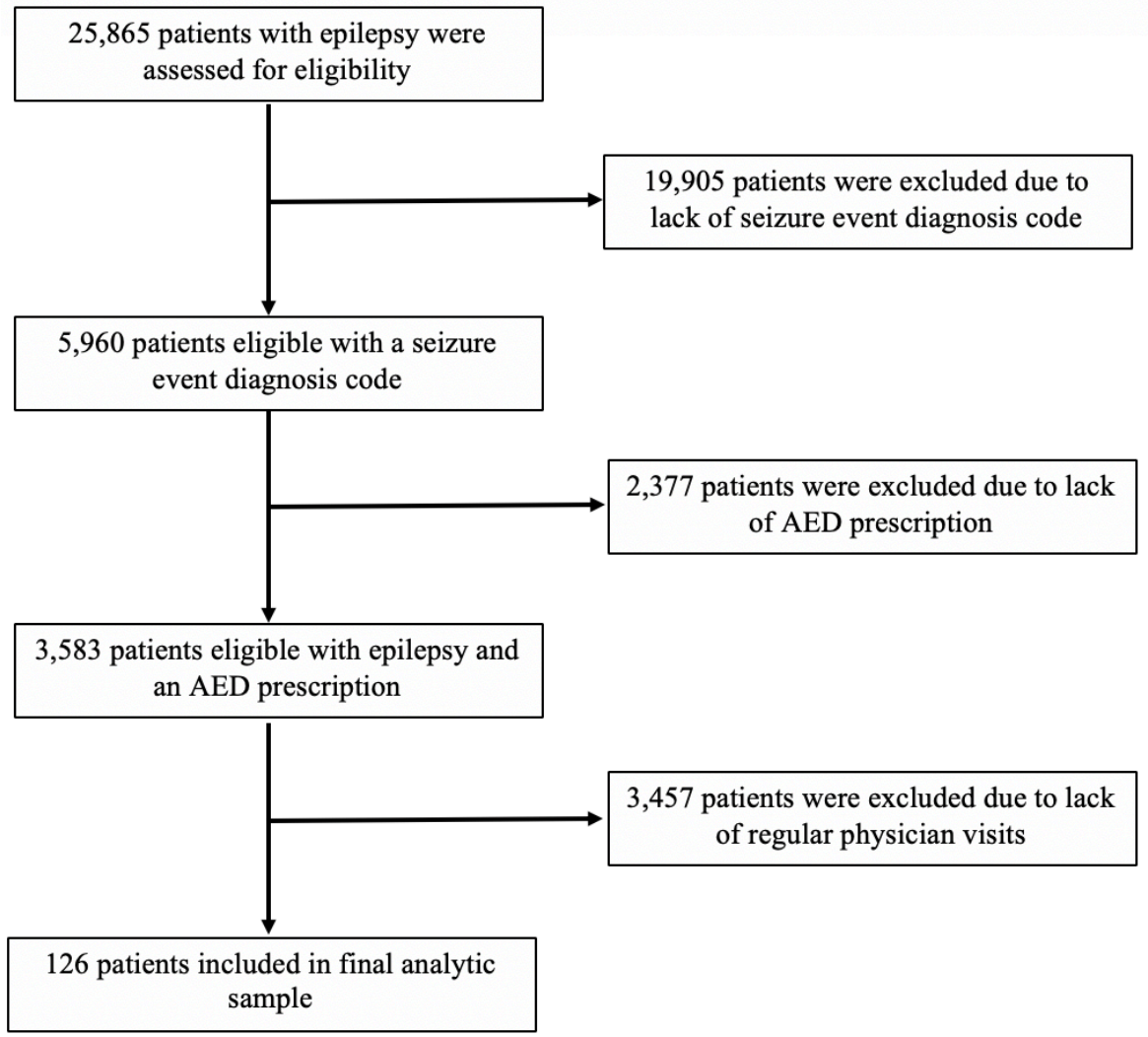

Figure 4. The flow diagram to represent how patients were selected as eligible cases for this case-crossover analysis.

Participant Selection

Patients were included in the analysis if they were over the age of 18, had an epilepsy diagnosis in their medical records between November 1, 2010 through October 5, 2015, indicated by the ICD-9 code for epilepsy, 345, and were prescribed an AED. Further selection of patients included evidence of a reported seizure in their medical

records, indicated by the ICD-9 code for a seizure event, 780.39. All patients had at least one seizure event for the case-crossover study design, since cases served as their own controls.

Exclusion Criteria

Patients were excluded from the study if they did not have a repeat medical encounter within 15 months. Patients were further excluded from the study if those prescribed antidepressant medications did not have repeat medical encounters every three months to indicate that they are consistently refilling their antidepressant prescription.

Study Design

This study utilized a case-crossover study design. This study design is a novel approach because the case serves as his/her own control and is used to investigate the effects of a transient exposure on the onset of an acute outcome (Maclure, 1991). This study design is often compared to the case-control study design, but there are several differences. The evaluation of transient versus fixed risk factors and the comparison of the exposure at the time of the event to within-person control periods rather than to the same period across individuals (resulting in separate controls) (Lombardi, 2010). In the field of pharmacoepidemiology, the case-crossover design is a more efficient approach than a case-control study because the design largely avoids the biasing effects of unmeasured, time-invariant confounding factors (Delaney & Suissa, 2009).

This study design was selected to evaluate the possible effect of drug-drug interactions among patients who are co-prescribed AEDs and antidepressant medications on seizure activity. This study design was selected due to several methodological challenges, affecting other possible designs. For instance, the study dataset lacked

information measuring how long patients were prescribed medications, making it difficult to determine when patients should enter an analytic cohort. For this reason, it was concluded that the best way to control for possible confounding factors would be to compare the cases with themselves (to have them serve as their own controls).

Another challenge was to select appropriate control periods where the exposure distribution (co-prescription of AEDs and antidepressant medications) best represented the exposure distribution among cases (seizure activity) during their time at-risk. The research team established two control periods, 3-6 months and 6-9 months preceding the first seizure event. These control periods were compared to the risk period, 0-3 months prior to the first seizure event. The first model used those time periods for antidepressant comparison, as shown in **Figure 2**. In the second model, the risk period and two control periods remained the same, however they used a 6-week long antidepressant medication prescription, rather than the entire risk and control window time (3 months), as shown in **Figure 3**.These windows were chosen because the 6-week medication use period accounts for normal adjustment to the medication, and the three-month control periods preceding the first seizure event accounts for persons who are regularly refilling their medications at the doctor's office. Both of these time points were established after conducting the literature search.

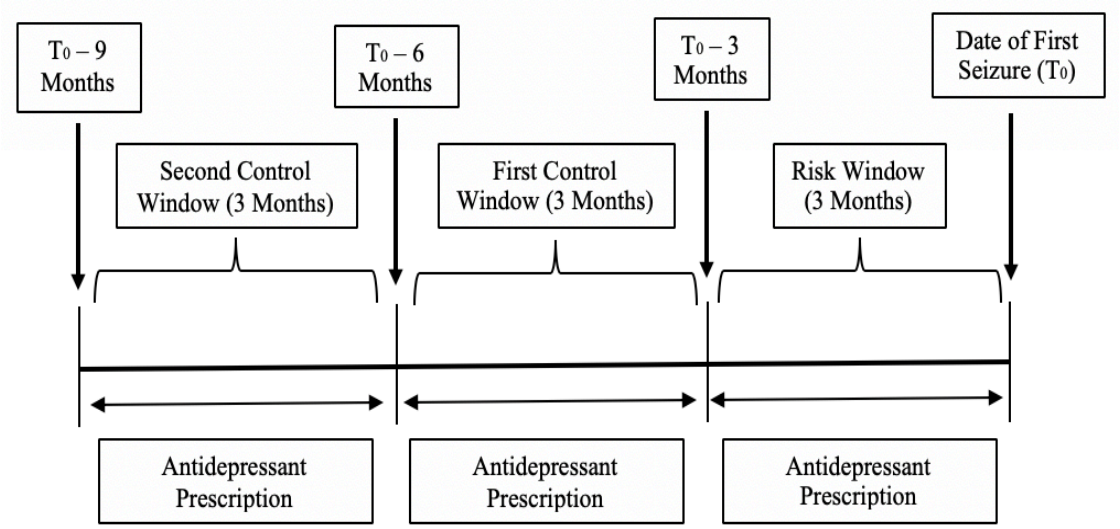

Figure 2. The case-crossover study design used in the first model of this study. The event occurs at an index date (T_0) and the periods for assessing the exposure are dependent on the width of the time window (W). Each subject has the possibility to be exposed during the risk window and each of the control windows with a 3-month antidepressant medication prescription.

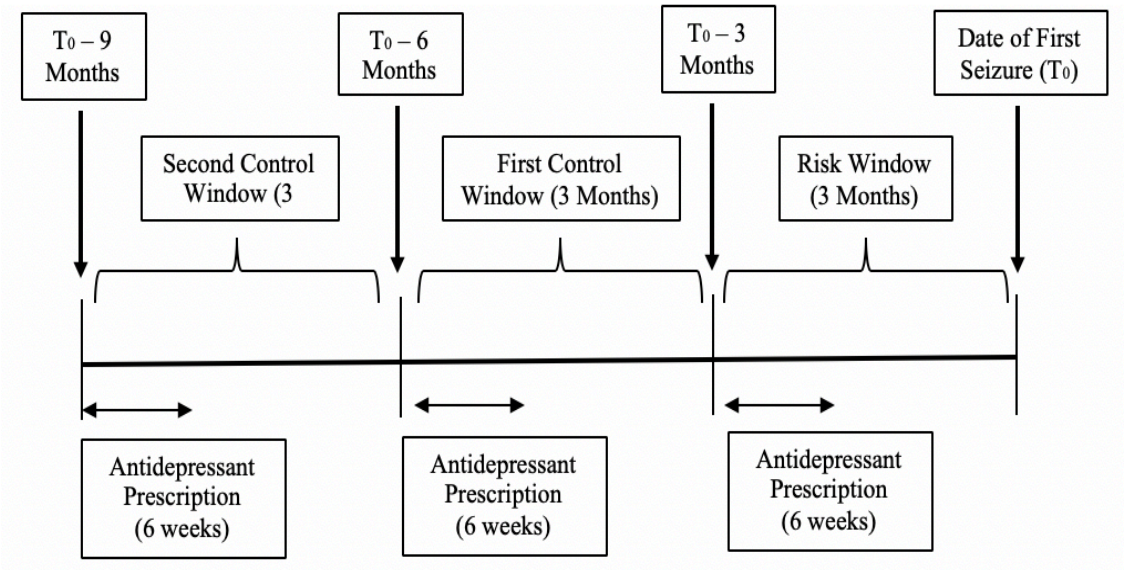

Figure 3. The case-crossover study design used in the second model of this study. The event occurs at an index date (T_0) and the periods for assessing the exposure are dependent on the width of the time window (W). Each subject has the possibility to be exposed during the risk window and each of the control widows with a 6-week antidepressant medication prescription.

Measures

Case and Control Time Periods

For this case-crossover study, case status is defined in time windows that are based on the date of the first seizure, as coded by ICD-9 code 780.39. The risk window extends from the date of the most recent seizure to the date 3 months preceding the seizure event. There will be two control time windows, which will be compared to the risk window. The first control time window extends from 3 months and one day preceding the seizure to 6 months preceding the seizure. The second control time window extends from 6 months and one day preceding the seizure to 9 months preceding the seizure. The 3 months between each window represents the time between regular physician visits for prescription refills. Because the data lacked access to prescription refill records, regular physician appointments were used to reduce bias, with the assumption that those persons regularly visiting their physicians are regularly refilling their prescription medications.

Exposure

All patients in this study were prescribed AEDs. Exposure was defined as a prescription to an antidepressant medication, in addition to the prescription of the AED.

Anti-Epileptic Drugs

The selection of AEDs that deemed a subject eligible for inclusion in the study were selected from a list of AEDs found on the Epilepsy Foundation website (Epilepsy Foundation, 2018). Patients were included in the study sample if they were prescribed either a brand name or generic brand of the identified medications. AEDs were then categorized into three classifications: category 1, category 2, and category 3. Category 1

represents those medications that act on ion channels; category 2 are the AEDs that enhance gamma-Aminobutyric transmission; and category 3 medications inhibit excitatory amino acid transmission. **Table 1**, Anti-Epileptic Drugs, represents the AEDs that were included in this study sample.

Table 1. Anti-Epileptic Drugs

ANTI-EPILEPTIC DRUGS		
Generic Name	**Brand Name(s)**	**Classification**
Acetazolamide		Category 3***
Brivaracetam	Briviact	Category 3
Carbamazepine	Carbagen Tegretol Tegretol Prolonged Release	Category 1*
Clobazam	Frisium Perizam Tapclob Zacco	Category 2**
Clonazepam		Category 2
Eslicarbazepine acetate	Zebinix	Category 2
Ethosuximide		Category 3
Gabapentin	Neurontin	Category 3
Lacosamide	Vimpat	Category 3
Lamotrigine	Lamitcal	Category 2
Levetiracetam	Desitrend Keppra	Category 3
Oxcarbazepine	Trileptal	Category 2
Perampanel	Fycompa	Category 2
Phenobarbital		Category 1
Phenytoin	Epanutin Phenytoin Sodium Flynn	Category 1
Piracetam	Nootropil	Category 3
Pregabalin	Alzain Axalid Lecaent Lyrica Rewisca	Category 3
Primidone		Category 1
Rufinamide	Inovelon	Category 2
Sodium valproate	Epilim	Category 2

	Epilim Chrono Epilin Chronosphere Episenta Epival	
Stitipentol	Diacomit	Category 3
Tiagabine	Gabitril	Category 3
Topiramate	Topamax	Category 2
Valproic acid	Convulex Epilim Chrono Epilim Chronosphere	Category 3
Vigabatrin	Sabril	Category 3
Zonisamide	Zonegram	Category 2

***Category 1:** Specific measures are necessary to ensure consistent supply of a particular product. This means that individuals should not be switched between versions of these AEDs but should always be kept on the same version. Also known as the medications that act on ion channels.

****Category 2:** The need for continued supply of a particular product should be based on 'clinical judgement' and in consultation with the individual. This means that a doctor should decide, with the individual, whether it is important to always stay on the same version or whether it is ok to switch between different versions. These are the AEDs that enhance gamma-Aminobutyric (GABA) transmission.

*****Category 3:** No specific measures are normally required, and these AEDs can be prescribed generically. This means that individuals can be switched between different versions of their AEDs. These AEDS inhibit excitatory amino acid (EAA) transmission.

Antidepressant Medications

The antidepressants, whose presence with an AED constituted exposure in a risk or control time period, were selected from a list of medications whose indications include treatment for major depressive disorder on the FDA website (Food and Drug Administration, 2018). Patients were included in the study sample if they were prescribed either a brand name or generic brand of the antidepressant medications, as shown in **Table 2**, Antidepressant Medications. Antidepressants were then categorized into five classes based on their mechanism of action: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic

antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants. SSRIs are the most commonly prescribed class of antidepressants that decrease the amount of serotonin that is taken out of the brain, leaving more available to work in the brain. SNRIs reduce depressive symptoms by improving serotonin and norepinephrine levels in the brain. TCAs are not yet fully understood in their treatment of depression but are often prescribed after other categories of antidepressants have failed to reduce depressive symptoms. MAOIs treat depression by preventing the breakdown of norepinephrine, dopamine, and serotonin in the brain. Lastly, atypical antidepressants are often prescribed as a last resort if a patient fails to respond to other classifications of antidepressant medications.

Table 2: Antidepressant Medications

ANTIDEPRESSANTS		
Generic Name	**Brand Name(s)**	**Classification**
Citalopram	Celexa	Selective Serotonin Reuptake Inhibitors (SSRIS)
Escitalopram	Lexapro	Selective Serotonin Reuptake Inhibitors (SSRIS)
Fluoxetine	Prozac	Selective Serotonin Reuptake Inhibitors (SSRIS)
Fluvoxamine	Luvox	Selective Serotonin Reuptake Inhibitors (SSRIS)
Fluvoxamine CR	Luvox CR	Selective Serotonin Reuptake Inhibitors (SSRIS)
Paroxetine	Paxil	Selective Serotonin Reuptake Inhibitors (SSRIS)
Paroxetine CR	Paxil CR	Selective Serotonin Reuptake Inhibitors (SSRIS)

Sertraline	Zoloft	Selective Serotonin Reuptake Inhibitors (SSRIS)
Desvenlafaxine	Pristiq	Selective Norepinephrine Reuptake Inhibitors (SNRIS)
Duloxetine	Cymbalta	Selective Norepinephrine Reuptake Inhibitors (SNRIS)
Venlafaxine	Effexor	Selective Norepinephrine Reuptake Inhibitors (SNRIS)
Venlafaxine XR	Effexor XR	Selective Norepinephrine Reuptake Inhibitors (SNRIS)
Milnacipran	Savella	Selective Norepinephrine Reuptake Inhibitors (SNRIS)
Levomilnacipran	Fetzima	Selective Norepinephrine Reuptake Inhibitors (SNRIS)
Amitryptiline	Elavil	Tricyclic Antidepressants (TCAS)
Desipramine	Norpramin	Tricyclic Antidepressants (TCAS)
Doxepine	Sinequan	Tricyclic Antidepressants (TCAS)
Imipramine	Tofranil	Tricyclic Antidepressants (TCAS)
Nortriptyline	Pamelor	Tricyclic Antidepressants (TCAS)
Amoxapine		Tricyclic Antidepressants (TCAS)
Clomipramine	Anafranil	Tricyclic Antidepressants (TCAS)
Maprotiline	Ludiomil	Tricyclic Antidepressants (TCAS)
Trimipramine	Surmontil	Tricyclic Antidepressants (TCAS)
Protriptyline	Vivactil	Tricyclic Antidepressants (TCAS)
Phenelzine	Nardil	Monoamine Oxidase Inhibitors (MAOIS)
Selegiline	Emsam	Monoamine Oxidase Inhibitors (MAOIS)

Tranylcypromine	Parnate	Monoamine Oxidase Inhibitors (MAOIS)
Bupropion	Wellbutrin	Atypical Antidepressants
Mirtazapine	Remeron	Atypical Antidepressants
Nefazodone	Serzone	Atypical Antidepressants
Trazodone	Desyrel Oleptro	Atypical Antidepressants
Vilazodone	Viibryd	Atypical Antidepressants
Vortioxetine	Brintellix	Atypical Antidepressants

Other Variables of Interest

This study used an existing real-world clinical dataset that was provided Grady Hospital. The information in the dataset was collected from patient electronic medical records and de-identified before being provided to the research team. The following information was available to the research team: admission date, discharge date, location, department, diagnosis, age, gender, marital status, latest diagnosis contact date, and all prescribed medications.

Recategorization of Variables

Some categories of the variable, *marital status,* were recategorized to reduce small frequencies. Marital status originally included nine groups: divorced, married, null, other, separated, significant other, single, unknown, and widowed. Shapiro and Keyes (2008) demonstrated that it is important to separate groups who are single (this will include those divorced, separated, widowed, and single), from those who are in a relationship because having a partner greatly impacts chronic disease management. They also discovered significant differences between those who are separated or divorced from those who are widowed, as well as significant differences in chronic disease management between the separated and divorced from those who are single. After an extensive review of the literature, the team decided to recategorize this variable into five groups:

significant other, separated, widowed, single, and other. The significant other group includes patients who self-report being married or having a significant other. The separated group includes patients who self-report being separated or divorced. Widowed includes those who self-report being widowed. Single includes those who self-report being single, and the other group includes those who self-reported their marital status as other, null, or unknown.

Procedures

Data Management

The Emory University Institutional Review Board approved this study, IRB# 00103748. The data for these analyses came from a dataset that was purchased from Grady Hospital including all African American patients with an epilepsy diagnosis, identified by ICD-9 diagnostic codes 345 and 780, between 2010 – 2015. These data were provided from medical record review, and patients did not need to provide informed consent for their participation in this study. When purchased, Grady Hospital deidentified the medical records for the study team, so there was little risk of confidentiality breach to the study patients.

The Emory University Institutional Review Board provided this study with a waiver for informed consent for the use of these medical records because the research involved no more than minimal risk to patients involved, and the research could not have been practicably carried out without the waiver of informed consent. These data were securely stored on an encrypted hard drive at the Rollins School of Public Health on password-protected devices and were only viewed by the study team. Once the analyses for this study were completed, the dataset was removed from the encrypted hard drive.

To create the study sample for this study, the data were thoroughly cleaned. Due to the nature of this study, with the outcome of seizure event, patients only were included if they had an ICD-9 code of 345 for epilepsy. Those with the ICD-9 code 780, indicating general symptoms, but without a 345 diagnosis, were excluded from the study sample. Those patients with diagnostic code 345 with missing medication data were then removed from the study sample. The remaining patients were included in the analyses for this study.

Analytic Methods

All of the statistical analyses for this study were conducted using SAS version 9.4. Descriptive statistics were computed for demographic, social, and clinical variables. Univariate descriptive statistics were conducted for all of the demographic variables: age, gender, and marital status. Mean and standard deviation were calculated for the age of the study sample, and frequencies were calculated for gender and marital status.

Matched analyses using logistic regression were conducted to calculate the odds of having a seizure event in association with co-prescription of AEDs and antidepressants. Due to the correlated nature of this data, as well as the binary outcome of seizure event, a generalized estimating equation (GEE) was used to estimate the odds ratio. The solution to the GEE will provide the estimate of the Beta that is normal with a covariance matrix; in order to solve the GEEs, the correlation must be known beforehand. Because the true correlation structure is almost always unknown, we used an unstructured correlation structure in this GEE model.

Figure 5 represents the GEE model used for this analysis.

$$logit(Seizure_i) = \beta_0 + \beta_1 Antidepressant_{ti} + \beta_2 Gender_i + \beta_3 MaritalStatus_i + \beta_4 Age_i + e_{ij}$$

Figure 5. The GEE model used for the analyses. In the first model, Antidepressant prescription is for 3 months, and in the second model, Antidepressant prescription is for 6 weeks.

The primary analysis involved 2:1 matching, where co-prescription of AEDs and antidepressants during the risk interval for any participant was compared with two control intervals. Paired analyses were conducted to analyze sensitivity in the tests, where a risk window was compared with a control interval (3 months) according to a participant reported medication prescription interval. Odds ratios (ORs), 95% confidence intervals (95%CIs), and p-values were calculated to compare the risk of seizure with an antidepressant medication co-prescription between cases and controls.

RESULTS

A total of 126 African Americans with seizure activity were included in the analyses. These patients remained after selecting for antidepressant use, history of seizure, and regular outpatient visits. The analytic sample had a mean age of 47.8 years (SD=16.5). Nearly half of the patients were male (n=61; 48.4%), and the majority of patients were single (n=78; 61.9%). **Table 3** presents these demographic variables for the overall study population, as well as for the exposed and unexposed groups at the case and control time windows.

An interesting finding during these analyses was the low prevalence of patients who were prescribed antidepressant medications in combination with their AEDs. In the risk window, 3 months preceding the first seizure, only 2 of the 126 patients (1.6%) were co-prescribed both an antidepressant and an AED. In the first control period, 6 months preceding the first seizure, 8 of the 126 patients (6.4%) were co-prescribed both medications; and in the second control period, 9 months preceding the first seizure, only 1 of the 126 patients (0.8%) was prescribed an antidepressant medication in combination with their AED.

In order to determine which variables to include in the GEE analysis, a logistic regression model was constructed evaluation the co-prescription of antidepressant medications with AEDs, and age, gender, and marital status, and only variables with p-values of less than 0.05 were included in the subsequent GEE analyses. The full model included age, gender, and marital status. The results of the full model, as shown in **Table 4 and 5**, respectively, suggest that age ($p < 0.0001$), gender ($p < 0.0001$), and marital status ($p = 0.02$) are significant predictors of a seizure event. Therefore, these three

variables were all included in the subsequent GEE models, along with the exposure variable of antidepressant use.

As shown in **Table 3**, there were a total of 126 study patients with a first seizure event during a five-year study period. Out of the 126 first seizure events, 124 had not received an antidepressant prescription within six weeks of their seizure event. The remaining 2 patients had received an antidepressant medication prescription within six weeks of their first seizure event. Thus, these 2 seizures were considered to be exposed to antidepressant use. Likewise, for the control period extending from 3 months and one day to 6 months, 8 of the 126 patients with a seizure event were considered to be exposed to antidepressant use and 118 were considered to be unexposed. For the second control window extending from 6 months and one day to 9 months, 125 patients had not been prescribed an antidepressant medication within that window. The remaining 1 subject was prescribed an antidepressant medication within that control window and were therefore considered to be exposed during the larger three-month risk window.

The results of the GEE model, shown in **Table 6**, suggest that the risk of having a seizure, after adjusting for age, gender, and marital status, is reduced by about half for those patients that have received an antidepressant prescription in the last six weeks (OR=0.44; 95%CI: 0.42, 0.45; $p<0.0001$). When using a longer medication use period of three months, the risk of seizure decreases even more for those prescribed antidepressant drugs. After adjusting for age, gender, and marital status, the risk of seizure decreases even more for those patients who have received an antidepressant prescription in the last three months (OR=0.39; 95%CI: 0.38, 0.40). These results indicate that the addition of an antidepressant prescription has a protective effect against seizure activity among this

population of patients. However, because the number of patients who were co-prescribed antidepressant medications with their AEDs was so low, these results should be interpreted with caution.

Table 3. Demographics.

Exposure Status	**Overall**	**E+ at Risk Window** (n=2)	**E- at Risk Window** (n=124)	**E+ at Control Window 1** (n=8)	**E- at Control Window 1** (n=118)	**E+ at Control Window 2** (n=1)	**E- at Control Window 2** (n=125)
Age (Years)	47.8 (16.5)	45.5 (13.4)	47.9 (16.6)	48.4 (15.1)	47.8 (16.6)	50 (0)	47.8 (16.5)
Gender (% Male)	61 (48.4%)	1 (50.0%)	60 (48.4%)	4 (50.0%)	57 (48.3%)	0 (0%)	61 (48.8%)
Marital Status							
% Single	78 (61.9%)	1 (50.0%)	77 (62.1%)	5 (62.5%)	73 (61.9%)	1 (100.0%)	77 (61.6%)
% Married	18 (14.3%)	0 (0%)	18 (14.5%)	1 (12.5%)	17 (14.4%)	0 (0%)	18 (14.4%)
% Divorced	22 (17.5%)	1 (50.0%)	21 (16.9%)	1 (12.5%)	21 (17.8%)	0 (0%)	22 (17.6%)
% Widowed	6 (4.8%)	0 (0%)	6 (4.8%)	1 (12.5%)	5 (4.2%)	0 (0%)	6 (4.8%)

*E+ represents the group that is exposed to antidepressant use and E- represents the group that is unexposed to antidepressant use.

Table 4. Full Model with a Six-Week Medication Use Window.

Variables Included in Model	**Adjusted Odds Ratio (aOR)**	**95% Confidence Interval**	**p-Values**
Age	0.9	(0.9, 0.9)	$p < 0.0001$
Gender	0.9	(0.9, 0.9)	$p < 0.0001$
Marital Status	1.0	(1.0, 1.0)	$p = 0.02$

Antidepressant Use	0.4	(0.4, 0.4)	p < 0.0001

Table 5. Full Model with a Three-Month Medication Use Window.

Variables Included in Model	**Adjusted Odds Ratio (aOR)**	**95% Confidence Interval**	**p-Values**
Age	0.9	(0.9, 0.9)	p = 0.0004
Gender	0.9	(0.9, 0.9)	p = 0.0004
Marital Status	1.0	(1.0, 1.0)	p < 0.0001
Antidepressant Use	0.4	(0.3, 0.4)	p < 0.0001

Table 6. GEE Analysis.

Exposure Classification Window	**Case Person-Moments**	**Control Person-Moments**	**Adjusted Odds Ratio**	**95% Confidence Interval**
	Risk window: W = 6 weeks			
Reference (unexposed)	124	118	0.44	(0.42, 0.45)
Antidepressant use	2	8		p < 0.0001
	Risk window: W = 3 months			
Reference (unexposed)	123	116	0.39	(0.38, 0.40)
Antidepressant use	3	10		p < 0.0001

These analyses were both controlled for age, gender, and marital status.

DISCUSSION

This observational analysis of epileptic patients from an electronic health record database found that [atients prescribed antidepressant medications have a reduced risk of having a seizure when compared to patients without an antidepressant prescription, when adjusted for age, sex, and marital status.

Comparison with Other Research

According to Perucca (2006), AEDs are prone to drug-drug interactions, especially when used in combination with other psychotropic medications, because AEDs are used for lifetime to manage psychiatric disorders. Spina and Perucca (2002) also found that patients with epilepsy experience higher than normal incidence of other psychiatric disorders and are commonly prescribed additional psychotropic drugs to treat their multiple disorders. Patients taking AEDs in addition to other psychotropic drugs are likely to experience drug-drug interactions due to the fact that the medications are metabolized by the same enzyme in the body (Spina & Italiano, 2015).

In 2015, Spina & Italiano reported that the combination of AEDs with antidepressant medications leads to a decrease in drug concentrations of the antidepressant drugs but does not seem to affect the concentrations of AEDs. However, in 2007, Hellan and Spigset suggested that when AEDs and antidepressant medications are co-prescribed, the efficacy of the AEDs are reduced, leading to increased seizure activity among those patients who are prescribed both medications.

The results of this study suggest that more research is necessary to explore possible drug-drug interactions between AEDs and antidepressant medications. There is a need to explore these possible drug-drug interactions in order to provide clinicians with

updated information to select a safe combination of medications to treat their patients' epilepsy and other psychiatric disorders.

Limitations

Several potential methodological limitations should be considered when interpreting the results of this case-crossover analysis. First, the precise time of antidepressant medication may not be known in this data due to the lack of access to pharmacy records. In order to control for this, a case-crossover study design was selected for the analysis to reduce misclassification bias. Another limitation of this study was that we did not have access to all medical records of patients, only those from Grady Hospital; if a patient received care at another hospital or clinic, it would not be accounted for in this study.

It is also important to note the sample size of this study as a limitation. The study sample originally began with over 25,000 patients, however once eligibility criteria were in place, the sample size was reduced to 126 patients. It is notable to mention that a large exclusionary determinant was that patients were not regularly visiting Grady Hospital to receive care. This could indicate that African Americans with epilepsy in Atlanta, GA do not have consistent doctor's appointments to receive care for their epilepsy. The study also found that there were very few patients considered to be exposed in this population. The small exposure groups could have affected the results of the overall GEE analysis. However, this does create an interesting idea that this population is not regularly prescribed antidepressant medications, which differs drastically from previous research (Spina & Italiano, 2015). One possible explanation could be that African Americans are under-diagnosed, misdiagnosed, or under-treated for depression (Sohail, Bailey, &

Richie, 2014). This disparity could also be due to the idea that African Americans are less likely to properly adhere to their medications than Caucasians (Bautista & Jain, 2011).

Strengths

Despite these limitations, this analysis contains several important strengths. First, the use of the case-crossover study design largely avoids the biasing effects of unmeasured, time-invariant confounding factors. This study design was chosen due to the methodological limitations mentioned above in order to reduce bias in the results. Another advantage of this research design was the use of a sample of patients from an understudied population – African American people with epilepsy.

PRECEDE-PROCEED Model Implications

The results of this study have several implications for the PPM that can be used to develop future interventions to improve the quality of life among PWE. The first phase of the PPM includes a social assessment of the issue, which in this study was the quality of life and health outcomes of possible drug-drug interactions between AEDs and antidepressants. Factors that affect quality of life among PWE include the high prevalence of MDD, as well as worrying about having a seizure. This study found that the co-prescription of antidepressants along with AEDs was not common among the population of African Americans with epilepsy. This could indicate that MDD is underreported or under-diagnosed among this population (Sohail et al., 2014). It is important for clinicians to screen their patients with epilepsy for MDD at their regular appointments in order to prevent adverse health outcomes associated with MDD.

The second phase of the PPM includes an epidemiological assessment that explores the effects of MDD on adherence to AEDs and antidepressant medications.

Results from the literature review indicate that symptoms of MDD are significantly more frequent among PWE compared to healthy controls (Ettinger, Good, Manjunath, Faught, & Bancroft, 2004). The literature review also revealed that the co-prescription of AEDs with antidepressant medications leads to non-adherence of both medications (Mula, Pini, & Cassano, 2007). However, this is also difficult to identify in the present study due to the small sample size. Because many patients were excluded from final analyses because of not attending regular visits, it could be concluded that these patients were also not adhering to their medications and not regularly refilling their prescriptions. It is difficult to make concrete conclusions regarding medication adherence among this population and further research needs to be conducted.

Phase 2 of the PPM also includes a behavioral and environmental assessment of factors that lead to drug-drug interactions between AEDs and antidepressant medications. The results of the literature review indicated that antidepressant medications are co-prescribed with AEDs as a solution to the high rates of MDD among PWE (Mula & Schmitz, 2009). The results of the behavioral assessment found that the side effects of both AEDs and antidepressant medications leads to the eventual non-adherence to both of the prescription medications (Getnet et al., 2016). The present study did not find high rates of the co-prescription of AEDs and antidepressant medications among African Americans with epilepsy, making it difficult to conclude if these behavioral and environmental factors hold true for this population.

The third phase of the PPM includes the educational assessment of the problem, possible drug-drug interactions between AEDs and antidepressant medications. There is a paucity in the current literature relating to health outcomes associated with the co-

prescription of AEDs and antidepressant medications. This study aimed to fill this gap by examining the longitudinal effects of co-prescription of AEDs and antidepressant medications. While they need to be interpreted with caution due to the limited sample size, these results indicated that those patients who are co-prescribed AEDs and antidepressant medications have a decreased risk of having a seizure.

The results of this study could be used to inform an intervention that encourages proper medication adherence to AEDs and antidepressants among PWE to further investigate the possible drug-drug interactions among PWE. The results of the intervention can be used to inform medical providers of the effects of the drug-drug interactions between the two medications as a way to improve quality of life among PWE.

Public Health Implications

The findings from this study could suggest several public health implications. If antidepressants truly have a protective effect against seizures when combined with AEDs, then clinicians who treat patients with epilepsy need to be aware of this interaction in order to better treat their patients. This aligns with the literature on epilepsy, which indicates that stress is a risk factor for seizures, so if stress is reduced through the use of antidepressant medications, then the risk of seizure also decreases (Dehn et al., 2017; Temkin & Davis, 1984). However, due to the small sample size of this study, further research is necessary to investigate the effect of antidepressants in combination with AEDs on seizure activity.

These results could also indicate that antidepressant medications are more commonly prescribed to those presenting with multiple seizures. This aligns with

previous research, which shows that patients with a history of epilepsy are at an increased risk of developing depression, and that risk increases with increased seizure activity (Hesdorffer, Hauser, Olafsson, Ludvigsson, & Kiartansson, 2006). This result shows that people who are prescribed antidepressant medications for MDD have fewer seizures, which is important to providers of people with epilepsy. It is important for providers to be aware of the increased risk of depression among these patients, and to be prepared to treat them with antidepressant medications.

On the other hand, patients with multiple seizures could be seen more frequently than patients with fewer seizure events, allowing providers to better detect their depressive symptoms. In order to be included in this analytic sample, patients had to visit Grady Hospital at least four times per year to ensure that they were regularly refilling their prescription medications. The small number of exposed patients in this analytic sample could indicate prescriptions for antidepressant medications are rare in this population, as a whole, as is receiving regular care for epilepsy. Thus, there is a very small sample who have both, as indicated by the small sample size of this study. However, further research is needed to confirm if regular clinician visits are associated with fewer depressive symptoms among people with epilepsy. If this is true, it is important for clinicians to encourage regular appointments for their patients with epilepsy.

The results of this study make it clear that future research is necessary in order to further understand the true relationship of the co-prescription of antidepressant medications with AEDs on seizure activity. In the future, it would be important to consider evaluating this relationship with the use of insurance claims data in order to

have access to prescription refill data. A randomized controlled trial would also be beneficial for this topic in order to reduce confounding of outside variables. It would also be interesting to conduct this study in other populations, such as Hispanics with epilepsy and Caucasians with epilepsy to be able to compare the results to better inform future interventions.

CONCLUSION

Epilepsy is an important medical condition that makes patients susceptible to developing other psychiatric disorders (Kwon & Park, 2014). Depression is the most frequently occurring comorbid psychiatric disorder among people with epilepsy (Kwon & Park, 2014). In order to treat people with epilepsy for both epilepsy and depression, patients are commonly co-prescribed AEDs with antidepressant medications (Spina et al., 2016). The possible drug-drug interactions between these two medications have been previously understudied in the current literature. This study used a case-crossover study design to assess potential drug-drug interactions between AEDs and antidepressants among African Americans with epilepsy. The findings of this study suggest that the addition of an antidepressant medication has a protective effect on seizure activity, meaning that patients who are co-prescribed both medications have a decreased risk of having a seizure compared with patients who are only prescribed AEDs. However, this study had a small sample size, especially among the individuals who were prescribed both medications, and more research needs to be conducted among this population to investigate the true effects of the co-prescription of AEDs and antidepressants on seizure activity.

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