Absence seizures and their relationship to depression and anxiety: Evidence for bidirectionality

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Abstract

Absence seizures (AS), presenting as short losses of consciousness with staring spells, are a common manifestation of childhood epilepsy that is associated with behavioral, emotional, and social impairments. It has also been suggested that patients with AS are more likely to suffer from mood disorders such as depression and anxiety. This systematic review and meta-analysis synthesizes human and animal models that investigated mood disorders and AS. Of the 1019 scientific publications identified, 35 articles met the inclusion criteria for this review. We found that patients with AS had greater odds of developing depression and anxiety when compared to controls (odds ratio = 4.93, 95% confidence interval = 2.91–8.35, $p < .01$). The included

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studies further suggest a strong correlation between AS and depression and anxiety in the form of a bidirectional relationship. The current literature emphasizes that these conditions likely share underlying mechanisms, such as genetic predisposition, neurophysiology, and anatomical pathways. Further research will clarify this relationship and ensure more effective treatment for AS and mood disorders.

Keywords

behavioral disorders; childhood absence epilepsy; GAERS; mood disorders; WAG/Rij

1 | INTRODUCTION

Absence seizures (AS) are characterized by recurrent 5–10-s episodes of unconsciousness and staring spells with distinct rhythmic 3–4-Hz spike-and-wave discharges (SWDs) on electroencephalogram.[1–3] AS are relatively common in the pediatric population, with about 10% of seizures in children with epilepsy considered typical AS.[4] Although absence epilepsy (AE) and childhood AE (CAE), which are characterized by AS, were initially thought to be benign epilepsy disorders without developmental or long-term sequelae, this notion has since been challenged. Several studies over the past 20 years have described relationships between CAE and developmental, cognitive, mood, and psychosocial impairments.[5–8]

For decades, numerous studies have described higher rates of psychiatric disorders observed in pediatric epilepsy.[9] In an early study of 146 children aged 5–16 years with one of three types of childhood epilepsy disorder, Ott et al. observed that 51% of their study cohort met criteria for a psychiatric disorder, including mood disorders in 13% and suicide ideation in 18% of the population.[10] In two separate studies, Caplan et al. reported anxiety rates of 22%–24% and depression rates of 4%–6% in patients with CAE, compared to anxiety rates of around 7% and depression rates of around 3% in children between the ages of 3 and 17 years in the general population.[7,11,12] Moreover, a prevalence of anxiety and depressive-like behaviors has also been reported in animal models, including in Wistar Albino Glaxo From Rijswijk (WAG/Rij),[13,14] Long–Evans (LE),[15] and Genetic Absence Epilepsy From Strasbourg (GAERS) rats.[16]

Young adults with CAE have more behavioral, emotional, and psychiatric difficulties, which can lead to avoidance of large gatherings, problematic family relationships, and poor performance at school.[17,18] Fastenau et al. found that AS are associated with less proficient language, attention/executive skills, and verbal memory.[19] These deficits have long-term sequelae and considerably impact the quality of life even after seizure management or remission.[18] Behavioral outcomes are significantly worse in patients with poor seizure control.[18]

The high rates of mood disorders in humans with AE and in animal models suggest an integral relationship between mood disorders and AS. However, it is unknown whether AS and mood disorders share an underlying pathology, or whether mood disorders are a consequence of AS. Furthermore, the therapeutic effects of antiepileptic drugs (AEDs) and

antidepressants on AS are unclear. The relatively small number of studies likely explains the inconsistent findings and speaks to the need for a meta-analysis and a systematic review. To better understand the relationship between anxiety, depression, and AS, we conducted a systematic literature review of both human and animal studies that evaluated depression and anxiety in AS. Clarifying the relationship between AS, neuropsychiatric disorders, and treatment modalities is crucial to mitigating the impacts of this complex disorder.

2 | MATERIALS AND METHODS

2.1 | Literature search

We performed a systematic search of the literature to identify studies that reported on depression and anxiety in patients with a history of AS or in animal models of AE. The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20]

An experienced medical librarian (M.C.F.) consulted on methodology and ran a Medical Subject Headings analysis of known key articles provided by the research team (https:// mesh.med.yale.edu/). In each database, we ran scoping searches and used an iterative process to translate and refine the searches. To maximize sensitivity, the search used controlled vocabulary terms and synonymous free-text words to capture the concepts of "psychiatric illness" and "epilepsy." On September 4, 2019, and again on June 24, 2020, the librarian performed a comprehensive search of multiple databases: MEDLINE (Ovid), Embase (Ovid), PsycINFO (Ovid), Web of Science Core Collection (Clarivate), Scopus (Elsevier), CINAHL (Cumulative Index to Nursing and Allied Health Literature; EBSCOhost), and the Cochrane Library (Wiley). The search strategy for Ovid MEDLINE is included in Appendix S1.

2.2 | Inclusion and exclusion criteria

This systematic review included original preclinical studies and retrospective or prospective clinical studies that examined the association between depression or anxiety and AS. We excluded studies without the right study design, including conference abstracts, editorials, case reports, case series, and reviews. Studies on other types of seizures without a clear separation of the cohort with AS and studies that did not explicitly study depression or anxiety were excluded due to wrong study parameters. Articles were limited to the English language. No date limit was applied.

2.3 | Study selection

Two authors (B.F.G. and M.R.S.S.) independently evaluated the titles and abstracts of the identified articles. Abstracts that did not include sufficient information to determine eligibility for inclusion were retrieved for full-text evaluation. The final search retrieved a total of 1552 references. This set was uploaded to Covidence (https://www.covidence.org/) for screening, which identified duplicates and left 1019 for screening. Authors B.F.G. and M.R.S.S. screened the titles and abstracts, and then reviewed the full text of the 121 eligible articles. Thirty-five articles met the inclusion criteria for extraction. The selected articles were categorized as human or animal studies. The animal studies were further classified

based on the models used in the study. Any disagreements were resolved by consensus. A PRISMA flow diagram is illustrated in Figure 1.

2.4 | Data extraction

Four reviewers (R.A.O.B., T.G.O.B., A.S., and A.K.) conducted study evaluation and data extraction. The data extracted included a general description of the study population, sample size, type of animal model, interventions, experiments, results, and conclusions. A qualitative summary composed of these descriptive properties was created for each study.

3 | RESULTS

3.1 | Human studies

Seven human studies describing the association of AS with depression and anxiety were included. With two exceptions,[21,22] all studies were conducted in a pediatric population with the Kiddie Schedule for Affective Disorders and Schizophrenia as the most commonly used diagnostic tool. The participants' characteristics, diagnostic tools, and outcomes are described in Table 1.

All studies showed a higher prevalence of depression and anxiety in patients with AE. Using structured psychiatric interview and mood self-report scales, Caplan et al.[11] showed that children with complex partial seizures (CPS) and CAE had a higher prevalence of suicidal ideation (20% vs. 9%, $p < .02$) and affective/anxiety disorders (33% vs. 6.5%, $p < .01$) than unaffected children. Moreover, higher rates of anxiety (50% vs. 27%, $p < .02$) and lower rates of depression (15% vs. 21.6%, $p < .02$) were found in the CAE group when compared to CPS. A subsequent study from Caplan et al.[7] revealed that 61% of the children with CAE had a psychiatric diagnosis, 31% of whom were diagnosed with an affective or anxiety disorder, compared with 9% in the control group with these diagnoses ($p = .01$). Girls with CAE were 5.8× more likely to have an anxiety disorder diagnosis than boys (95% confidence interval [CI] = 1.05–31.95). For every additional year of CAE diagnosis, there was a 1.35× greater chance of having a psychiatric disorder (95% CI = 1.05–1.73, $p < .02$), and children with 10 or more seizures per year were 1.2× more likely to have a psychiatric diagnosis (95% CI = 1.02–1.38, $p < .03$).

Vega et al.[23] assessed depression and anxiety symptoms with the Behavior Assessment System for Children (BASC) Anxiety and Depression subscales, a parent-report questionnaire. Clinically significant symptoms were defined as one and a half standard deviations from the BASC normative sample mean. In the CAE group, 11% of the patients had Anxiety and 25% had Depression subscale scores in the clinically significant range, whereas only one control patient (2.4%) met this criterion for each subscale. Statistical analysis revealed significantly higher questionnaire scores in the CAE group for anxiety (50.7 1; 9.3 vs. 43.3 ± 7.5, $p = .001$) and depression (50.4 ± 12.9 vs. 43.3 ± 7.7, $p = .007$) when compared to healthy controls. Contrary to the results from Caplan et al.,[7] no association between seizure frequency or disease duration was found with the development of anxiety or depression.

A statistically significant difference ($p < .003$) was found by Schreibman Cohen et al.[24] regarding the presence of a psychiatric diagnosis between healthy children (17%) and a CAE cohort (60%), with 20% diagnosed with affective–anxiety disorder and 24% with attention-deficit/hyperactivity disorder. Similarly, Precenzano et al.[25] showed higher scores on anxiety (59.2 ± 7.3 vs. 48.9 ± 10, $p < .001$) and depression symptoms (15 ± 7.5 vs. 8.7 ± 1.88, $p < .001$) in the CAE group compared to the control group.

Abarrategui et al.[21] found that patients with CAE and juvenile absence epilepsy (JAE) persisting into adulthood presented the highest anxiety scores on ISRA (Inventory of Anxiety Situations and Responses) when compared to controls and to other idiopathic generalized epilepsy syndromes. The CAE/JAE group also showed a higher prevalence of depression (17%) when compared to control (0%); however, both disorders failed to show statistical significance. Another study by Gabriel et al.[22] found that patients with JAE had more mood disorders (19.6%), but less anxiety (17.4%) than the general population (19.3% and 25.8%, respectively), although this difference failed to reach significance.

Finally, a meta-analysis was conducted on five studies. Two studies were not included because they did not have a control group[22] or there were too few subjects with a diagnosis of anxiety and/or depression.[25] Patients with AS had greater odds of developing depression and anxiety when compared to controls (odds ratio = 4.93, 95% CI = 2.91–8.35, $p < .01$; Figure 2).

3.2 | Animal studies

We divided the studies based on the animal models. We further divided the studies based on interventions, including pharmacological, environmental, and nutritional. The animal studies are described in Tables 2 and 3.

3.2.1 | WAG/Rij rats—The WAG/Rij strain is an inbred rat strain that spontaneously emits cortical SWDs together with clinical manifestations of seizures. WAG/Rij rats begin to show SWDs at the age of 2–3 months.[26,27] WAG/Rij rats behave similarly to nonepileptic rats in terms of spontaneous activity, reproductive behaviors, feeding, social interactions, and learning positively or negatively reinforced tasks.[28,29] It has been suggested that WAG/Rij rats display more depressive-like and anxious behaviors than control rats.[30–35] Depressive-like behavior and anxiety in rats is standardly evaluated through two different behavioral tests, the forced swim test and the sucrose preference test, and anxiety is evaluated through tests involving an open field or an elevated plus maze. Studies have shown an increase in immobility time in forced swim tests, reduced sucrose intake in WAG/Rij rats compared to Wistar control rats,[33–35] and less exploration of the field and elevated plus maze.[30–32]

Antidepressants: A series of pharmacological interventions have been evaluated to explore new avenues of treatment that link depression and anxiety to AS in WAG/Rij rats. Antidepressants have been used to explore the interplay between AS and depressive-like behaviors in rat models of AS.[32,36,37] Imipramine, a tricyclic antidepressant (TCA) noted for its antiepileptogenic effects, was found to decrease depressive behavior by reducing immobility times during the forced swim test and by increasing the preference for sucrose

in the sucrose preference test.[37] This was particularly evident with subchronic administration (e.g., 15 days). However, imipramine had no significant effects on anxiety as measured by elevated plus maze.[37] The mechanism of action was explored further through the introduction of parlodel, a dopamine agonist, and raclopride, a dopamine antagonist.[32] It was found that raclopride was able to block antidepressant effects of imipramine as suggested by longer duration of immobility in a forced swim test, suggesting that dopamine was involved in mediating depressive-like behaviors in the WAG/Rij model.[32]

The effects of clomipramine, a TCA, were investigated under a similar premise. It was found that early subchronic administration of clomipramine significantly reduced SWDs. However, clomipramine also evoked behavioral symptoms of depressive-like behaviors in the rat model, indicated by a decreased score on the sucrose preference test as compared to the control group. One possible explanation could be that early clomipramine treatment may restrain the normal development of serotonergic, monoaminergic, and cholinergic systems.[34] An alternative explanation is that clomipramine may have been administered for an insufficient duration to reduce depressive behaviors. Citraro et al. attempted to address the latter possibility by introducing different timelines of treatment.[33] It was found that early chronic treatment with selective serotonin reuptake inhibitor antidepressants, such as fluoxetine and duloxetine, had antiepileptogenic effects when administered before seizure onset in WAG/Rij rats. Early chronic treatment with fluoxetine also significantly decreased immobility times during forced swim tests.[33] These findings reinforce the importance of intervention windows and length of treatment to developmental and behavioral outcomes. Results from these diverse studies suggest that antidepressants have potential benefits in terms of treatment of AS and its behavioral comorbidities, depending on dose, time of intervention, and length of treatment.

Anticonvulsants: Ethosuximide (ESX) has been an extensively studied anticonvulsant therapy due to its clear clinical benefits in AS treatment.[8,38,39] Several studies showed that early and chronic treatments with ESX prevented the occurrence of AS and comorbid depressive-like symptoms by blocking the occurrence of SWDs in a WAG/Rij model.[13,40] Van Luijtelaar et al.[40] demonstrated a significant increase in sucrose preference, whereas Sarkisova et al.[13] showed complete resolution of SWDs and a considerable increase in sucrose preference. These findings suggest that it is possible that full resolution of AS is required for improvement of behavioral symptoms. The beneficial effects of ESX were further confirmed through an early intervention, which reduced both epileptic and depressive features in comparison to other anticonvulsants.[41] ESX has also been shown to significantly decrease immobility time during forced swim tests as compared to controls.[35] However, whereas ESX intervention seemed to be successful in reducing depressive symptoms, it did not have any significant effects on anxious behaviors.

Other anticonvulsant interventions have also been shown to reduce behavioral markers of depression and anxiety. Although less applicable from a clinical perspective, it was found that early chronic intervention with vigabatrin, an AED and a γ-aminobutyric acid (GABA) analogue, decreases the incidence of AS and reduces immobility time during forced swim tests.[42] The authors attributed the antidepressant effect of vigabatrin to its effects on seizure development.[42] This result motivated further research on aripiprazole,[43]

an atypical antipsychotic, and rapamycin, a mammalian target of rapamycin,[44] which were observed to decrease the number of seizures and depressive behavior when administered at subchronic doses (7 days).

Although early chronic (119 days) intervention with rapamycin decreased the development and number of seizures, it also evoked depressive behaviors, which could be due to the direct effects of rapamycin on appetite.[44,45] Furthermore, the beneficial antidepressant and anticonvulsant effects of subchronic rapamycin administration were reversed through lipopolysaccharide administration.[46] Lipopolysaccharide was later also found to have convulsant and depressive outcomes even upon acute administration.[46] These studies support earlier claims that the presence of AS and depressive symptoms are interconnected.

The optimal duration of intervention may vary among anticonvulsant medications, with some antipsychotic medications ineffective with early chronic administration,[33] and other early chronic AED treatments successful.[47] Similarly, only early chronic treatments with combined valproic acid and sodium butyrate reduced the incidence of both AS and depressive behaviors, and a shorter duration of treatment increased the incidence of depressive behaviors.[48] However, anxiety behaviors were not affected by any combination of anticonvulsant administration.

Nutrition and environment: Although the development of AS is believed to be partially genetically determined, there is evidence that nutrition and other environmental factors have an impact on seizure development. Early chronic administration of statins significantly reduced the occurrence of AS and produced both antidepressant and anxiolytic effects on behavior.[30] A high ketone diet was also noted to have antiepileptogenic and anxiolytic effects.[31] Chronic and subchronic ketone supplements reduced AS and anxiety-related behavior in WAG/Rij rats that were tested on the elevated plus maze.[31]

It was also found that defective hippocampal melatoninergic systems could contribute to the presence of depressive symptoms in WAG/Rij rats.[49] Lower levels of melatonin in the hippocampus correlated with lower sucrose preference test scores and increased immobility during forced swim tests.[49] Chronic intervention (18 days) with melatonin after pinealectomy caused an increase in the sucrose preference test score.[49] There has also been evidence that rearing affects the development of AS. WAG/Rij rats had fewer seizures and displayed fewer depressive behaviors when fostered with control mothers immediately after birth.[50]

3.2.2 | LE rats—The LE rat strain is characterized by high-voltage rhythmic spike discharges accompanied by immobility and whisker twitching. These rhythmic spike discharges share similarities with SWDs in AS.[51]

Anticonvulsants: As with other AS rat models, anticonvulsant medication has been the primary vehicle of pharmacological intervention for LE rats. Lamotrigine (LTG), an AED, was found to decrease the frequency and duration of SWDs in an LE model.[15] Chronic administration of LTG effectively reduced AS and ameliorated anxious and depressive behaviors.[15] Similarly, acute administration of ESX effectively reduced depressive-like

symptoms 30 min after treatment in LE rats but did not have any effect on anxious behaviors.[52]

3.2.3 | GAERS rats

The GAERS model is a strain of rats that exhibit the spontaneously occurring AE phenotype, which is similar to human AE.[53] GAERS display recurrent generalized nonconvulsive seizures based on bilateral and synchronous SWDs that are accompanied by staring, behavioral arrest, and at times twitching of the whiskers.[54]

Anticonvulsants: Similar to its application for WAG/Rij and LE models, ESX has been used as one of the main pharmacological interventions in the GAERS model. In GAERS rats, ESX has been observed to reduce the frequency of seizures and anxious behavior.[8] Another intervention that has been studied is Z944, a pan-T-type calcium channel antagonist, which has been shown to increase anxious behavior.[55]

Environment: The effect of environmental exposures on epilepsy development and severity has been studied in multiple models. For GAERS rats with environmental enrichment or standard housing before or after the onset of epilepsy, a decrease in the development and frequency of seizures, along with a decrease in anxious behavior, was observed.[56]

4 | DISCUSSION

The bidirectional relationship between epilepsy and psychiatric disorder, including depression and anxiety, is not a new concept.[16,57] Patients with depression and anxiety are at increased likelihood of a diagnosis of epilepsy later in life, and epilepsy is associated with a higher incidence of various psychiatric disorders such as depression, anxiety, and suicidal ideation.[58,59] A recent study conducted using 10 million patient health records suggested a relationship between depression and epilepsy, with each condition considered a risk factor for the other.[59] Similarly, a longitudinal cohort study conducted using the UK General Practice Research Database and several other worldwide studies have described the bidirectional association between anxiety and epilepsy.[58,60–65] Another study reported higher rates of depressive disorders and anxiety disorders in children with recent onset epilepsy, along with the observation that in some cases, psychiatric disorder antedates epilepsy onset.[9] The presence of mood disorders before seizures, therefore, suggests common neurobiological influences and challenges the observation that mood disorders result from AS.

Our systematic review of the literature presents evidence describing a robust association between AS and depression and anxiety. All of the human studies included in this review showed a significant interaction between these behavioral comorbidities. The meta-analysis also revealed significantly higher odds of a diagnosis of depression or anxiety in patients with AE. The bidirectionality was further supported by studies of animal models, which showed the time-dependent and dose-dependent antidepressant effects of AEDs as well as the anticonvulsive effects of antidepressants. Figure 3 illustrates the effects of various AEDs and antidepressants on AS and associated behavioral disorders. These findings suggest a bidirectional relationship between AE and psychiatric disorders, which hints at the possibility of shared factors, such as similar genetic predisposition, neurobiological

pathways, and anatomical connections that have an effect on both AE and psychiatric disorders.

In animal models of AE, depressive-like behaviors exist before and after the emergence of seizures, suggesting that psychiatric comorbidities are seen not only secondarily to AE.[16] Although the exact pathogenesis of AE in humans and animal models is not clearly understood, there is strong evidence for a genetic component. Current consensus holds that AE has a complex genotype, with a 16%–45% positive family history.[66] Concordances of 70%–85% and 33% have been reported in monozygotic twins and first-degree relatives, respectively.[66,67] Mutation in the $GABA_A$ receptor has been associated with CAE.[68] Also, alteration in the $GABA_A$ receptor has been shown to contribute to the etiology of major depressive disorder.[69] Deficits in $GABA_A$ neurotransmission in $GABA_A$ receptor-deficient mice caused behavioral and cognitive disorders.[70] Similarly, deficits in GABA neurotransmission are also implicated in anxiety spectrum disorders.[71–73]

Disturbances in several key neurotransmitter systems are implicated in AE and depression, notably GABAergic and glutamatergic systems. Impaired functioning of glutamatergic and GABAergic pathways has been recognized in AS[74,75] as well as in depression and anxiety.[76] Although the actual mechanisms are complex and not fully understood,[77,78] many pharmacologic and neuroimaging studies have described the role of these neurotransmitters in depression. Specifically, using proton magnetic resonance spectroscopy, abnormal concentrations of glutamate[79] and GABA[80,81] were identified in patients with depression. The possible therapeutic role of glutamate receptor modulators in AS[82] and depression[77] also suggests bidirectionality between the two conditions.

Neuroanatomically, various cortical and thalamic areas are implicated in AS, depression,[83,84] and anxiety disorders.[85] Specifically, Holmes et al. demonstrated that the spikes in AS are generated unilaterally in the dorsolateral frontal region and spread to other frontal cortical areas before evolving into spike-and-wave cycles.[86] Additionally, cortical spike generation requires an intact thalamocortical network,[87] implicating corticothalamic circuits in pathogenesis of AS. The corticothalamic circuit also plays a central role in cognition[88] and depression.[89] Disruption of the corticostriatal–thalamic circuit has been shown to impair cognitive control and regulation of emotions in patients with depression.[89] Furthermore, animals exhibiting AS have increased serotonin metabolism in the prefrontal cortex and decreased metabolism in the thalamus.[90] Ventrolateral prefrontal cortex involvement[85] and impaired 5-hydroxytryptamine metabolism[7,91] are also found in anxiety disorders.

Furthermore, several studies have suggested that limbic structures, such as the nucleus accumbens, and hypothalamic–brain stem changes may play an important role in both AS epileptogenesis and its behavioral comorbidities.[92] Vega et al. found that a few subsets of affective symptoms including social isolation and low self-esteem are more prevalent in children with AE than their peers.[23] Interestingly, a recent study showed that a prefrontal–paraventricular thalamus circuit is involved in juvenile social isolation.[93] Moreover, a study conducted by van Luijtelaar et al. showed that the chronic treatment of ESX, a thalamic calcium channel blocker and the drug of choice for AE, decreases immobility score on the

forced swim test and has no effect on the sucrose preference test.[40] The forced swim test is despair related,[94] likely involving corticolimbic regions, whereas the sucrose preference test reflects the hedonic pleasure experienced by the animal,[95] thus primarily involving the striatal circuits. Selective modulation of depressive symptoms by anticonvulsants and selective subsets of affective symptoms in AE highlight the finding that the behavioral deficits associated with AE appear to follow specific circuits common to both diseases rather than being a global or distributed effect of epileptogenesis.

Limitations of this review include the difficulty of isolating factors that contribute to AS and depression. The most recent literature has not been able to determine conclusively the underlying mechanisms of conditions such as AS and depression due to their complex neuronal network integrations, which makes their secondary effects difficult to compare. In addition, although AE is primarily a pediatric disorder,[4] previous studies with both GAERS and WAG/Rij rats have also reported age-dependent phenotypic features of SWDs, although they differ from what is observed in clinical AE.[96] Although it has been established that long-term psychiatric comorbidities are worse in patients with longer duration of illness and persist even after seizures subside,[18] the possible effects of age on the relationship between seizures and mood disorders have not yet been reported. Another limitation is the relatively small size in the clinical studies, which could lead to publication bias. Further extensive and well-designed studies are still required to understand these integral associations better. Similarly, the review is limited by fewer studies on anxiety than depression, as anxiety is an understudied topic that is harder to diagnose, especially in animal models.

4.1 | Conclusion

Genetic, neuropathological, neuroanatomic, environmental, and neurotransmitter disturbances associated with both AS and behavioral comorbidities support a bidirectional relationship between these psychiatric and neurological disorders. However, it is essential to emphasize that not all associations and findings observed in animal studies will translate to humans. Therefore, rigorous testing of these hypotheses with additional experiments in different animal models and humans is necessary. Nevertheless, there is diverse and strong evidence that suggests a bidirectional causality in behavioral and seizure phenotypes of AE. As the shared causal antecedents of these disorders continue to be elucidated, they may be utilized to study the pathogenesis of AE, depression, and anxiety, and to provide new therapeutic options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- The meta-analysis shows that patients with absence seizures had greater odds of developing depression and anxiety

- The known genetic animal models of absence seizures exhibit behavioral disorders

- Antiepileptic drugs and antidepressant drugs affect both absence seizures and mood disorders, suggesting common psychopathology

- This systematic review suggests bidirectionality between absence seizures and associated depression and anxiety
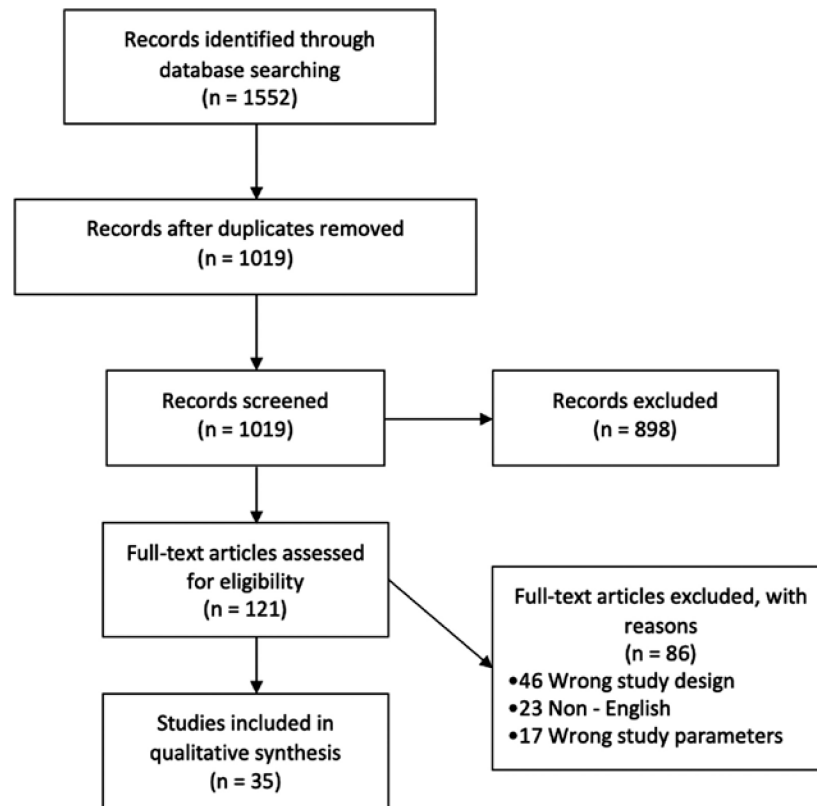
FIGURE 1.

Study flow chart. Of 1019 screened records, 35 studies met the inclusion criteria. Seven studies were done on human populations, and the rest of the studies ($n = 28$) were conducted on animal models of absence epilepsy. Of 86 excluded articles, 46 articles were either conference abstracts, reviews, editorials, or case reports (wrong study design); 23 articles were published in languages other than English (non-English); and 17 studies did not specifically study absence seizures and depression or anxiety as an outcome (wrong study parameters)

Study or Subgroup	CAE/JAE Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI	Odds Ratio M–H, Fixed, 95% CI
Abarrategui 2018	4	20	0	21	2.8%	11.73 [0.59, 233.52]	
Caplan 2005	20	71	6	93	27.3%	5.69 [2.14, 15.08]	
Caplan 2008	20	69	9	103	37.4%	4.26 [1.81, 10.07]	
Cohen 2009	7	26	4	23	22.7%	1.75 [0.44, 6.98]	
Vega 2011	16	45	2	41	9.8%	10.76 [2.29, 50.51]	
Total (95% CI)		231		281	100.0%	4.93 [2.91, 8.35]	
Total events	67		21				

Heterogeneity: Chi^2 = 3.65, df = 4 (P = 0.46); I^2 = 0%
Test for overall effect: Z = 5.93 (P < 0.00001)

FIGURE 2.

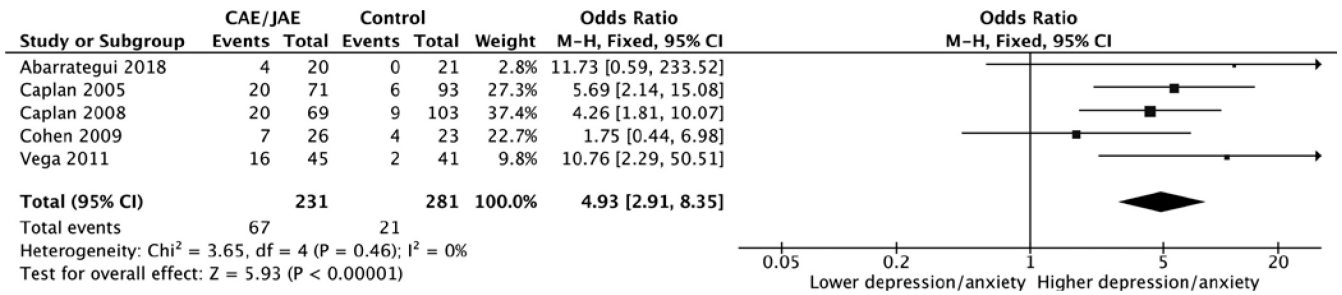Forest plot assessing the odds of developing anxiety and/or depression in patients with absence epilepsy. The analysis of five studies showed that patients with absence seizures had higher odds of developing depression and/or anxiety (odds ratio = 4.93, 95% confidence interval [CI] = 2.91–8.35, $p < .01$). CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; M-H, Mantel-Haenszel
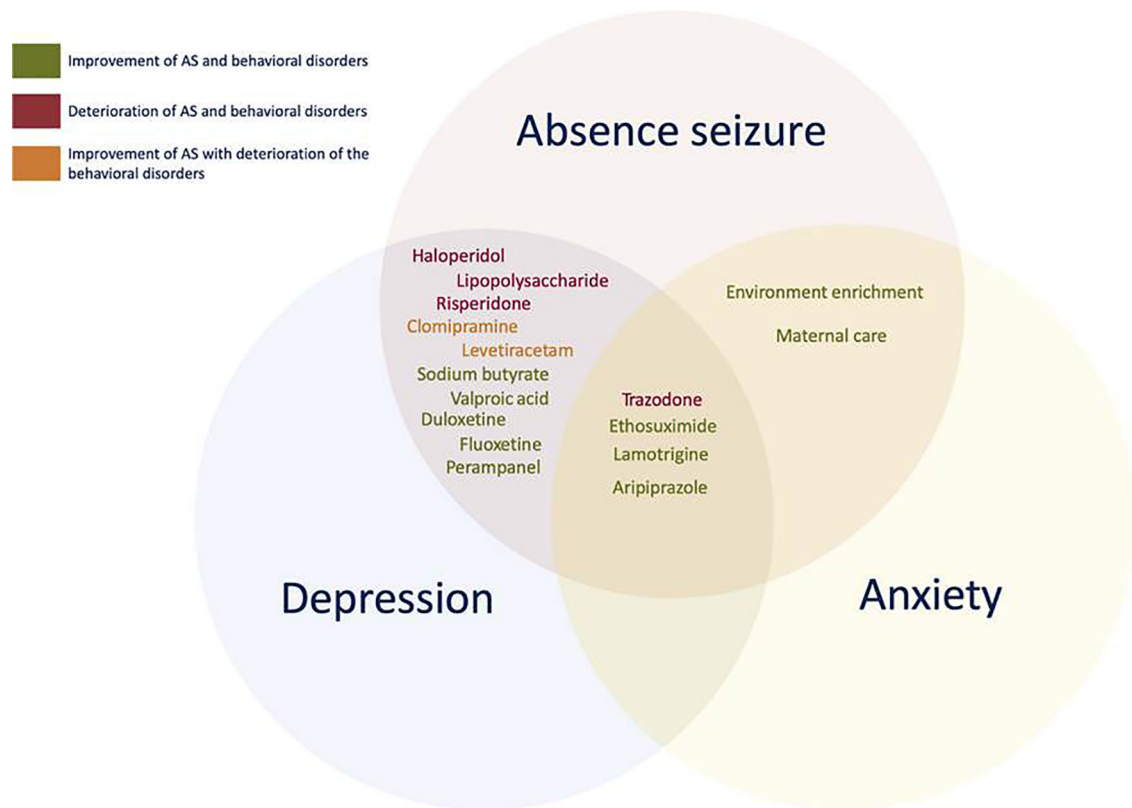
FIGURE 3.

Effect of different interventions on absence seizures (AS) and associated depression and anxiety in the genetic models of absence epilepsy. Each circle represents AS or associated behavioral disorders (depression or anxiety). The drugs in each circle were administered to the animals to test their effects on seizures along with respective behavioral disorder(s). The color of the text illustrates the type of effect for each drug: improvement of both seizures and associated behavioral disorder(s) (green), improvement of seizures with the deterioration of the behavioral disorder(s) (orange), or deterioration of both seizures and behavioral disorder(s) (red)

TABLE 1

Human studies demographics, methods of assessment, and results

Article	Year of publication	Age range, years	Male, n (%)	Groups (n)	Diagnostic tools	Anxiety/depression/both,n	Main findings
Caplan et al.[11]	2005	5–16	125 (47)	CAE (71) CPS (100) Control (93)	K-SADS	CAE: 17/3/0 Control: 6[a]	Children with CPS and CAE had higher rates of suicidal ideation, and affective and anxiety disorders, with higher rate of anxiety and lower of depression in the CAE group compared to CPS
Caplan et al.[7]	2008	6.7–11.2	76 (44)	CAE (69) Control (103)	K-SADS, CBCL	CAE: 15/4/1 Control: 9[a]	Significantly more CAE subjects had a psychiatric diagnosis, with 31% having affective or anxiety disorder against 9% in the control group
Schreibman Cohen et al.[24]	2009	6.6–15.18	21 (43)	CAE (26) Control (23)	K-SADS	CAE: 7[b] Control: 4	Psychiatric diagnosis prevalence was higher in children with CAE, of whom 20% had affective-anxiety disorder and 24% had ADHD
Vega et al.[23]	2011	6–16	33 (38)	CAE (45) Control (41)	BASC	CAE: 5/11/0 Control: 1/1/0	CAE children scored significantly higher on the anxiety and depression subscales
Precenzano et al.[25]	2016	8–11	19(31)	CAE (18) Control (43)	SAFA-A scale, CDI test	N/R	Higher scores of anxiety and depression symptoms were found in the CAE group compared to control
Abarrategui et al.[21]	2018	18–55	27 (44.3)	CAE/JAE (20) Control (21)	ISRA, NDDI-E, BDI-II	CAE/JAE: 4[c] Control: 0	Patients with CAE/JAE presented the highest anxiety scores; however, it was not statistically significant; 17% of patients had major depression compared to none in the control group
Gabriel et al.[22]	2020	21–43	19(41.3)	JAE (46) General population as control	Clinical notes	JAE: 8/9	JAE had more mood disorders and anxiety than general population, however, not statistically significant

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BASC, Behavior Assessment System for Children; BDI-II, Beck Depression Inventory II; CAE, childhood absence epilepsy; CBCL, Child Behavior Checklist; CDI, Children's Depression Inventory; CPS, complex partial seizure; ISRA, Inventory of Anxiety Situations and Responses; JAE, juvenile absence epilepsy; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia; N/R, not reported; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; SAFA-A, Self-Administrated Psychiatric Scales for Children and Adolescents–Anxiety scale.

[a] Diagnosis of anxiety and depression not discriminated.

[b] Anxiety, depression, and ADHD.

[c] Only depression included.

TABLE 2

Animal studies reporting an association between absence seizures and depression or anxiety without any intervention

Article	Year of publication	Model	Behavioral tests	Analysis type	Main findings
Bouilleret et al.[97]	2009	GAERS	Open field	Volumetric MRI (region-of-interest analysis)	Increase in amygdala, cortices, and ventricular volumes when compared to NEC rats. HDM-LD shows hippocampal volume loss. Increase in anxious behavior due to open field test.
Jones et al.[16]	2008	GAERS	Open field, elevated plus maze, sucrose preference	NA	Increase in depressive and anxious behavior due to behavioral tests.
Marks et al.[53]	2016	GAERS	Elevated plus maze, open field	NA	Increase in anxious behavior due to behavioral tests.
Marques-Carneiro et al.[98]	2014	GAERS	Open field, elevated plus maze	Stereological analysis	Increase in anxious behavior due to behavioral tests. Decrease in amygdala and increased thalamic volume when compared to NEC rats. Hippocampal volume was similar in all strains.

Abbreviations: GAERS, Genetic Absence Epilepsy From Strasbourg; HDM-LD, large-deformation high-dimensional mapping; MRI, magnetic resonance imaging; NA, not available; NEC, nonepileptic controls.

TABLE 3

Animal studies reporting an association between absence seizures and depression or anxiety along with interventions

Article	Year of publication	Model	Behavioral tests	Intervention	Administration	Effect of intervention on seizures	Effect of intervention on behavioral disorders
Sarkisova et al.[37]	2003	WAG/Rij	Forced swim, sucrose consumption, open field, light-dark choice, elevated plus maze	Imipramine	Subchronic (15 days)	NA	↓ depressive behavior; no effect on anxious behavior
Sarkisova et al.[32]	2008	WAG/Rij	Forced swim, sucrose consumption, sucrose preference, open field, light-dark choice	Imipramine, parlodel	Subchronic (15 days)	NA	↓ depressive behavior; no effect on anxious behavior
Shaw et al.[52]	2009	Long-Evans	Forced swim, sucrose consumption, elevated plus maze, open field	Ethosuximide	Acute	↓ number of seizures	↓ depressive behavior; no effect on anxious behavior
Sarkisova et al.[13]	2010	WAG/Rij	Forced swim, sucrose consumption, sucrose preference, light-dark choice, open field	Ethosuximide	Early chronic (P21, 17 days), prolonged early chronic (P21, 152 days)	↓ number of SWDs	↓ depressive behavior; no effect on anxious behavior
Russo et al.[41]	2011	WAG/Rij	Forced swim	Carbamazepine, ethosuximide, levetiracetam, zonisamide	Early chronic (P30, 119 days)	↓ development of seizures and sharp-wave discharges with ethosuximide, levetiracetam, and zonisamide; no effect with carbamazepine	↓ depressive behavior with ethosuximide; ↑ depressive behavior with levetiracetam; no effect with carbamazepine and zonisamide
Russo et al.[42]	2011	WAG/Rij	Forced swim	Vigabatrin	Subchronic (5 days), early chronic (P30, 119 days)	↑ number of seizures with subchronic; ↓ number of seizures with early chronic	↓ depressive behavior
Huang et al.[15]	2012	Long-Evans	Forced swim, sucrose consumption, sucrose preference, elevated plus maze, open field	Lamotrigine	Chronic (35 days)	↓ number and duration of SWDs	↓ depressive behavior and anxious behavior
Kovacs et al.[34]	2012	WAG/Rij	Sucrose preference	Clomipramine	Early subchronic (<P21, 14 days)	↓ sharp-wave discharge activity	↑ depressive behavior
Russo et al.[43]	2013	WAG/Rij	Forced swim, sucrose preference, elevated plus maze, open field	Aripiprazole	Subchronic (>14 days)	↓ number and duration of SWDs	↓ depressive and anxious behavior
Russo et al.[44]	2013	WAG/Rij	Forced swim, sucrose preference	Rapamycin	Acute, subchronic (7 days), early chronic (P45, 119 days)	↓ number and duration of seizures; ↓ seizure development with early chronic	↓ depressive behavior with subchronic; ↑ depressive behavior with early chronic; no effect with acute
van Luijtelaar et al.[40]	2013	WAG/Rij	Forced swim, sucrose preference	Ethosuximide	Two months treatment and 4 months treatment	↓ development of SWDs	↓ immobility score on forced swim test and no effect on sucrose preference

Article	Year of publication	Model	Behavioral tests	Intervention	Administration	Effect of intervention on seizures	Effect of intervention on behavioral disorders
Citraro et al.[30]	2014	WAG/Rij	Forced swim, open field	Statins	Acute, chronic (119 days), early chronic (<P45, 119 days)	↓ development of seizures with early chronic; no effect with acute or chronic	↓ depressive and anxious behavior with early chronic; no effect with acute or chronic
Russo et al.[46]	2014	WAG/Rij	Forced swim	Lipopolysaccharide	Acute	↑ number and duration of seizures	↑ depressive behavior
Citraro et al.[33]	2015	WAG/Rij	Forced swim	Haloperidol, risperidone, quetiapine, fluoxetine, duloxetine	Subchronic (49 days), chronic (119 days), early chronic (<P45, 119 days)	↑ seizure incidence with chronic haloperidol and risperidone; no effect on seizure incidence with chronic quetiapine; no effect on seizure development with early chronic haloperidol, risperidone, or quetiapine; ↓ incidence of nonestablished seizures with early chronic fluoxetine and duloxetine; ↓ incidence of established seizures with chronic duloxetine	↑ depressive behavior with early chronic haloperidol and risperidone; no effect with quetiapine and duloxetine; ↓ depressive behavior with early chronic fluoxetine
Ari et al.[31]	2016	WAG/Rij	Elevated plus maze	Ketone supplements	Subchronic (7 days), chronic (83 days)	NA	↓ anxious behavior
Citraro et al.[47]	2017	WAG/Rij	Forced swim, sucrose preference, open field	Perampanel	Acute, subchronic (7 days), early chronic (<P30, 152 days)	No effect with acute and subchronic; ↓ seizure development with chronic	↓ depressive behavior with early chronic; no effect on anxious behavior
Moyanova et al.[49]	2018	WAG/Rij	Sucrose preference, forced swim	Melatonin	Acute, subchronic (18 days)	No effect on incidence or circadian rhythm of seizures	↓ depressive behavior with subchronic
Sarkisova & Gabova[50]	2018	WAG/Rij	Forced swim	Maternal care	Prolonged early chronic (>212 days)	↓ number and duration of seizures	↓ depressive behavior
Leo et al.[35]	2019	WAG/Rij	Forced swim	Ethosuximide	Chronic (17 days)	NA	↓ depressive behavior
Aygun[36]	2020	WAG/Rij	forced swim, open field	trazodone	Acute	↑ number and duration of SWDs	↑ depressive and anxious behavior
Citraro et al.[48]	2020	WAG/Rij	Forced swim, elevated plus maze	Valproic acid, sodium butyrate	Early chronic (P30, 152 days), prolonged early chronic (P30, 212 days)	↓ number and duration of SWDs	↓ depressive behavior with early chronic; ↓ depressive behavior with prolonged early chronic combined administration only; no effect on anxious behavior
Dezsi et al.[8]	2013	GAERS	Open field	Ethosuximide	Early chronic (P21, 154 days)	↓ frequency of seizures	↓ anxious behavior
Dezsi et al.[56]	2016	GAERS	Open field, elevated plus maze, light-dark box	Enriched vs. standard environment	Chronic (42 days), early chronic (P21, 77 days) prolonged early chronic (P30, 140 days)	↓ development and frequency of seizures	↓ anxious behavior

Article	Year of publication	Model	Behavioral tests	Intervention	Administration	Effect of intervention on seizures	Effect of intervention on behavioral disorders
Marks et al.[55]	2019	GAERS	Open field locomotion, elevated plus maze	Z944, pan–T-type calcium channel antagonist	Acute	NA	↑ anxious behavior

Note: Imipramine: antidepressant; parlodel, dopamine agonist; ethosuximide, antiepileptic; carbamazepine: antiepileptic; levetiracetam: antiepileptic; zonisamide: antiepileptic; vigabatrin: antiepileptic; lamotrigine: antiepileptic; clomipramine: antidepressant; aripiprazole: antipsychotic; rapamycin: mammalian target of rapamycin inhibitor; statins: cholesterol synthesis inhibitor; haloperidol: antipsychotic; risperidone: antipsychotic; quetiapine: antipsychotic; fluoxetine: antidepressant; trazodone: antidepressant; perampanel: antiepileptic; valproic acid: antiepileptic.

Abbreviations: GAERS, Genetic Absence Epilepsy From Strasbourg; NA, not available; P, postnatal day; SWD, spike-and-wave discharge; WAG/Rij, Wistar Albino Glaxo From Rijswijk.