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The Relationship Between Bipolar Disorder and Epilepsy: Challenging the Dichotomy of Mental and Physical Health

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Mental and Physical Health

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Abstract

The body of literature associating epilepsy with mood disorders is vast and can be traced as far back as Hippocrates. The comorbidity of the two is notoriously high. The prevalence of depressive symptoms among people with epilepsy has been widely reported for decades, though these symptoms may not be considered or treated as successfully in people with epilepsy as they are in their non-epileptic counterparts. More recently, evidence has been found suggesting that psychiatric symptoms may serve as a precursor to epilepsy. The episodic nature of the illnesses and their congruent model of progression suggest a possible connection. The goal of this literature review is to present evidence of the relationship between the two disorders. Similarities in pathophysiology, structural changes associated with the conditions, and biochemical abnormalities link these two disorders and challenge the distinction between "psychological" and "neurologic" illness.

Keywords: bipolar disorder, epilepsy, depression, comorbidity, catamenial epilepsy antidepressants, anticonvulsants

Introduction

The association between epilepsy and mood disorders is widely known and has been studied for centuries. In fact, the English translation of a well-known quote by Hippocrates reads "Melancholics ordinarily become epileptics, and epileptics, melancholics" (Lewis, 1934). Since Hippocrates' claim in 400 B.C., modern medicine has developed a body of evidence to support this. The two kinds of disorders often co-occur, further complicating treatment. Though, historically, most research focuses on the development of depressive symptoms among people with epilepsy, emerging research appears to suggest that primary depression may lead to secondary epilepsy (Kanner, 2011). While epilepsy and bipolar disorder (BD) have strikingly dissimilar diagnostic criteria, patients may have some common symptoms. Both disorders are characterized by periods of illness with intermittent periods of remission (Jobe, 2003).

Depression in people with epilepsy may be classified as preictal (occurring before a seizure), postictal (occurring after a seizure), ictal (occurring during a seizure), or interictal (occurring during periods of remission with no relation to seizure presence) (Kwon & Park, 2014). Emerging research has found a genetic link between the two disorders: specific variants of the ANK3 gene appear to cause excessive neuron excitation, leading to severe epilepsy, sudden death, and behavior analogous to BD in mice (Lopez et al., 2017). Additionally, a review of the pathophysiology of both disorders confirms common precipitating factors, functional deficits, and structural abnormalities. Unsurprisingly, given their biological similarities, the two disorders can benefit from overlapping treatments. In fact, treatment for depression in epileptic patients may even help reduce seizures (Kanner, 2009; Favale et al., 2003).

Kindling Model of Progression

Originally developed in regard to epilepsy, the kindling model has been expanded and applied to BD. In the original study, Graham Goddard et al. (1969) demonstrated that in animal models analogous to human epilepsy, daily exposure to a certain level of brain stimulation eventually induced seizures. This level of stimulation was not originally intense enough to invoke a seizure, yet repeated exposure lowered the seizure threshold. In a 2007 review, Robert M. Post summarized two and a half decades worth of his research applying this principle to affective disorders. Like the kindling process in epilepsy, Post demonstrated that subsequent mood episodes require less stimulation - like psychosocial stressors. He also concludes that both seizures and mood episodes may become more severe with repetition.

Assessing the role of stressful life events in the course of mania, Bostock et al. found that life events were more closely related to early episodes of mania rather than subsequent episodes (2015). While some later events of mania occurred in the month after a stressful event, others began spontaneously. Additionally, a history of more mood episodes was linked to shorter periods of remission between episodes in some groups. As such, it can be inferred that BD and epilepsy often share a similar course of progression. This information emphasizes the importance of treating both seizures and affective disorders as early as possible.

Overlap of Symptoms

Sensory/Cognitive Disturbances

While diagnostic criteria for the disorders suggest little overlap at first glance, a study from 1985 compared the experiences of people with complex partial epilepsy, affective disorders, and controls (Silberman et al., 1985). Of the 44 people with affective disorders, 34 were diagnosed with BD. The patients were generally euthymic and had no history of seizures.

Of the 87 patients included, 14% had epileptiform waves or other sharp activity. This can be compared to a 0.5% occurrence of epileptiform waves among 13,658 Royal Air Force training candidates (Gregory et al., 1993).

While Drange's study found no significant difference in the likelihood of rapid cycling between the groups with and without abnormal EEG activity, the group with abnormal EEG activity experienced significantly more hypomanic episodes per year and had a much higher ratio of hypomania to depression than those without abnormal EEG activity. The medications of the two groups did not significantly differ. The language barrier between Norwegian doctors and English-speaking researchers was one possible limitation of this study. In some cases, Norwegian terms were used to describe abnormalities in EEG activity, and when these terms didn't directly translate to the set English categories, the abnormalities were labeled as "other sharp activity" (Drange et al., 2020). The study's authors noted that a standardized procedure could produce more reliable results in future studies.

Comorbidity

The comorbidity of mood disorders and epilepsy is increased in both directions. One study examining the comorbidity of other illnesses in BD compared results with a parallel study in unipolar depression and control groups (Forty et al., 2014). The occurrence rate of epilepsy among individuals with depression was 3.88 when compared with the control group, resulting in a p-value of 0.001. The statistics for BD were even more staggering. People with BD were found to have epilepsy at 6.19 times the expected rate. The BD group was even at a significantly increased risk of epilepsy when compared to the depression group. When the authors compared BD I and BD II they found no difference. Interestingly, however, they found that a lifetime history of rapid cycling presentation was significantly correlated with multiple medical illnesses.

Both mood disorder groups experienced a significantly increased risk of asthma, elevated lipids, type 2 diabetes, gastric ulcers, memory loss/dementia, osteoarthritis, rheumatoid arthritis, and stroke. The study additionally found kidney disease, type 2 diabetes, and thyroid disease to be significantly more common in the BD group versus the depression group as well as the controls (Forty et al., 2014).

Also correlated with a higher burden of medical illnesses was a history of ECT (Forty et al., 2014), though it is unclear whether these medical illnesses are a direct result of the procedure or the consequence of a more severe course of psychiatric illness. Typically, ECT is used as a last resort due to its potentially severe side effects such as memory loss. Subsequently, the use of ECT may serve as a marker for a more severe course of psychiatric impairment. Taken together, this information may suggest that the severity of an individual's mood disorder has an impact on the development of comorbid physical illnesses.

Conversely, the rate of mood disorders among epilepsy populations is also significantly higher than expected. An increased prevalence rate of both depression and bipolar disorder was noted in a cross-sectional analysis carried out in Scotland. Of 12,720 patients determined to have epilepsy, the prevalence rate of depression (after being adjusted for age, sex, and deprivation) was 1.73 times higher than that of the individuals without epilepsy. After being adjusted for the same variables, the prevalence rate of psychotic disorders (such as BD) was 2.36 (Weatherburn et al., 2016). One limitation of this study, however, is the grouping of BD with other psychotic disorders such as schizophrenia. Though schizophrenia and BD feature similar characteristics, and people with epilepsy are more likely to experience symptoms of psychosis, data regarding individuals with a nonpsychotic presentation of BD are confounded with those experiencing only psychosis.

The percentage of people with epilepsy and comorbid BD symptoms is estimated to be about 10% (Kanner, 2003; Lau et al., 2012). Estimates of the percentage of people with epilepsy who experience depressive symptoms range from 16-39% with wide variability (Weatherburn et al., 2016; Kanner, 2003; Ottman et al., 2011; Vacca et al., 2021). Some of this variability may be due to inconsistent methods and screening tools used between studies. Patients and doctors may also under-report and underrecognize comorbid depression (Kanner, 2003). Regardless, controlled studies consistently show an increased rate of depression among people with epilepsy (Weatherburn et al., 2016; Kanner, 2003).

In prior decades, researchers have focused on the psychosocial effects of epilepsy diagnosis as a cause for depressive symptoms in these patients (Ridsdale et al., 1996). More recently, however, depression has been suggested as a precursor to epilepsy (Seidenberg et al., 2009; Kanner, 2011). A study of psychiatric comorbidities among children with epilepsy found that psychiatric symptoms preceded seizures in 45% percent of participants (Jones et al., 2007). One significant analysis of The Health Improvement Network in the United Kingdom hypothesized that more severe depression would be linked to a higher risk of developing epilepsy (Josephson et al., 2017). They found that the presence of epilepsy increased the risk of depression and the presence of depression increased the risk of epilepsy. The risk was over two times that of controls in both cases. Further, the authors compared the risk of epilepsy in various groups: patients who were not depressed, who had depression requiring counseling, who had depression requiring medication, and who had depression requiring a combination of counseling and medication, assuming an increase in depression severity with each respective group. They found that the risk of developing epilepsy increased with each level of treatment. Additionally, they found that current depression treatment was associated with worse seizure outcomes. Those

who required depression treatment were less likely to attain a full year of seizure freedom by a factor of about 1.75 (Josephson et al., 2017). In his commentary on the study, Jay Salpekar encourages further research in pediatric populations. He postulates that treating young people for depression or epilepsy may lower their vulnerability to subsequent epilepsy and depression, respectively (Salpekar, 2017). Indeed, the use of antidepressant medications in epileptic populations has been under scrutiny throughout history for the possibility of increasing seizure frequency (Jobe, 2003; Peck et al., 1983; Prasher, 1993), a topic that will be discussed in greater detail in other sections. Overall, a 2016 review concluded that most modern antidepressants are safe for people with epilepsy (Kanner, 2016).

In his 2003 article, Andres M. Kanner discusses the undertreatment and underrecognition of depressive disorders among epilepsy patients. He states that 70% of patients had a presentation akin to dysthymic disorder, though the symptoms were disrupted and thus failed to qualify for a diagnosis under the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2022). As such, both patients and healthcare providers may fail to notice and treat these symptoms in a timely manner. In this case, 60 out of the 97 patients exhibited depressive symptoms for over a year. Of these, only 33% were treated within 6 months of symptom onset. Harrowingly, this percentage did not differ between those exhibiting major depression and those exhibiting milder, dysthymic-like symptoms.

While the association between mood disorders and epilepsy is becoming more clear, there is some conflict within the literature. Currently, there is some discrepancy over the risk of depression in focal versus generalized seizures. A study from Rwanda, as well as one conducted in Italy, have found generalized seizures (in comparison to focal seizures) to carry an increased risk of depression (Sezibera & Nyirasafari, 2013; Vacca et al., 2021). In contrast, a study from

Sweden concluded that people with partial epilepsy were at a significantly higher risk of depression (Forsgren & Nyström, 1990). A few key differences characterize these articles. In the study from 1990, epilepsy participants were newly diagnosed with a seizure disorder at the time of the study – an event that could reasonably cause significant psychosocial stress (Salpekar, 2016). In addition, the researchers screened for depression by asking "Have you had a depression in the last 6 months?" This question may have lacked sufficient nuance to collect accurate data on all cases (Forsgren & Nyström, 1990). In contrast to the research by Vacca et al., (2021), and Sezibera & Nyirasafari (2013), participants were screened for depression using the Beck Depression Inventory (BDI-II) and Hamilton Depression Rating Scale (HDRS) respectively. Generally, most studies report a higher depressive symptom burden in women (Vacca et al., 2021; Sezibera & Nyirasafari, 2013; Josephson et al., 2017) which may be in part due to cyclical hormonal fluctuation (Teatero et al., 2014).

Shared Precipitating Factors

A 2017 literature review by Emmanuelle Bostock et al. examined precipitating factors of both mania and partial seizures. Of the factors included in the review, stress, menstruation, and sleep reduction were found to have an impact on both mood episodes and partial seizures. The authors of the study concluded that these shared precipitating factors may be due to common pathological mechanisms.

Stress

Stress is commonly a contributing factor in psychiatric disorders. A study done by Gilman et al. (2015) examined the effect of social stressors on the initial onset and subsequent episodes of mania through surveys spanning three years. They found that individuals with a history of childhood physical abuse or sexual maltreatment were more likely to experience

mania. In addition, financial instability, interpersonal conflict, and personal loss occurred at an increased rate during the year before a manic episode. One limitation the authors acknowledged, however, is the heritability of BD, stating that individuals who have parents with BD may both a) have a higher chance of inheriting the disorder and b) have a higher chance of experiencing adverse childhood events, so the social stressors may not be independently correlated. A collection of interviews with 62 BD patients over two years found an overrepresentation of stressful life events in the month prior to relapse (Hunt et al., 1992). The researchers interviewed participants every 3 months. If the participant maintained a state of euthymia, it was considered a "control period." Of the 62 patients, 36 relapsed. There were a total of 52 instances of relapse. Five percent of participants experienced severe events a month during control periods, but in the month prior to a relapse, 19% of participants experienced severe events. There was no statistically significant difference between episodes of mania and depression (Hunt et al., 1992). This claim conflicts with the conclusion of a similar study (Johnson et al., 2000). In the 2000 study, the authors obtained information about the participants' baseline mood state to further clarify the impact of life events. They concluded that goal-attainment events, but not adverse life events, carried an increased risk of inciting mania. Stressful life events, on the other hand, were more closely associated with depressive relapse. These results were later replicated with a similar study (Johnson et al., 2008 as cited in Bostock et al., 2015

Similarly, stress was the most commonly reported factor in a study of 400 people with epilepsy. Thirty percent of individuals in all groups and 46% of individuals with temporal lobe epilepsy (TLE) linked seizure occurrence to stress (Frucht et al., 2000). Other studies have found similar results (Ferlisi & Shorvon, 2014; Nakken et al., 2005 as cited in Bostock et al., 2015). A study of seizure diaries involving a 1-10 scale for daily stress and anxiety produced supportive

results. A one-point increase on the scale was significantly correlated with seizure occurrence (Haut et al., 2007).

Population-level stressors (such as natural disasters, evacuations, war, etc) have been found to cause increased frequency of seizures and mood episodes. In one instance, Aronson and Shukla (1987) observed BD patient outcomes following a hurricane. Their symptoms were well controlled with lithium before the event and their levels of lithium did not change. However, the individuals experienced significantly increased symptoms of depression and mania post-hurricane (Aronson and Skula, 1987). Similarly, controlled studies in people with epilepsy found that epileptic individuals who were previously adequately treated experienced more seizures during a time of war and following an evacuation for flooding (Bosnjak et al., 2002; Swinkels et al., 1998).

In a 2003 review article, Phillip Jobe demonstrated that genetically predisposed individuals are more likely to experience mood episodes following a stressful life event. Physiologically, increased hypothalamic-pituitary-adrenal (HPA) axis activity is associated with depressive episodes and mixed states (combined symptoms of (hypo)mania and depression) and may instigate cell death and atrophy within the hippocampus likely leading to memory disruption (Manji et al., 2003).

Sleep Reduction

The relationship between sleep and bipolar disorder is multifaceted. A reduced need for sleep is a key feature of (hypo)mania according to the DSM-V (American Psychiatric Association, 2022), and sleep disturbances are also frequent in depression. Interestingly, in a study involving sleep deprivation of depressed patients with BD, 7 out of 67 patients switched to

mania or hypomania after 40 hours of sleep deprivation (Wehr, 1982). Sleep reduction has also been found to be a predictor of mania in other studies (Leibenluft et al., 1996).

Sleep reduction and seizure occurrence also share a bidirectional relationship. In a previously mentioned study, sleep reduction was a commonly reported seizure trigger (Frucht et al., 2000). A study of seizure diaries and sleep duration in epileptic patients found that a decrease of as little as 1.5 hours of sleep per night was related to seizure occurrence the next day (Rajna & Veres, 1993). Seizure occurrences also impact the quality of sleep. People with TLE experience less REM sleep the night following a seizure (Bazil et al., 2000).

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Similar Pathophysiology

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Serotonin/Norepinephrine Transmission

Deficits in the serotonin and norepinephrine pathways in the brain are commonly involved in both epilepsy and mood disorders. Animal studies are often carried out on Genetically Epilepsy Prone Rats (GEPRs) which exhibit both seizure disorders and mood disorders in a manner similar to humans. Deficits in serotonin and norepinephrine transmission are common in GEPRs, and increases in these neurotransmitters can help suppress their seizures (Jobe, 2003). In humans, mood disorders (and especially suicidal ideation) are associated with a lack of serotonin within brain tissue, plasma, and platelets (Brown et al., 1982; Brown & Linnoila 1990). One study has found lower serotonin platelet concentration in unaffected relatives of people with BD (Quintin et al., 2001). An experimental study involved administering α-methyl-p-tyrosine, a substance that inhibits norepinephrine synthesis, to GEPRs. This caused an increase in seizures in the rats. This substance also contributes to depressive episodes in humans with a history of depression and hypomanic episodes in people with bipolar disorder who were previously in remission (Jobe, 2003).

Controlled studies of PET scans have demonstrated lower serotonin transmission in the frontal lobe, temporal lobe, and limbic cortex of people with depression or epilepsy (Kanner, 2009, Drevets, et al., 1999; Sargent et al., 2000). Similarly, sensitivity to serotonin deficits may be a possible contributing factor to BD. In an experiment, Quintin et al., (2001) studied the effects of acute tryptophan depletion in unaffected relatives of BD patients and healthy control subjects. As a dietary precursor to serotonin, tryptophan is essential for serotonin synthesis. The relatives of BD patients experienced lower moods and more impulsivity after treatment, but not with the placebo. The controls, however, were unaffected (Quintin et al., 2001). A later study monitored the cognitive performance of first-degree relatives of BD patients and controls under similar conditions. The relatives had lower baseline skills in planning and memory and experienced lower information processing speeds following the tryptophan-depletion treatment, unlike controls (Sobczak et al., 2002). Taken together, this information suggests a possible role for serotonin and norepinephrine transmission in both affective disorders and epilepsy. Medication use – such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) – based on these conclusions is discussed in later sections.

Gamma-aminobutyric Acid/Glutamate Transmission

Research also implicates gamma-aminobutyric acid (GABA) and glutamate imbalance in mood disorders and epilepsy. It is suggested that deficiency in GABA transmission and excessive glutamate transmission contribute to epilepsy (Jobe, 2003). Experimentally reduced GABA transmission induced audiogenic seizures in otherwise normal animals (Faingold, 2002). Studies conducted on individuals with Major Depressive Disorder found decreased GABA levels in multiple regions, including the dorsomedial, dorsal anterolateral prefrontal, ventromedial

prefrontal regions, and the occipital lobe (Kanner, 2011). Medications that increase GABA levels, however, have not shown any significant antidepressant effect - likely due to their inhibition of serotonin (Seethalakshmi & Krishnamoorthy, 2007). Instead, glutamatergic drugs have been found to have an antidepressant effect (Kanner, 2011).

Common Regions/Structures

In addition to deficits in neurotransmission, BD and epilepsy share similar structural differences. An imaging study from 2013 found patients with Bipolar Disorder to have reduced white matter in the thalamic region (Barysheva et al., 2013). A worldwide review of structural brain abnormalities among epilepsy patients found significant structural compromise in the thalamus, regardless of the type of epilepsy (Whelan et al., 2018). The mesial temporal lobe is typically implicated in TLE, often involving hippocampal atrophy (Kanner, 2009; Mathern et al., 2008). Similarly, hippocampal atrophy has been demonstrated in patients with depression in multiple studies, with one even suggesting that the length of depression is directly correlated with a reduction in hippocampal volume (Bell-McGinty et al., 2002; Posener et al., 2003).

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Association with Reproductive Dysfunction

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As hormone levels - such as estrogen, progesterone, and the androgen testosterone - fluctuate during the menstrual cycle and across the lifespan, many women experience wide-ranging physical and psychological symptoms. These symptoms are particularly intense in women with irregular cycles or menstrual-related disorders such as Premenstrual Syndrome (PMS) or Premenstrual Dysphoric Disorder (PMDD). Not only can these hormonal fluctuations affect the course of BD, but women with BD may also be more likely to experience reproductive system dysfunction - including conditions like PMS, PMDD, polycystic ovary syndrome (PCOS), endometrial hyperplasia, and menstrual cycle irregularity (Teatero et al., 2014).

Reproductive structures, events, and functions may exacerbate and/or incite mood episodes in some women, though these effects are not widely understood. Examples of these events and time periods include menarche, menstruation, pregnancy, postpartum, and menopause. According to clinical interviews of women diagnosed with BD, 18% experienced an onset of mood disorder within one year of menarche. Additionally, 67% reported postpartum mood episodes (Freeman, et al., 2002).

During the menstrual, premenstrual, and periovulatory phases of the menstrual cycle, women with BD may experience entrainment (an increased likelihood of a new episode) or exacerbation (worsening of the symptoms of a current episode) (Teatero et al., 2014). In a prospective study involving 25 women with rapid-cycling BD, five experienced a significant elevation in mood in the postmenstrual phase versus the premenstrual phase. Conversely, six women experienced a significantly lower mood under the same conditions. While there was no clear pattern of the direction of menstrual cycle effects on mood, 44% of these women experienced significant mood changes (Leibenluft et al., 1999). Some women with mood episodes impacted by the menstrual cycle have normal hormonal profiles, suggesting that a hypersensitivity to normal hormonal fluctuation may underlie the psychological distress in these women (Teatero et al., 2014). A 2014 literature review of the menstrual cycle and BD found approximately three times more cases of premenstrual hypomania or mania versus depression. A majority of these cases involved episode entrainment to the menstrual phase. A combined analysis determined that "64-68% of women with BD report premenstrual changes in mood" (Teatero et al., 2014). Research is limited by inconsistent methods and definitions of menstrual-related disorders and symptoms (Endicott, 1993 as cited by Teatero et al., 2014). Additionally,

up to 50% of women experience menstrual problems before a BD diagnosis, but women with irregular cycles are generally excluded from existing research (Teatero et al., 2014).

Puberty may increase seizure frequency in children with epilepsy - specifically those with generalized seizures, but this effect appears to subside after menarche (Niijima & Wallace, 1989; Diamantopoulos & Crumrine, 1986). As many as 40% of women who experience epilepsy may experience a worsening of seizures during the menstrual cycle and may be diagnosed with catamenial epilepsy. This worsening of seizures may be related to increases in estrogen around ovulation and/or changes in levels of progesterone around menstruation (Maguire & Nevitt, 2021). Standard treatments for catamenial epilepsy differ depending on the patient's cycle regularity. People with regular menstrual cycles may be prescribed hormonal supplements to raise progesterone levels or non-hormonal antiepileptics such as clobazam and acetazolamide. Those with irregular cycles are typically prescribed medroxyprogesterone or gonadotropin-releasing hormone (GnRH) analogues to cessate menstruation (Maguire & Nevitt, 2021). A review of randomized, controlled trials of medication interventions found no trials for non-hormonal treatments in women with irregular cycles that met the inclusion criteria, highlighting a lack in the existing literature. Overall, the study compared the effectiveness of norethisterone and progesterone versus placebo. Of the norethisterone trials, neither reported a significant difference in seizure reduction versus placebo. Of the progesterone trials, one reported a significantly higher seizure reduction with treatment, though the other found no difference. The authors evaluated the strength of the trials they reviewed and concluded that the results of the progesterone and norethisterone studies were of moderate-to-low and very low certainty, respectively. They also emphasized the need for more precise methods and further research into other treatment options (Maguire & Nevitt, 2021).

Polycystic ovary syndrome (PCOS) is a clinical disorder of infrequent ovulation and hyperandrogenism (HA) and occurs in about 10% of women (Morrill, 2022). Rates of PCOS are as much as double for women with bipolar disorder and/or epilepsy (Zhang et al., 2016; Qadri et al., 2018). A broad-spectrum antiepileptic drug, valproate, may influence this rate. Zhang et al. (2016) in a review study found that the incidence of PCOS during valproate treatment in women with epilepsy was 24.1%. This rate is slightly higher than the 23% rate found in women with bipolar disorders in a hospital setting irrespective of medication (Qadri et al., 2018). In the review study, Zhang et al. (2016) conclude, "Although the onset of PCOS has its inherent reasons, our findings suggest that VPA [valproate] is more likely to be associated with elevated levels of testosterone and HA than non-VPA drugs in women with bipolar disorder."

Relevant Treatments

Use of Antidepressants in Epilepsy

Throughout history, medical providers have been hesitant to treat depression in epilepsy patients out of fear of inducing iatrogenic seizures (Kanner, 2003). There have been case reports of antidepressant-induced seizures (Peck et al., 1983; Prasher 1993; Rosenstein et al., 1993), though newer research has found most modern antidepressants to be safe in people with epilepsy – selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), specifically (Kanner, 2016). One study exemplifying this concept found that in patients with epilepsy and depressive symptoms, following treatment with these SSRIs or SNRIs, 27.5% of epileptic patients who had been experiencing one or more seizures a month experienced a reduction of their seizures to >1/month (Ribot et al., 2017). Seventy-three percent of the patients included in the study showed considerable improvement in their depressive symptoms as a result of the medication. The authors of the study suggest, based on their data,

that SSRIs and SNRIs may be useful for patients with treatment-resistant epilepsy (Ribot et al., 2017). Future research to support this position is necessary, including double-blind and placebo-controlled trials. In one study of sertraline, seizures worsened for 6 of 100 patients but subsided after dose adjustments to anticonvulsant medications (Kanner et al., 2000). Specific antidepressants posing a risk of increased seizures in people with epilepsy include amoxapine, bupropion, clomipramine, and maprotiline. Increases in seizures are most often related to excessive serum levels (Johannessen-Landmark, et al., 2016). While the risk ratio for epilepsy in patients taking tricyclic antidepressants is higher than in the general population, it is even higher in patients who are actively depressed with no treatment (Jobe, 2003).

Use of Anticonvulsants in Bipolar Disorder

What is more consistently demonstrated is the adverse effects of antidepressants in BD. Antidepressants have been associated with switching to mania and more rapid cycling (Ghaemi et al., 2003) necessitating safer alternatives. Given the biochemical and structural similarities previously discussed, it is unsurprising that anticonvulsants have a place in the treatment of BD. Investigators have researched psychiatric uses for carbamazepine, oxcarbazepine, lamotrigine, valproate, zonisamide, and topiramate with varying levels of success (Jobe, 2003). Evidence suggests that anticonvulsant medications including lamotrigine, carbamazepine, and valproate increase monoamine transmission, contributing to their mood-stabilizing effects. Carbamazepine was found to increase serotonin, but not norepinephrine transmission (Yan et al., 1992). Lamotrigine was found to inhibit serotonin reuptake at dose-dependent levels (Southam et al., 1998). Valproate raised serotonin levels in animal experiments, suggesting this change may mediate some of its anticonvulsant and mood-stabilizing effects (Whitton & Fowler, 1991).

However, as mentioned previously, valproate may also contribute to reproductive system dysfunction (Zhang et al., 2016).

Use of Electroconvulsive Therapy, Magnetic Seizure Therapy, and Vagus Nerve Stimulation

There is some evidence that seizures may be antidepressant. While vagus nerve stimulation is effective in epilepsy, lesions of the locus coeruleus - part of the norepinephrine system - reduce its efficacy (Jobe, 2003). A 1994 review (Mukherjee et al., 1994) of ECT found that the procedure resulted in significant improvement or remission of acute mania symptoms in 80% of participants, even those who had previously failed to respond to medication. Interestingly, the authors noted a lower seizure threshold in manic versus depressed patients. The study suggested future research on the subject of relapse and cognitive changes due to ECT (Mukherjee et al., 1994). Another study of ECT with 522 BD patients in various mood states found ECT to be effective in at least two-thirds of the participants (Perugi et al., 2017). The study reported similar results in manic patients, with 75% responding to treatment. Importantly, the authors concluded the practice was safe and involved virtually no risk of inducing mania (Perugi et al., 2017). An earlier study by White et al., (2006) found that magnetic seizure therapy (MST), a similar practice to ECT, was safer than ECT albeit less effective.

<center>**Discussion**</center>

Clearly, the relationship between BD, depression, and epilepsy is intricate and goes beyond traditional classifications of "physical" and "mental" illnesses. Psychiatric symptoms are commonly present in epileptic patients and episodes of mania and depression involved with BD can have serious medical consequences. The presence of one disorder increases the risk of the other, and similar biologic processes and structures are involved in each. Based on this

bidirectional association of epilepsy and BD, Jay Salpekar concluded that "the notions of mental illness differing from 'organic' illness must be revised" (2017). Undoubtedly, mental illnesses can have very physical, and even somatic effects. As stated earlier, both depression and BD were strongly correlated with a multitude of physical ailments (Forty et al., 2014). The presence of depression among epilepsy patients is correlated with worse seizure outcomes (Josephson et al., 2017) and these symptoms are known to have a significant impact on the quality of life of these patients (Kanner, 2003). As medical professionals and researchers alike become more informed on the interaction of these disorders and effective treatment strategies for comorbidity, we can expect the quality of life to improve for people with one or both of these disorders. Insight into precipitating factors for both epilepsy and mood episodes can help patients retain a sense of control (Bostock et al., 2015). Additionally, combined application of the kindling model and the fact that psychiatric symptoms may commonly predate epilepsy diagnosis suggests that successful treatment of one disorder may decrease vulnerability to the other. Future research in pediatric populations could provide support for this theory (Salpekar, 2017). Mood symptoms around the time of menarche and/or reproductive dysfunction may also be a predicting factor for BD in women. Reproductive dysfunction and menstrual exacerbation are common in epilepsy as well. There is an alarming lack of conclusive data on the relationship between reproductive dysfunction and each of these disorders, though a relationship is evident (Teatero, 2014). More standardized methods and definitions of "depression" could help produce more reliable, reproducible information on the prevalence of depression and BD among people with various types of epilepsy. It is unclear whether depressive symptoms affect individuals with partial seizures or generalized seizures more frequently (Sezibera & Nyirasafari, 2013; Vacca et al., 2021; Forsgren & Nyström, 1990). Further clarification on the role of serotonin and

norepinephrine transmission in each disorder may improve treatment strategies. Randomized, controlled trials for catamenial epilepsy treatments are necessary. Trials including women with irregular menstrual cycles are especially needed (Maguire & Nevitt, 2021). Additionally, studies regarding the use of antidepressants in treatment-resistant epilepsy populations may lead to promising results (Kanner, 2003).

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