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Can mindfulness-based cognitive therapy reduce seizure activity in people with epilepsy?

By

Heather Bailey

Master of Public Health

Epidemiology

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Nancy J. Thompson, Ph.D., MPH
Committee Chair

# Can mindfulness-based cognitive therapy reduce seizure activity in people with epilepsy?

By

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B.A.
The University of Georgia
2007

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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# Abstract

Can mindfulness-based cognitive therapy reduce seizure activity in people with epilepsy?

By Heather Bailey

Epilepsy is a common neurological disorder characterized by recurrent and unprovoked seizures. Physical and psychological comorbidities regularly accompany chronic epilepsy, with psychological comorbidities often considered the most debilitating. Prominent among these comorbidities is depression. Persons with epilepsy show higher levels of depression than the general population, with an estimated prevalence between 32% and 48%.

Project UPLIFT is a home-based intervention program designed to treat comorbid depression in people with epilepsy. It is a collaboration between the Centers for Disease Control and Prevention and the Emory University Rollins School of Public Health. The program delivers mindfulness-based cognitive therapy to patients by web and telephone. These methods of distance delivery allow the program to target hard-to-reach populations that may have limited access to mental health care. For example, persons with epilepsy are often limited by social and vocational restrictions, and they may depend on others for transportation. In randomized controlled trials, the intervention group showed a significant reduction in depressive symptoms compared to the treatment-as-usual group.

The recommended treatment for depression among people with epilepsy parallels that of other depressed persons: medication, psychotherapy, or their combination. Both antidepressant medications and cognitive-behavioral therapies show efficacy for treating depression in epilepsy. Of interest, however, is the finding of limited studies that these treatments also reduce seizure activity.

The current study investigates the associations between Project UPLIFT and self-reported seizure activity in people with epilepsy. After IRB review and informed consent were attained, persons with epilepsy completed the survey instrument, which included questions about demographics, depressive symptoms, health-related quality of life, and seizure activity. Participation in Project UPLIFT was not associated with a reduction in seizure activity over time (seizure severity: $F\ [1,146] = 0.19$, $p = 0.6634$; seizure frequency: $F\ [1,144] = 0.28$, $p = 0.5985$). However, both measures showed decline in the intervention group.

Combined with the limited evidence base, these findings support the need for further research into the effect of psychotherapies on seizure activity. Given the harsh potential side effects of antiepileptic drugs and antidepressants, this research provides valuable insight into the concurrent and potentially convergent treatment of depression and epilepsy.

# Can mindfulness-based cognitive therapy reduce seizure activity in people with epilepsy?

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## Background

### *Epilepsy*

Epilepsy refers to a group of neurological disorders characterized by recurrent and unprovoked seizures (Cardamone et al., 2013). Recent definitions allude to the comorbidities prevalent among cases. For example, Fisher and colleagues (2005) define epilepsy as "a chronic condition of the brain characterized by an enduring propensity to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition" (p. 471).

In clinical terminology, epilepsy is classified as focal or generalized (Cardamone et al., 2013), and disease etiology may be genetic, structural/metabolic, or unknown (Berg & Scheffer, 2011). The estimated incidence rate in developed countries is 80 per 100,000 person years (Cardamone et al., 2013), with an estimated point prevalence between one and ten cases per 1,000 individuals (Shorvon, 2010).

### *Comorbidities in epilepsy*

While seizures can be stressful and even fatal for people with chronic epilepsy (Cardamone et al., 2013), comorbidities also represent a substantial proportion of their suffering through disability and reduced quality of life (Cardamone et al., 2013; Gaitatzis et al., 2004; Hesdorffer & Krishnamoorthy, 2011). Common somatic comorbidities include: 1) cardiac and respiratory disorders; 2) injuries such as burns and broken bones; 3) adverse side effects of antiepileptic drugs; and 4) fertility issues (Gaitatzis et al., 2012; Cardamone et al., 2013). Common psychiatric comorbidities include: 1) depression; 2)

anxiety; 3) ADHD; and 4) psychoses (Cardamone et al., 2013; Gaitatzis et al., 2004; Hesdorffer & Krishnamoorthy, 2011).

Many consider these comorbidities to be particularly debilitating and costly (Cardamone et al., 2013; Gaitatzis et al., 2004; Hesdorffer & Krishnamoorthy, 2011). As a result, public health agencies have encouraged research into improving outcomes for persons with multiple chronic conditions (CDC, 2011; Institute of Medicine, 2012; Thompson et al., 2010; U.S. Department of Health and Human Services, 2013). Among people with chronic epilepsy, depression is the most frequent comorbidity (Hermann et al., 2000; Kanner, 2000; Thompson et al., 2015).

*Depression*

Depression may refer to: 1) major depressive disorder; 2) dysthymic disorder; 3) adjustment disorder; 4) bipolar disorder; and 5) interictal dysphoric disorder (Cardamone et al., 2013). In the United States, lifetime prevalence is 16.2% (Kessler et al., 2003). This risk greatly increases among persons with chronic illness (Carroll et al., 2003; Evans et al., 2005), and the estimated prevalence in people with epilepsy ranges from 32% to 48% (Jones et al., 2003).

*Depression in epilepsy*

Depression is especially common in people with newly-diagnosed epilepsy (Panelli et al., 2007; Velissaris et al., 2009), with patients reporting symptoms immediately before, during, or after a seizure (Cardamone et al., 2013). Compared with the general population, persons with epilepsy report consistently higher rates of depression (Cardamone et al.,

2013; Gilliam, 2005; Hermann et al., 2000; Thompson et al., 2015). These rates remain elevated when compared to people with other chronic illnesses (Cardamone et al., 2013; McLaughlin et al., 2008; Fuller-Thomson & Brennenstuhl, 2009). For example, patients with epilepsy (34%) are more likely to be depressed than those with Type I diabetes (27%) or blood donors (7%) (Beghi et al., 2002). Ettinger et al. (2004) found 37% of persons with epilepsy were depressed compared with 28% of patients with asthma and 12% of healthy controls.

Comorbid depression further impairs quality of life in epilepsy, where it may intensify cognitive deficits and increase health care utilization (Cardamone et al., 2013). It is associated with lower income, more social concerns, and fewer working days (Ettinger et al., 2004). Depression may predict quality of life better than epilepsy-related measures (Cardamone et al., 2013; Kanner, 2009). Epilepsy patients with comorbid depression also report more severe and more frequent adverse events related to antiepileptic medications (Cramer et al., 2003; Ettinger et al., 2004; Kanner et al., 2012).

A combination of social, vocational, and psychological factors may contribute to depression in epilepsy (Gilliam, 2005). One school of thought describes depressive symptoms as an "understandable psychological reaction to the stresses and challenges of living with epilepsy" (Cardamone et al., 2013, p. 1533). For example, people with epilepsy often need accommodation in the workplace, and unemployment is high (Thompson et al., 2010). Additionally, all states restrict drivers' licenses "for persons with active, uncontrolled seizures" (Thompson et al., 2010, p. 247; Wiegartz et al., 1999). These circumstances severely limit independence for people with epilepsy, which may decrease access to mental health care and increase depressive symptoms.

Other experts claim brain dysfunction, more so than psychosocial factors, explains depression in people with epilepsy (Gilliam, 2005). Comorbid depression is depicted as a fundamental characteristic of the brains of epilepsy patients (Salzberg, 2011), with some calling depressive symptoms "neurobiological epi-phenomena of the epileptic brain" (Cardamone et al., 2013, p. 1533). This line of research focuses on two main theories of causation.

First, depression may play a role in the onset of epilepsy through some psychological and/or neurobiological pathway (Cardamone et al., 2013). Prospective studies have found that depression predates the onset of epilepsy, which suggests that depression is a risk factor for the disease (Cardamone et al., 2013; Hesdorffer et al., 2000; Hesdorffer et al., 2012).

Second, depression and epilepsy may have similar etiologies. As early as 1997, researchers found an association between depressed mood and hypoperfusion in epilepsy patients and controls (Schmitz et al., 1997). Subsequent neuroimaging studies have linked epilepsy and mood disorders (Blum et al., 2002; Cramer et al., 2003; Gilliam et al., 2007; Salzberg, 2011). In 2010, Salgado et al. found an association between depression and diminished extra-temporal cortical thickness among people with mesial temporal lobe epilepsy, and this thinning is also observed in non-epileptic persons with depression (Labate et al., 2011). While these studies are cross-sectional and cannot determine causation, they do provide insight into the biological plausibility of a common antecedent. This common cause for epilepsy and for depression could be genetic, neurobiological, or otherwise.

*Treating epilepsy*

Epileptic seizures may be provoked or unprovoked, and physicians prescribe antiepileptic drugs (AEDs) for the control of spontaneous seizures. These medications act to suppress seizures and to prevent epileptogenesis, or "the process by which a brain becomes epileptic or starts generating spontaneous seizures" (Temkin, 2001, p. 515). However, antiepileptic drugs carry a risk of adverse side effects and potential interactions with other medications.

Common side effects include dizziness, drowsiness, and mental slowing (Walia et al., 2004). Patients also believe their AEDs to influence mood and cause depressive symptoms (Cardamone et al., 2013). While anecdotal evidence supports their beliefs, there are no reliable studies of this relationship. Some AEDs linked to depressive symptoms are: carbamazepine, benzodiazepines, lamotrigine, phenobarbital, phenytoin, pregabalin, tiagabine, and zonisamide (Cardamone et al., 2013; Schmitz, 2011). However, it is difficult to discern whether these symptoms are caused by antiepileptic drug use, pre-existing depression, or epilepsy itself (Cardamone et al., 2013).

Despite the complex relationships between psychological symptoms and AED use, these connections are serious and potentially life threatening. For example, a recent meta-analysis found an association between AED use and increased risk of suicide (Cardamone et al., 2013). This finding prompted the U.S. Food and Drugs Administration to issue an immediate warning regarding all AEDs (Cardamone et al., 2013).

Despite these potential adverse side effects, AEDs effectively and safely treat a majority people with epilepsy (CDC, 2015). For cases of resistance, alternative treatments include vagus nerve stimulation and adopting a ketogenic diet (CDC, 2015). Prospective

studies suggest that a history of depressive symptoms is a risk factor for treatment-resistance to AEDs (Hitiris et al., 2007; Petrovski et al., 2010) and to epilepsy surgery (Cardamone et al., 2013; Kanner et al., 2009). Experts call for more research to investigate how treatments for depression may influence epilepsy outcomes (Cardamone et al., 2013; Gilliam, 2005).

*Treating depression*

The causes of depression may be biological and/or cognitive in nature (Thompson et al., 2010). Subsequently, current recommendations in the treatment of depression and depressive disorders in the general population are: 1) psychotherapies, including interpersonal and cognitive therapy; 2) pharmacotherapies such as antidepressant medications (e.g., SSRIs and SNRIs); or 3) their combination (Cardamone et al., 2013; Gilliam, 2005).

Evidence suggests that taking antidepressants effectively reduces depressive symptoms in the general population (Cardamone et al., 2013; Thompson et al., 2010). Cognitive behavioral interventions are equally effective (DeRubeis et al., 2005; Thompson et al., 2010), and psychotherapies may better prevent relapse compared with antidepressants (Cardamone et al., 2013).

The way a person thinks may also explain some aspects of depression (Thompson et al., 2010). Cognitive behavioral therapy (CBT) aims to change the content of thoughts (Segal et al., 2002; Thompson et al., 2010), and many advocate the particular use of mindfulness in cognitive therapy (Finucane & Mercer, 2006; Kenny & Williams, 2007; Segal et al., 2002; Thompson et al., 2010).

Mindfulness-based cognitive therapy (MBCT) aims to promote recovery and to prevent relapse among depressed individuals (Segal et al., 2002; Thompson et al., 2010). The program effectively reduces residual depressive symptoms (Thompson et al., 2010; Thompson et al., 2015), particularly for patients with current and treatment-resistant depression (Finucane & Mercer, 2006; Kenny & Williams, 2007). Mindfulness adds elements of acceptance and non-judgment. Originally defined as "paying attention in a particular way: on purpose, in the present moment, and non-judgmentally" (Kabat-Zinn, 1994, p. 4), it allows an individual to view thoughts as passing events (Thompson et al., 2010). Perhaps most importantly, mindfulness considers suffering as "worthy of attention, not something to be blocked out or fixed" (Thompson et al., 2010, p. 247). Paying attention to suffering and letting go of the thoughts attached to suffering may minimize hardship for people with depression and epilepsy (Thompson et al., 2010).

Alternative therapies for treatment-resistant depression include: electroconvulsive therapy, psychosurgery, deep brain stimulation, and transcranial magnetic stimulation (Cardamone et al., 2013). Vagal nerve stimulation has demonstrated efficacy in treating resistant cases of depression as well as resistant cases of epilepsy (Cardamone et al., 2013; Furmaga et al., 2012). Furthermore, certain antiepileptic drugs are used to treat specific types of depression, such as mania and bipolar depression, and AEDs also act as mood stabilizers in the treatment of bipolar and schizoaffective disorders (Cardamone et al., 2013; Schmitz, 2011). This collection of evidence supports the idea of shared neurobiological factors between depression and epilepsy.

*Diagnosing depression in epilepsy*

Depression may be underdiagnosed and undertreated in people with epilepsy (Cardamone et al., 2013; Gilliam, 2005; Thompson et al., 2015). While epilepsy patients regularly visit their physician, they are not routinely screened for depression (Gilliam, 2005). However, this practice may have increased in recent years due to the focus on comorbidities in epilepsy.

In a general clinical setting, systematic screening for depression is beneficial (Gilliam, 2005). For high-risk populations such as those with epilepsy, it is essential. Standardized screening instruments (e.g., Beck Depression Inventory, Centers for Epidemiologic Studies Depression Scale) provide relatively quick and easy methods of identifying depression and may be self-administered in a clinical setting (Gilliam, 2005). Still, the results can be misleading. For example, multiple conditions inherent to epilepsy can confound depression-related outcomes: adverse effects of medications, cognitive deficits, and sleep problems (Gilliam, 2005). Despite these caveats, the importance of screening is undeniable.

In addition, available evidence suggests that a large number of individuals with epilepsy may not present with major depression (Gilliam, 2005), and several studies report unusual presentations of depression in people with epilepsy. Researchers found that 50% of depressive disorders in a cohort of epilepsy patients were classified as ‘atypical’ (Mendez et al., 1986) and 25% were ‘not otherwise specified’ (Wiegartz et al., 1999), according to criteria from *the Diagnostic and Statistical Manual of Mental Disorders* (DSM; Gilliam, 2005). In a study of patients with uncontrolled seizures, Blumer (1997) reported that 30% to 50% met the definition of interictal dysphoric disorder, which is not

a designated disorder in the DSM-V. This evidence only reinforces the importance of screening with tools effective in people with epilepsy, and may have implications for the treatment of depression in epilepsy.

*Treating depression in epilepsy*

To minimize the negative consequences of depression, clinicians recommend a prompt response using interventions targeted to patients with epilepsy that account for potential drug interactions (Gilliam, 2005). However, the evidence base concerning the treatment of depression in epilepsy is somewhat limited (Cardamone et al., 2013). As a result, current treatment guidelines are similar to those for other depressed persons (Gilliam, 2005). Recommendations include: 1) psychotherapies; 2) pharmacotherapies; or 3) their combination (Gilliam, 2005; Cardamone et al., 2013).

First, psychotherapies alone may be used to treat depression in people with epilepsy. Studies have shown that cognitive behavioral interventions effectively reduce depressive symptoms in epilepsy patients (Gillham, 1990; Thompson et al., 2010; Thompson et al., 2015; Walker et al., 2010), and recent work advocates mindfulness-based therapies in particular (Segal et al., 2002; Thompson et al., 2010; Thompson et al., 2015; Walker et al., 2010). Mindfulness-based cognitive therapy is particularly effective for current depression and may be better than antidepressants at reducing relapse (Cardamone et al., 2013; Finucane et al., 2006; Kenny et al., 2007; Thompson et al., 2010). Thus, MBCT may be especially attractive to persons with treatment-resistant depression where antidepressants were unsuccessful (Finucane et al., 2006; Kenny et al., 2007).

Furthermore, psychotherapy alone is medically practical; clinicians need not worry about the potential interactions between AEDs and antidepressant medications. For patients, treatment with psychotherapy alone avoids any additional drug-related side effects.

Second, various medications are available for the treatment of depression. Most commonly prescribed are selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs). These second-generation antidepressant medications offer better tolerability, reduced side effects, and relative safety compared to first-generation tricyclic antidepressant drugs (Cardamone et al., 2013).

Antidepressants (e.g., SSRIs and SNRIs) are often the initial treatment option for depression in the general population. However, there is a relative lack of research on their effectiveness and safety in people with epilepsy. Clinical studies showed no increase in seizure frequency over time for epilepsy patients taking SSRIs/SNRIs (Gigli et al., 1994; Harmant et al., 1990; Hovorka et al., 2000; Kanner et al., 2000; Kuhn et al., 2003; Thome-Souza et al., 2007; Okazaki et al., 2011). Few individuals reported a worsening of seizure activity (Gigli et al., 1994; Kanner et al., 2000; Specchio et al., 2004), and some trials showed significant improvements in seizure outcomes (Favale et al., 1995; Favale et al., 2003; Specchio et al., 2004). Depressive symptoms decreased for a majority of patients. While these results are promising, the relatively small evidence base supports the need for further research.

In addition, there are practical and clinical limitations to antidepressant use in people with epilepsy. Epilepsy patients may hesitate to add antidepressants to their medication regimen because adverse side effects are unpleasant. Clinicians must also

consider the potential interactions between AEDs and antidepressants. Some AEDs increase clearance of antidepressants, and some antidepressants inhibit clearance of AEDs (Cardamone et al., 2013).

Third, there is no evidence base for the treatment of depression with a combination of psychotherapy and pharmacotherapy in people with epilepsy. Comparable research in the general population suggests additive or synergistic effects (Cardamone et al., 2013; Busch & Sandberg, 2012), with combined treatment outperforming either SSRI or cognitive therapy alone (Keller et al., 2000).

Finally, psychiatrists and neurologists must consider many factors when treating epilepsy patients with depression: 1) the specific syndrome; 2) previous treatment response; 3) physical comorbidities; 4) other medications and potential drug interactions; 5) risk of suicide; and 6) suitability for psychotherapy (Cardamone et al., 2013). In particular, cost, access to mental health care, and patient preferences are important considerations. Other barriers, including driving limitations for people with epilepsy, may prevent face-to-face psychotherapy.

*Project UPLIFT*

Project UPLIFT is a home-based intervention program designed to treat comorbid depression in people with epilepsy (Thompson et al., 2010). It is a collaboration between the Centers for Disease Control and Prevention and the Emory University Rollins School of Public Health. The program delivers mindfulness-based cognitive therapy to patients by web and telephone. These methods of distance delivery allow the program to target hard-to-reach populations that may have limited access to mental health care. For example,

persons with epilepsy are often limited by social and vocational restrictions, and they may depend on others for transportation.

Groups comprised of six to eight individuals are instructed via telephone or Internet using an adapted version of mindfulness-based cognitive therapy. Originally designed by Segal and colleagues in 2002, MBCT has proven effective in treating depression and preventing relapse, especially among treatment-resistant cases (Finucane & Mercer, 2006; Kenny & Williams, 2007).

The telephone and the Web-based methods of delivery cover similar topics over eight separate sessions (Thompson et al., 2010; Thompson et al., 2015). Each session involves: 1) a check-in period, 2) instruction on that week's topic, 3) a skill-building exercise, 4) group discussion, and 5) a homework assignment. Topics and activities focus on: increasing knowledge about depression; monitoring, challenging, and changing thoughts; coping and relaxing; attention and mindfulness; focusing on pleasure; the importance of reinforcement; and preventing relapse. Telephone sessions averaged one hour in length, while Web-based instruction was completed at the convenience of the participant. Telephone sessions strictly adhered to a script, which was also used as a template for the pre-recorded online instruction video and online discussion board.

In randomized controlled trials, Project UPLIFT showed a significant reduction in depressive symptoms compared to a treatment-as-usual control group (Thompson et al., 2010; Thompson et al., 2015). There was no difference between the telephone and the web-based intervention groups.

*The bidirectional relationship between epilepsy and depression*

Considerable evidence suggests that brain dysfunction may be the most important predictor of depression in epilepsy (Gilliam, 2005) and that shared factors give rise to both disorders (Cardamone et al., 2013; Kanner, 2011). Prospective studies propose that depression is a risk factor in epilepsy, as depressive symptoms predate the subsequent onset of epilepsy (Cardamone et al., 2013; Hesdorffer et al., 2000; Hesdorffer et al., 2012).

Neurobiological investigations contribute greatly to this hypothesis. Both depression and epilepsy involve disturbances in neurotransmitter systems (e.g., serotonergic, noradrenergic, and glutamatergic; Cardamone et al., 2013). Neuroimaging studies have visualized the shared neurological processes between epilepsy and mood disorders (Blum et al., 2002; Cramer et al., 2003; Gilliam et al., 2007; Salzberg, 2011).

Further investigations provide indirect evidence for shared neurobiological factors in epilepsy and depression. For example, certain antiepileptic drugs successfully treat both epilepsy and mood disorders (Cardamone et al., 2013). Clinicians use valproate, carbamazepine, and lamotrigine as mood stabilizers in bipolar and schizoaffective disorders, while lamotrigine treats bipolar depression (Cardamone et al., 2013). Likewise, vagal nerve stimulation is effective for treatment-resistant depression and treatment-resistant epilepsy (Furmaga et al., 2012). A history of depression may be a risk factor for treatment resistance to AEDs (Hitiris et al., 2007; Petrovski et al., 2010) and epilepsy surgery (Cardamone et al., 2013; Kanner et al., 2009).

*Implications for seizure control*

This bidirectional relationship between depression and epilepsy may have implications for seizure control; treatments for depression might also affect seizure activity in people with epilepsy. Of particular interest is the finding of limited studies that treatments for depression also reduce seizure activity. It is important considering many patients with chronic epilepsy never achieve total seizure control despite the plethora of AEDs on the market (Cramer et al., 2003).

Antidepressant drugs may have an overall anti-seizure effect (Cardamone et al., 2013; Favale et al., 1995; Favale et al., 2003; Specchio et al., 2004). In a review of clinical trials, Alper and colleagues (2007) found a significant difference in seizure incidence between patients taking antidepressants and those taking placebo. Patients taking antidepressants reported fewer incident spontaneous seizures. Similarly, Gillham (1990) found that psychotherapy improved seizure rates among epilepsy patients.

## Introduction

Epilepsy is a common neurological disorder characterized by recurrent and unprovoked seizures. In developed countries, the estimated prevalence is up to ten per 1,000 persons (Shorvon, 2010). Physical and psychological comorbidities regularly accompany chronic epilepsy, with psychological comorbidities often considered the most debilitating (Cardamone et al., 2013; Gaitatzis et al., 2004; Hesdorffer & Krishnamoorthy, 2011). Prominent among these comorbidities is depression (Hermann et al., 2000; Kanner, 2000; Thompson et al., 2015). Persons with epilepsy show higher levels of depression than the general population, with an estimated prevalence between 32% and 48% (Jones et al., 2003).

The recommended treatment for depression among people with epilepsy parallels that of other depressed persons: medication, psychotherapy, or their combination (Cardamone et al., 2013; Gilliam, 2005). Both medication and cognitive-behavioral therapies show efficacy for treating depression in epilepsy (Cardamone et al., 2013; DeRubeis et al., 2005; Thompson et al., 2010). While equally effective in treating current depression, psychotherapies may better prevent relapse compared with medication alone (Cardamone et al., 2013; Thompson et al., 2010).

Of interest is the finding of limited studies that these treatments also reduce seizure activity (Cardamone et al., 2013; Favale et al., 1995; Favale et al., 2003; Specchio et al., 2004). In a review of clinical trials, Alper and colleagues (2007) found patients taking antidepressants had a lower incidence of spontaneous seizures than those taking placebo. Similarly, Gillham (1990) found that psychotherapy improved seizure rates among epilepsy patients.

Project UPLIFT is a program that delivers mindfulness-based cognitive therapy (MBCT) by web and telephone (Thompson et al., 2010). In clinical trials, this program has been demonstrated to reduce depression among people with epilepsy (Thompson et al., 2010; Thompson et al., 2015). The current study aims to investigate whether Project UPLIFT is also effective in reducing seizure activity among people with epilepsy. Specific hypotheses are that seizure severity and frequency are significantly lower among people attending the Project UPLIFT program than among a comparison group of people receiving usual treatment.

## Materials and Methods

### *Intervention*

Project UPLIFT was developed as a home-based intervention program to treat depression in people with epilepsy (Thompson et al., 2010). Groups comprised of six to eight individuals were instructed via telephone or Internet using an adapted version of mindfulness-based cognitive therapy (MBCT). Originally designed by Segal and colleagues in 2002, MBCT has proven effective in treating depression and preventing relapse, especially among treatment-resistant cases (Finucane & Mercer, 2006; Kenny & Williams, 2007).

The telephone and the Web-based methods of delivery covered similar topics over eight separate sessions (Thompson et al., 2010 and 2015). Each session involved: 1) a check-in period, 2) instruction on that week's topic, 3) a skill-building exercise, 4) group discussion, and 5) a homework assignment. Topics and activities focused on: increasing knowledge about depression; monitoring, challenging, and changing thoughts; coping and relaxing; attention and mindfulness; focusing on pleasure; the importance of reinforcement; and preventing relapse. Telephone sessions averaged one hour in length, while Web-based instruction was completed at the convenience of the participant. Telephone sessions strictly adhered to a script, which was also used as a template for the pre-recorded online instruction video and online discussion board.

All sessions were co-facilitated by an adult with epilepsy and a graduate student research assistant. The primary investigator, a Georgia-licensed clinical psychologist and professor of behavioral sciences and epidemiology, trained facilitators in delivery of the

program and supervised sessions throughout the study period. To further ensure consistency and fidelity, telephone sessions were audio-recorded and Web-based discussions were available to project staff. The primary investigator reviewed all telephone recordings and online discussion boards to monitor adherence to the script and to review the responses to questions that might arise during the course of a session. All telephone and Web-based sessions were also independently reviewed by project staff to ensure fidelity to the original intentions of the program.

*Treatment-as-usual*

Participants randomized to the treatment-as-usual condition (TAU) followed the standard of care treatment for depression at their epilepsy clinic. They were placed on a waitlist and offered the intervention during the second stage of Project UPLIFT (Thompson et al., 2010; Thompson et al., 2015). The current study does not address this stage. The design allowed for some participants taking antidepressant medications and/or attending psychotherapy sessions to be included in the TAU waitlist condition.

*Participants*

Thompson and colleagues (2010 and 2015) recruited a total of 425 participants for two separate studies: a pilot study conducted between June 2007 and November 2008 and a prevention study conducted from May 2010 through June 2012. Informed consent was acquired after completing the institutional review board process at each of the four participating sites, and participants completed survey instruments with questions about demographics and self-reported symptoms. The current study analyzes the resulting

combined dataset. All data were de-identified and the institutional review board at Emory University marked the study as "exempt" from review.

In the pilot study, 58 participants were recruited from an epilepsy clinic in Georgia (Thompson et al., 2010). Inclusion criteria required participants to: 1) have a diagnosis of epilepsy at least one year prior to enrollment; 2) have depressive symptoms indicated by a score of >13 on the Center for Epidemiological Studies Depression scale (CES-D; Devins & Orme, 1985; Radloff, 1977); 3) be at least 21 years old; 4) be an English speaker; 5) be willing to be audiotaped; and 6) have no prominent cognitive impairment indicated by a score of ≥20 on the Telephone Mini Mental State Examination (Newkirk et al., 2004). Participants currently in psychotherapy and/or taking antidepressant medications were allowed to enroll. However, those with active suicidal ideation were excluded. Only 40 of the 58 original participants met all inclusion criteria and were not missing values for measures. These people were included in the current study.

In a follow-up study, Thompson and colleagues (2015) recruited 367 participants from epilepsy clinics at four university sites: Georgia, Michigan, Texas, and Washington. Inclusion criteria required participants to: 1) have a diagnosis of epilepsy at least three months prior to enrollment; 2) be currently taking epilepsy medication or physician approval to participate; 3) have depressive symptoms indicated by a score between 8 and 27 on the CES-D (i.e. absence of moderate-to-severe depression); 4) be at least 21 years old; 5) be an English speaker; 6) have access to a telephone; and 7) be mental stability indicated by a score of >23 on the Telephone Mini-Mental State Examination (Newkirk et al., 2004). Again, individuals in psychotherapy and/or taking antidepressant drugs could enroll so long as they met the inclusion criteria, and persons with active suicidal ideation

were excluded. Only 108 persons were eligible for the prevention study and all of these individuals were included in the current investigation. After exclusions, a total of 148 of 425 recruited participants remained. All were included in the combined dataset used in the current study.

*Design*

The previous Project UPLIFT studies were randomized controlled trials, and both used a crossover design (Thompson et al., 2010 and 2015). First, eligible participants were randomly assigned to the intervention condition or to the treatment-as-usual waitlist condition. These groups were further randomized to the telephone or the Web-based method of delivery. This design resulted in four randomized strata, and all participants were assessed at baseline, interim, and follow-up (Thompson et al., 2010; Thompson et al., 2015; see Figure 1a).

After combining data from both investigations, the current study analyzed the relationship between measures at the baseline and the interim time intervals. It did not include the post-assessment measures and did not address the original crossover design. Because there was no difference in the effectiveness between the telephone and the Web-based methods of delivery (Thompson et al., 2010; Thompson et al., 2015), the randomized strata were limited to two groups for the purposes of the current study: the intervention condition versus the treatment-as-usual waitlist condition (see Figure 1b).

*Measures*

The listed measures were assessed at baseline and interim, and all were self-reported using reliable and validated scales.

**Seizure severity.** Seizure severity was measured using the revised Liverpool Seizure Severity Scale. Adapted to increase its content validity and its ability to detect changes from antiepileptic drugs, the revised scale demonstrated good internal consistency and test-retest reliability (Baker et al., 1998). The measure was comprised of 16 points (Baker et al., 1991) and was easily administered (Thompson et al., 2010).

Seizure severity was chosen as an outcome of interest in this study. Recent studies have suggested that seizure severity might best indicate the true status of chronic epilepsy (Cramer & French, 2001).

**Number of seizures.** Accompanying seizure severity, total number of seizures in the past month acted as a second outcome of interest. The count allowed us to determine whether Project UPLIFT affected an additional aspect of epilepsy.

**Depressive symptoms.** The modified Beck Depression Inventory (mBDI; Dori & Overholser, 2000) assessed the severity of depressive symptoms in the past two weeks. The measure was adapted from the 21-item Beck Depression Inventory (Beck et al., 1979; Beck et al., 1996) to include a positive response category for each item. Responses ranged from 0 (*positive*) to 4 (*severe*) (i.e., not from 1 (*mild*) to 4 (*severe*) as before). The mBDI better detected differences in the lower depression scores as a result of this added category (Dori & Overholser, 2000; Walker et al., 2012; Thompson et al., 2015). The modified version demonstrated good internal consistency and test-retest reliability (Dori &

Overholser, 2000). Both the BDI (Jones et al., 2005) and the mBDI (Thompson et al., 2010; Thompson et al., 2015) effectively measured depression in people with epilepsy.

**Health-related quality of life.** Quality of life (QOL) was assessed using a subset of CDC's Behavioral Risk Factor Surveillance System questionnaire (U.S. Department of Health and Human Services, 2000). The 9-item health-related quality of life scale included questions regarding self-perceived health, activity restrictions, and the number of mental and physical healthy days. Subscales comprised of items measuring mental health quality of life and physical health quality of life have proven reliable and valid (Horner-Johnson et al., 2009). We used separate mental and physical health constructs in this study. Because chronic epilepsy severely limits the physical aspects of day-to-day life, any improvement in aspects of mental health might be overshadowed in a composite measure.

**Sociodemographic measures.** Age (years) and gender (male/female) were recorded at baseline and used to assess randomization. The literature review indicated no association between demographic characteristics and seizure severity in people with epilepsy, and none were included in the statistical analyses.

*Analysis*

Analyses were performed using SAS Version 9.3 (Cary, NC). Due to the repeated measures design, only participants who completed the interim assessment were included in the analyses. For persons missing fewer than 10% of items on a scale, mean values were substituted for missing data. Descriptive statistics were recorded at baseline, and differences were assessed using a Fisher's exact test, a Pooled Student's t-test, or a

Wilcoxon-Mann-Whitney test. Bivariate statistical tests were two-sided, and p-values less than 0.05 were considered statistically significant.

Repeated-measures analyses of variance (ANOVAs) were used to determine the change in seizure activity over time between the intervention and the treatment-as-usual waitlist conditions. A repeated-measures ANOVA was used to assess the association between condition and seizure severity over time. A second ANOVA was used to assess the association between condition and number of seizures over time. For these analyses, statistical significance was determined using a Bonferroni correction. With two hypothesis tests, Bonferroni-corrected p-values less than 0.025 were considered statistically significant.

## Results

### *Sample description at baseline*

Project UPLIFT was delivered to 148 participants, with 71 persons receiving the intervention condition during the first eight weeks of study. Ages ranged from 21 to 70 years, with a mean of 39.4 years (sd = 12.9). A majority of participants identified as female (55%). Although some individuals reported zero healthy days, most reported the maximum number of healthy days for both the mental and the physical health constructs (i.e., 30 healthy days in the past month). Depressive symptoms ranged from 1 to 54 points on the mBDI scale, with an average of 22.6 (sd = 11.1). Roughly one-third (30%) were currently taking antidepressant medications. Although scores spanned from 0 to 85, median seizure severity at baseline was 7.5 on the Liverpool Seizure Severity scale, with an interquartile range (IQR) of zero to 47.5 units. While most people had zero seizures in the past month, some reported as many as 40 independent seizures. The median number of seizures in the past month was 1 (IQR: 0, 4).

### *Assessment of control variables*

All extraneous variables were controlled through randomization. Differences between the intervention condition and the treatment-as-usual waitlist condition at baseline were summarized in Table 1. The only significant difference was for antidepressant medication use, which was greater for the intervention group compared to the treatment-as-usual group (39% versus 22%; $X^2 = 5.26$, $p = 0.0218$). However, randomization was considered unbiased even though there appeared to be an imbalance in baseline measures.

Based on previous literature and biological plausibility, no potential confounders were considered. A directed acyclic graph (DAG) was constructed to visualize these relationships between: 1) the exposure of interest, condition; 2) the outcome of interest, seizure activity (e.g., seizure severity and seizure frequency); and 3) potential confounders (see Figure 2). Epilepsy was controlled through the study design (i.e., all participants had been diagnosed with epilepsy), and this status was represented by a box in Figure 2. As a result, there were no potential confounders and no open, backdoor paths from condition to seizure activity at time 2 (i.e., at the interim assessment). Depression appeared to be a mediator in this relationship and was not controlled. Health-related quality of life was a collider, and controlling for it could lead to confounding bias; neither mental nor physical health constructs were controlled. Sociodemographic variables showed no associations with seizure activity, the dependent variable, or mindfulness-based cognitive therapy, the independent variable (Thompson et al., 2010). Age and sex were not controlled.

The direction of relationships represented in the DAG were based on a literature review. Mindfulness-based cognitive therapy was developed to reduce symptoms of depression (Segal et al., 2002), and studies confirm this relationship (Thompson et al., 2010; Thompson et al., 2015). Multiple investigations have shown a significant positive association between depressive symptoms and seizure severity (Cramer et al., 2003; Thompson et al., 2010) as well as between depressive symptoms and number of seizures (Gillham, 1990; Thompson et al., 2015). Johnson and colleagues (2004) found depression to be a strong predictor of health-related quality of life in people with epilepsy. In the literature, sex was associated with depressive symptoms (Nolen-Hoeksema et al., 1999).

Differences in depressive symptoms have also been linked to age and life characteristics (Mirowsky & Ross, 1992).

Antidepressants may have a general anti-seizure effect (Cardamone et al., 2013), and antidepressant medication use was weakly associated with the independent variable, condition. However, antidepressant medication use was not controlled because controlling for epilepsy through study design blocked all confounding pathways.

*Seizure severity*

There was no association between condition and seizure severity over time ($F[1,146] = 0.19$, $p = 0.6634$). However, seizure severity scores decreased from baseline to interim in the intervention group (see Table 2). These findings support the hypothesized relationship between condition and seizure severity.

The cross-sectional relationships between condition and seizure severity for each time interval were summarized in Table 3. Seizure severity did not differ by condition at baseline ($F[1,146] = 0.16$, $p = 0.6900$) nor at interim ($F[1,146] = 0.13$, $p = 0.7192$).

*Number of seizures*

Likewise, there was no association between condition and number of seizures over time ($F[1,145] = 1.86$, $p = 0.1747$). When a single outlier was removed, this relationship did not change ($F[1,144] = 0.28$, $p = 0.5985$). Again, the number of seizures dropped from baseline to interim in the intervention group (see Table 4), which was the hypothesized effect of the intervention condition on seizure frequency.

The cross-sectional relationships between condition and seizure frequency for each time interval were summarized in Table 5. After removing an outlier, the number of seizures did not differ by condition at baseline ($F[1,145] = 1.54$, $p = 0.2160$) nor at interim ($F[1,144] = 0.32$, $p = 0.5729$). However, the number of seizures dropped from baseline to interim in the intervention group, while the number of seizures stayed the same in the treatment-as-usual group (see Table 5).

## Discussion

### *Summary of findings*

Among people with epilepsy and comorbid depressive symptoms, there was no association between participation in Project UPLIFT and seizure activity. However, the intervention condition showed a decline in both the number of seizures and their severity over time. This pattern was especially apparent for seizure frequency, where the number of seizures went down by approximately three occurrences in the past month for the intervention group and stayed the same for the treatment-as-usual group. As the aim of this study was to improve epilepsy outcomes, these results are promising. This evidence supports the need for future research into the effect of psychotherapy on seizure activity.

### *Clinical significance*

It is important to consider clinical significance in this study. For example, a reduction in the number of seizures in the past month by approximately three occurrences might be significant to physicians as well as epilepsy patients. Since most participants reported fewer than 10 seizures at baseline, three fewer occurrences could correspond to a ~30% drop in seizure frequency.

In addition, there was no established standard for the drop in seizure severity or number of seizures prior to conducting these analyses. Future investigations could consult a range of experts, including clinicians with anecdotal evidence, to set an accepted value for clinical significance.

*Public health importance*

Adults with chronic diseases consistently report increased rates of psychiatric comorbidities compared to the general population (Carroll, Cassidy, & Cote, 2003; Evans et al., 2005; Thompson et al., 2015). Among those with chronic epilepsy, psychiatric comorbidities add to the overall burden of disease through reduced quality of life and increased disability (Cardamone et al., 2013; Gaitatzis et al., 2004; Hesdorffer & Krishnamoorthy, 2011). Subsequently, public health agencies have encouraged research focused on improving outcomes in people with multiple chronic conditions (CDC, 2011; U.S. Department of Health and Human Services, 2013).

Project UPLIFT was developed as a home-based intervention program to treat comorbid depression in people with epilepsy (Thompson et al., 2010). Persons with epilepsy are limited by social and vocational restrictions, and they may depend on others for transportation. Through distance delivery, Project UPLIFT targets this difficult-to-reach group that may have limited access to mental health care. Although the current study focuses on those with epilepsy, Project UPLIFT is easily adapted to other hard-to-reach populations.

*Potential bias*

Randomized controlled trials (RCTs) are the gold standard of study design. Randomization ensures that the comparison groups are balanced with respect to measured and unmeasured factors, which may reduce selection bias. However, the effect estimate may be biased if randomization is compromised. In this study, randomization was considered unbiased despite the difference in antidepressant medication between the

intervention and the treatment-as-usual conditions at baseline. Still, controlling for measures that differ at baseline will increase precision, and this influence may or may not change the results of the study (Saquib et al., 2013). Future studies should follow pre-set adjustment plans (Saquib et al., 2013).

Finally, all measures were self-reported. Any reporting bias might be attributed to the nature of the intervention, which prevented a double-blind study. Participants knew whether they received Project UPLIFT, and this knowledge could have affected their reporting. For example, those assigned to the intervention condition might report greater improvements than those in the treatment-as-usual waitlist condition.

*Limitations and strengths*

The original data were collected with the intention to study comorbid depression among people with epilepsy, and the studies were powered to detect a change in depressive symptoms (Thompson et al., 2010; Thompson et al., 2015). However, the current study investigated the change in seizure activity. It included 148 participants and produced small to medium effect sizes ($F = 0.19$ and $0.28$). To ensure 80% power in an ANOVA, a sample size of 64 individuals was needed to detect a medium effect and 393 individuals for a small effect size (Cohen, 1992). The current study might have been insufficiently powered to detect a change in seizure activity.

In this study, Project UPLIFT was compared with a treatment-as-usual condition only. Future research would benefit from including another active intervention as well as a control.

An additional limitation was the relative lack of geographic diversity, with only one-to-two clinics in each of four states participating. Prior research has suggested that depression-related outcomes might vary by region (Jia et al., 2008; Polednak, 2012). Unfortunately, mental health professionals are licensed at the state level, and there has been limited discourse on how to regulate distance delivery (Thompson et al., 2015).

This study is prospective due to its randomized controlled trial design. Participants reported seizure activity before and after undergoing the intervention, which allowed for change over time in the analyses. The current literature is comprised mainly of descriptive studies, which cannot establish time order and cannot assume causation. This study is a valuable contribution to the literature regarding a possible intervention for seizure-related outcomes in people with epilepsy.

The present study adds to the literature on whether cognitive behavioral therapy can influence outcomes other than depression in epilepsy, specifically seizure activity. Combined with the limited evidence base, these findings support the need for further research into the effect of psychotherapies on seizure activity. Given the harsh potential side effects of antiepileptic drugs and antidepressants, this research provides valuable insight into the concurrent and potentially convergent treatment of depression and epilepsy.

**Table 1**
Demographic and clinical characteristics of people with epilepsy (N=148) at baseline by condition, mindfulness-based cognitive therapy intervention (UPLIFT) or treatment-as-usual (TAU); Project UPLIFT combined dataset, 2010 & 2015

| | UPLIFT (N=71) | TAU (N=77) | *p*-value[a] |
|---|---|---|---|
| ***Demographic measures***[ǂ] | | | |
| Sex (M/F) | | | |
| Female | 40 (57%) | 40 (53%) | 0.5843 |
| Age (years) | 39.5 (12.2) | 39.4 (13.5) | 0.9463 |
| ***Clinical measures***[ǂ] | | | |
| Depressive symptoms[b] | | | |
| Yes | 22.4 (10.2) | 22.8 (12.0) | 0.8295 |
| Antidepressant medication use[c] | | | |
| Yes | 28 (39%) | 17 (22%) | 0.0218* |
| Number of healthy days[d] | | | |
| Physical | 30 (30, 30) | 30 (30, 30) | 0.0874 |
| Mental | 30 (30, 30) | 30 (30, 30) | 0.4674 |
| ***Outcomes of interest***[ǂ] | | | |
| Seizure severity[e] | 7.5 (0, 47.5) | 10.0 (0, 45) | 0.9420 |
| No. of seizures[f] | 1 (0, 3) | 1 (0, 4) | 0.8789 |

[a] Bivariate analyses used: chi-square test for categorical variables; Student's t-test (pooled) for normally distributed continuous variables; Wilcoxon-Mann-Whitney test for non-normally distributed continuous variables
[b] Calculated using the modified Beck Depression Inventory (mBDI)
[c] Current antidepressant medication use only
[d] Calculated using CDC's HRQOL-4 measure and based on the number of healthy days in the past month; possible scores range from 0 to 30
[e] Calculated using the revised Liverpool Seizure Severity Scale
[f] Total number of seizures in the past month
* Statistically significantly different at baseline
[ǂ] Reported as: N (%) for categorical measures; mean (sd) for normally distributed measures; and median (IQR) for non-normally distributed measures

**Table 2**

The relationship between condition and seizure severity over time (N=148); Project UPLIFT combined dataset, 2010 & 2015

| | | | Least squares means estimate | | | |
|---|---|---|---|---|---|---|
| Measure | Condition[b] | *n* | Baseline | Interim | F[1,146] | *p*-value[c] |
| Seizure severity[a] | UPLIFT | 71 | 22.25 | 18.49 | 0.19 | 0.6634 |
| | TAU | 77 | 23.96 | 19.90 | | |

[a] Calculated using the revised Liverpool Seizure Severity Scale
[b] Intervention condition, mindfulness-based cognitive therapy intervention (UPLIFT), versus treatment-as-usual waitlist condition (TAU)
[c] Calculated using a repeated-measures ANCOVA with condition and antidepressant medication use in the model

**Table 3**

The relationship between condition and seizure severity at each time interval (N=148); Project UPLIFT combined dataset, 2010 & 2015

| Measure | Time interval | UPLIFT[b] | TAU[b] | F-statistic | *df* | *p*-value[c] |
|---|---|---|---|---|---|---|
| Seizure severity[a] | Baseline | 22.25 | 23.96 | 0.16 | 1,146 | 0.6900 |
| | Interim | 18.49 | 19.90 | 0.13 | 1,146 | 0.7192 |

[a] Calculated using the revised Liverpool Seizure Severity Scale
[b] Intervention condition, mindfulness-based cognitive therapy intervention (UPLIFT), versus treatment-as-usual waitlist condition (TAU)
[c] Calculated using cross-sectional ANCOVAs with condition and antidepressant medication use in the model

**Table 4**

The relationship between condition and seizure frequency over time (N=146); Project UPLIFT combined dataset, 2010 & 2015

| | | | Least squares means estimate | | | |
|---|---|---|---|---|---|---|
| Measure | Condition[b] | *n* | Baseline | Interim | F[1,144] | *p*-value[c] |
| No. of seizures[a] | UPLIFT | 70 | 5.89 | 2.83 | 0.28 | 0.5985 |
| | TAU | 76 | 3.26 | 3.74 | | |

[a] Total number of seizures in the past month
[b] Intervention condition, mindfulness-based cognitive therapy intervention (UPLIFT), versus treatment-as-usual waitlist condition (TAU)
[c] Calculated using a repeated-measures ANCOVA with condition and antidepressant medication use in the model

**Table 5**

The relationship between condition and seizure frequency at each time interval (N=146); Project UPLIFT combined dataset, 2010 & 2015

| Measure | Time interval | UPLIFT[b] | TAU[b] | F-statistic | *df* | *p*-value[c] |
|---|---|---|---|---|---|---|
| No. of seizures[a] | Baseline | 5.89 | 3.26 | 1.54 | 1,145 | 0.2160 |
| | Interim | 2.83 | 3.74 | 0.32 | 1,144 | 0.5729 |

[a] Total number of seizures in the past month
[b] Intervention condition, mindfulness-based cognitive therapy intervention (UPLIFT), versus treatment-as-usual waitlist condition (TAU)
[c] Calculated using cross-sectional ANCOVAs with condition and antidepressant medication use in the model

| Condition | Baseline Assessment | Intervention | Interim Assessment | Intervention | Follow-up Assessment |
|---|---|---|---|---|---|
| UPLIFT | x | Telephone | x | | x |
| UPLIFT | x | Web-based | x | | x |
| TAU | x | | x | Telephone | x |
| TAU | x | | x | Web-based | x |
| **Time interval** | **0 weeks** | | **8 weeks** | | **16 weeks** |

**Figure 1a.** The randomized, crossover design used in the previous Project UPLIFT studies (Thompson et al., 2010; Thompson et al., 2015)

| Condition | Baseline Assessment | Intervention | Interim Assessment |
|---|---|---|---|
| UPLIFT | x | Telephone or Web-based | x |
| TAU | x | | x |
| **Time interval** | **0 weeks** | | **8 weeks** |

**Figure 1b.** The randomized, controlled trial design used in the current study

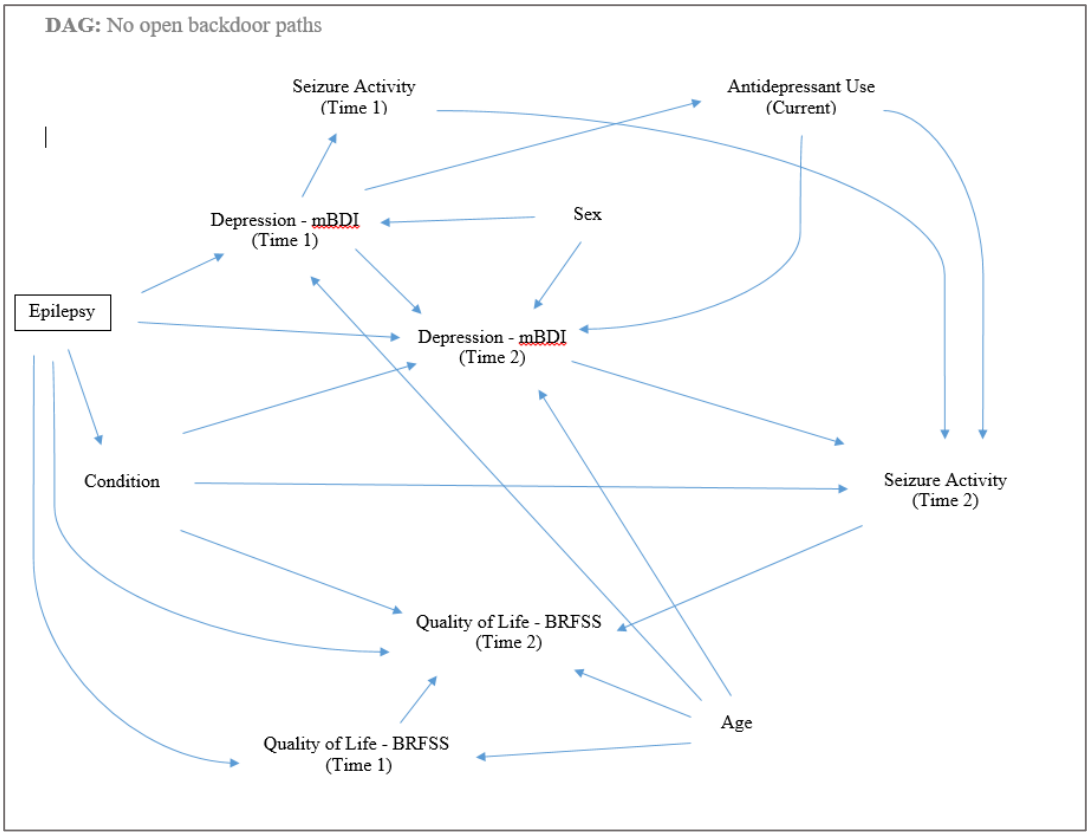


**Figure 2.** The directed acyclic graph (DAG) visualizing the relationship between: 1) the exposure of interest, condition; 2) the outcome of interest, seizure activity (e.g., seizure severity and seizure frequency); and 3) potential confounders; Project UPLIFT combined dataset, 2010 & 2015

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