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REVIEW

Key Treatment Issues for Epilepsy in the Context of Autism Spectrum Disorder

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Abstract

The relationship between epilepsy and autism spectrum disorder (ASD) is complex and multifaceted. The prevalence of ASD in children with epilepsy is notably high, particularly in those with developmental epileptic encephalopathies (DEEs). DEEs, characterized by co-occurring epileptic activity and developmental impairments, often overlap with ASD, further complicating clinical presentations of difficulties in motor skills, language, social interaction, and adaptive behavior. The co-occurrence may be attributable to shared pathophysiological mechanisms, common genes, pre- and peri-natal risk factors, and disruptions in neurotransmitter pathways, particularly the glutamatergic and GABAergic systems. The presence of ASD in epilepsy profoundly impacts treatment choices and necessitates a careful balance between seizure control and behavioral management. Effective management of epilepsy in individuals with ASD requires a comprehensive approach, including anti-seizure medications (ASMs) like valproate and levetiracetam, which may address both seizures and behavioral issues. EEG monitoring is crucial for accurate diagnosis, distinguishing between epileptic and ASD-related behaviors. This review carefully details the overlap and physiological underpinnings of both disorders and underscores the necessity of tailored therapeutic approaches to medical care, emphasizing a multidisciplinary strategy to optimize outcomes.

Keywords Autism · Epilepsy · Behavior · Treatment · Psychiatry · Drug therapy

Autism is Common

The prevalence of autism spectrum disorder (ASD) has been rising globally over the past few decades. According to the Centers for Disease Control and Prevention (CDC), approximately 1 in 36 children in the United States are diagnosed with ASD [1]. The prevalence is four times higher among males than females and is reported to occur in all racial, ethnic, and socioeconomic groups [1]. There is no single cause of the disorder, although a specific genetic diathesis may be present in as many as 25% of cases [2]. Family studies and twin studies support a genetic association with sibling risk exceeding that of the general population [3]. Specific genetic syndromes and mutations, such as those affecting the SHANK3 gene or duplication of the 15q11-13 region, have also been linked to ASD [4].

Core symptoms of ASD include atypical or impaired communication, impaired social relatedness and restricted, repetitive, and stereotyped patterns of behaviors or interests [5]. Similar to many other neuropsychiatric conditions, there is no definitive diagnostic test and clinicians must rely on behavioral observations and developmental history. The DSM-5 criteria for ASD emphasizes two core features [6]:

1- **Deficits in Social Communication and Interaction:** Deficits persist across various contexts; examples include nonverbal communication issues (difficulty understanding and using gestures, lack of facial expressions, and poor eye contact), lack of social reciprocity (challenges in sharing interests and emotions, difficulty in engaging in conversations), and problems developing and maintaining relationships (difficulty making friends, absence of interest in peers, and empathetic interactions)
2- **Restricted, Repetitive Patterns of Behavior:** Two or more across various contexts:

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repetitive motor movements or speech (hand-flapping, rocking, repeating sounds, or phrases (echolalia), or using idiosyncratic phrases), insistence on sameness, highly restricted interests, hyper- or hypo-reactivity to sensory input (indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects)

Diagnosis relies on a variety of assessment tools, information received from caregivers, in addition to the continuous clinical observations that capture the multifaceted nature of the disorder. The Autism Diagnostic Observation Schedule (ADOS) is a semi-structured assessment used to evaluate communication, social interaction, and restricted and repetitive behaviors through a series of structured and semi-structured tasks tailored to the individual's language and developmental level [7]. The Childhood Autism Rating Scale (CARS) rates autism severity based on observation in 15 areas, such as emotional response and adaptability, providing scores that help differentiate levels of autism severity [8]. The Ritvo Autism and Asperger Diagnostic Scale-Revised (RAADS-R) is a self-report questionnaire designed for adults with adequate cognitive abilities, focusing on distinguishing autism from other similar conditions by assessing lifelong behavior patterns in language, social relatedness, sensory-motor functions, and specific interests [9]. Clinicians must identify enduring behavioral patterns that manifest across multiple domains that significantly impair functional abilities in social, occupational, or other key areas from early development.

Autism is a Spectrum Disorder

Despite DSM criteria, ASD symptoms vary widely in their presentation and intensity, hence the term "spectrum". The term "spectrum" not only reflects the broad variability in the type and severity of symptoms experienced, but also the wide range of skills and levels of disability that individuals can exhibit. Behavioral challenges in ASD range from mild disruptions caused by perseveration or insistence on sameness to severe outbursts and self-injurious behaviors. From a neurodevelopmental perspective, the diversity within the autism spectrum may be attributed to a complex interplay of genetic and environmental factors affecting early brain development. ASD is associated with a broad range of genetic mutations and alterations, from single-gene mutations to complex chromosomal rearrangements [10]. The heterogeneity in genetic profiles can also provide insight to the diversity in behavioral and cognitive outcomes observed in individuals with ASD. Some individuals on the autism spectrum can live independently, while others may require significant support for activities of daily life due to severe cognitive deficits or social isolation. The "spectrum" nature of autism complicates diagnosis of neuropsychiatric comorbidity which is problematic given that ASD is known to have comorbidity with many other conditions. In fact, between 20–30% of children with ASD get a diagnosis of epilepsy throughout their life [11, 12]. A nationwide cohort study found a tenfold increased risk of ASD in people with epilepsy, and a bidirectional relationship was also identified. Individuals with epilepsy also had a higher likelihood of having a prior ASD diagnosis reported [13].

Epilepsy is Common in ASD

Epidemiological studies have consistently demonstrated a higher prevalence of epilepsy among individuals with ASD compared to the general population. While the prevalence of epilepsy in the general pediatric population is about 0.5—1% [14], this co-occurrence is over 25% in children with ASD [15]. Although seizures may begin at any time, in patients with ASD they often have been reported to emerge most commonly at two developmental stages: infancy and adolescence [16]. The neurobiological underpinnings that might explain the overrepresentation of epilepsy in ASD include shared genetic factors, neuroanatomical abnormalities, and neurotransmitter disruptions. Neuroimaging studies have revealed abnormalities in brain volume, cortical thickness, and white matter organization in individuals with ASD [17] and those with epilepsy [18].

Additionally, both disorders involve disruptions in the glutamatergic and GABAergic pathways, with imbalances leading to altered neuronal excitability, common features in both ASD and epilepsy. Intellectual disability stands as a profound determinant, with epilepsy rates escalating in tandem with the severity of cognitive impairment [19]. Certain rare conditions like Landau-Kleffner syndrome include autistic features presumably as a direct result of seizure activity. These features can potentially improve or resolve with effective treatment of the epilepsy, highlighting at least an indirect causal relationship in specific cases.

Developmental and Epileptic Encephalopathies (DEEs) are a group of neurological disorders where frequent epileptic activity is accompanied by developmental impairments, worsening the developmental trajectory beyond what might be expected from the seizure disorder alone [20]. Often characterized by the onset of seizures in infancy or early childhood, and commonly resistant to medical treatment, the illness has a profound impact on brain function and development. Developmental regression or stagnation is common [21]. Management is particularly challenging when DEEs co-occur with ASD, as both disorders independently affect neurodevelopment, and their overlap can significantly

amplify difficulties in motor skills, language, social interaction, and adaptive behavior.

Common Seizure Types in Autism

Focal Unaware and Generalized Seizures are most common in individuals with ASD, with EEGs frequently showing seizure foci in the temporal and parietal lobes [22]. These seizures typically involve a loss of awareness or altered consciousness and can be particularly challenging to decipher in children with ASD. A lack of responsiveness to the environment during a seizure may be difficult to differentiate from behaviors associated with ASD, such as withdrawal or lack of interactivity.

Children with ASD also experience **Focal Aware Seizures** with sensory disturbances, motor symptoms, or autonomic symptoms. These can be difficult to recognize if the child already has difficulty communicating or if their sensory or motor symptoms are mistaken for behavioral aspects of ASD.

Children with ASD and **Generalized Tonic–Clonic Seizures** may have post-ictal confusion and fatigue which could complicate co-existing sensory sensitivities and difficulties understanding or communicating. **Absence Seizures** are commonly mistaken for typical behavior in children with ASD as they are subtle and brief, these seizures might be overlooked as the child appearing to be daydreaming or not paying attention. Similarly, sudden jerks or twitches in **Myoclonic Seizures** may not be immediately recognized particularly if motor stereotypies are already a feature of the child's behavior.

Physiologic Underpinnings of ASD and Epilepsy

ASD and epilepsy have shared biopsychosocial aspects, neurodevelopmental abnormalities, genetic factors as well as neurotransmitter imbalances. In autism, early brain development diverges from typical patterns, affecting connectivity and perhaps even the structure of certain brain regions like the amygdala and prefrontal cortex. Epilepsy also involves disruptions in typical neural activity leading to seizures, which can also be linked to structural brain changes. In both epilepsy and ASD, overactivity of glutamate signaling can lead to neural hyperexcitability, and abnormalities in glutamate receptors have been found in both disorders [23, 24]. Excessive glutamatergic activity can overwhelm the brain's capacity to maintain normal neuronal homeostasis, leading to seizures in epilepsy and contributing to sensory overload and behavioral symptoms in ASD.

In addition to dysregulation of glutamate signaling, both disorders exhibit shared neuropathological features in γ-aminobutyric acid (GABA) neurotransmission. GABA, the main inhibitory neurotransmitter, is crucial for counterbalancing the excitatory actions of glutamate. In autism, studies have shown that there can be a reduction in GABAergic signaling, leading indirectly to an overall increase in cortical excitability [25]. Both disorders are linked to abnormalities in inhibitory GABA neurotransmission, marked by diminished expression of GABA-A and GABA-B subunits. These irregularities can disrupt the balance between excitation and inhibition, leading to cortical hyperexcitability and consequently lowering the threshold for seizures to occur.

Molecular abnormalities in synaptic structures and functions in ASD and epilepsy often involve neuroligins, neurexins, and the SHANK3 scaffolding protein, which play crucial roles in aligning and activating synapses [16]. Disruption of GABAergic interneuron development, implicated in both disorders, can result from mutations in multiple genes. Specifically, mutations in GABA-A receptor subunit genes, such as GABRA5, GABRB3, and GABRG3 located on chromosome 15q11, have been associated with ASD. Neurexins, presynaptic proteins that bind to postsynaptic neuroligins, are consistently linked to postsynaptic differentiation and the balance of inhibitory GABAergic and excitatory glutamatergic signaling.

In a recent finding, researchers uncovered shared genetic pathways between ASD and epilepsy, shedding light on potential mechanisms linking epileptic seizures and cognitive deficits. Both ASD and epilepsy have been associated with various conditions stemming from genomic copy number variations or mutations in single genes [26]. Some of these genetic syndromes include Tuberous Sclerosis Complex (TSC), Fragile X Syndrome, Rett Syndrome, Down Syndrome, and Phelan-McDermid Syndrome/SHANK3 deletion. These findings underscore the complex interplay between genetic mutations, synaptic dysfunction, and neurodevelopmental abnormalities in epilepsy and ASD [26].

Furthermore, focal cortical dysplasias leading to abnormalities in regions such as the prefrontal cortex, cerebellum, hippocampus, and amygdala have been linked to sensory and motor deficits, as well as epileptic seizures observed in ASD [27]. These structural anomalies are often accompanied by structural disruptions, as evidenced by neuroimaging studies revealing abnormalities in brain volume, cortical thickness, and white matter organization. These along with abnormal neuronal excitability may disrupt synaptic homeostasis in individuals with both ASD and epilepsy [28]. MRI imaging has provided further insight, revealing hypoplasia of both the cerebellar vermis and hemispheres, while autopsy studies have documented a decrease in the count of cerebellar Purkinje cells [28]. These findings underscore the complex

interplay between structural and functional alterations in the brains of individuals affected by ASD and epilepsy.

Difficulties with Differential Diagnosis

In ASD, certain behaviors such as stereotyped movements, repetitive rocking, or hand-flapping can resemble seizure semiology as in automatisms often seen in epilepsy. Repetitive rocking or complex motor stereotypies can be mistaken for motor seizures. Conversely, some seizure activities may manifest subtly, resembling behavioral or attentional lapses that could easily be mistaken for aloof or disconnected behavioral symptoms of ASD. This overlap can lead to misinterpretation of symptoms, either over-diagnosing epilepsy in individuals with ASD or missing epilepsy because behaviors are attributed solely to ASD. Differentiating these symptoms is greatly assisted by video EEG monitoring to correlate behaviors of concern with epileptiform activity in the brain.

Children with ASD often display behaviors that can resemble absence seizures, such as staring spells or brief disengagement from interactions. Distinguishing these from true epileptic events again may require video EEG assessment to correlate potential electrical changes coincident with characteristic episodes. Non-verbal patients or those with limited communication skills may not be able to express their experiences and sensations preceding a seizure, or to describe their internal states. This lack of verbal communication necessitates reliance on observations from caregivers and other physicians. Differential diagnosis must carefully consider and exclude conditions that mimic or coexist with ASD symptoms such as epilepsy, intellectual disabilities, and language disorders.

Treatment Approach

Management of epilepsy even without ASD requires a comprehensive and blended approach, often leveraging medications that may address both seizures and behavioral symptoms. Antiseizure medications (ASMs) can be effective beyond just controlling seizures, and have been part of the psychopharmacologic armamentarium for many decades [29] ASMs target neuroreceptors subtending GABA and glutamate directly and indirectly, not only treating neuronal hyperexcitability, but also psychiatric symptoms such as impulsivity or disruptive behavior. Selecting ASMs that have efficacy in improving both behavior and seizures would be preferred, in order to reduce the total number of medications being given. A range of anti-seizure medications commonly used for psychiatric illness have been evaluated for benefits and adverse effects [27].

Anti-Seizure Medications

Although the literature is sparse, it does seem clear that some ASMs have a "dual" therapeutic role due to their efficacy for treating seizures and other comorbidities [15]. Valproate is widely used for addressing behavioral issues in ASD additional to controlling seizure activity. Valproate modulates mood and improves impulse control by increasing GABAergic inhibition, alleviating symptoms of hyperarousal and sensory overload. Valproate has been shown to enhance language skills and reduce irritability and aggressive behaviors in some individuals with ASD [30].

Some case study reports suggest that certain ASMs may aid in improving cognitive functions and language skills in some individuals with ASD, possibly due to enhanced synaptic connectivity. For instance, valproate has been shown to benefit individuals with ASD as well as a history of EEG abnormalities or seizures, especially with symptoms of mood instability, impulsiveness, and aggression [31]. Additionally, levetiracetam is known for its utility in managing a broad spectrum of seizure types in patients with ASD, as well as in some cases, a positive impact on behavioral and cognitive functions [32].

Table 1 summarizes common ASMs used in patients with ASD.

Psychopharmacology and Seizure Threshold

With ASD, treatment is focused widely on behavioral targets can be addressed through psychopharmacological methods. However, there is a significant concern that certain medications could exacerbate seizures. However, that concern may be largely unfounded as many medicines appear to be safely used without lowering the seizure threshold. A variety of medications, including ASMs, may be synergistically beneficial in managing both seizure activity and behavioral symptoms [37]. Fluoxetine and sertraline are common for managing symptoms of anxiety and obsessive–compulsive behaviors in ASD by acting on the serotonergic system and plays a crucial role in mood regulation, anxiety, and neuroplasticity [38]. Reducing anxiety may be an indirect way to improve the seizure threshold.

Risperidone and aripiprazole is often used for treating behavioral dysregulation, irritability and aggression in children and adolescents with ASD by balancing the neurotransmitter systems including dopamine and serotonin [39]. To date, risperidone and aripiprazole are the only FDA-approved medications for youth with ASD [37]. Both second-generation antipsychotic drugs have the lowest seizure incidence among patients with epilepsy and

Table 1 Evidence of ASM usage in Patients with ASD

Medication	Study report	Study design	Outcome measures	Results
Oxcarbazepine	Douglas et. al., 2013 [33]	Retrospective case series, N = 30 (age 5–21)	CGI-I, CGI-S	14 patients (47%) 'much improved' during treatment. 10 patients (33%) had an improvement on their CGI of severity score
Lamotrigine	Belsito et. al., 2001 [34]	12 wk, double-blind, placebo-controlled, parallel group N = 27 (age 3–11)	Autism Behavior Checklist, the Aberrant Behavior Checklist, the Vineland Adaptive Behavior scales, the PL-ADOS, or the CARS	No significant differences were found in improvements between lamotrigine or placebo groups
Valproic acid	Aliyev, 2018 [35]	12-wk double-blind placebo-controlled, N = 100	CGI-I	Significantly greater improvement in global severity < behaviors, according to CGI rating scale was found
Divalproex sodium	Hollander et. al., 2006 [31]	8-wk, double-blind, placebo-controlled, N = 13	C-YBOCS	A significant group difference on improvement in repetitive behaviors was found
Levetiracetam	Wasserman et.al., 2006 [36]	10-wk, double-blind, placebo-controlled, N = 20 (age 5–17)	CGI-I, the Aberrant Behavior Checklist, CY-BOCS or Conners' scales	No significant difference was found between levetiracetam and placebo groups

CGI-I clinical global impression –improvement, *CGI-S* clinical global impressions – severity, *C-YBOCS* Children's Yale-Brown Obsessive Compulsive Scale

may be employed to address behavioral challenges while controlling seizures in individuals diagnosed with both epilepsy and ASD [40].

Benzodiazepines remain important agents in the management of epilepsy due to the rapid onset of action, high efficacy rates, and minimal toxicity. Benzodiazepines also have anxiolytic and sedative properties particularly in acute management of anxiety and agitation in patients with ASD [41]. Benzodiazepines allosterically bind to the GABA-A receptor, enhancing the inhibitory effects of GABA [42]. Increasing GABAergic signaling might improve behavioral outcome by compensating for excessive glutamatergic neurotransmission. Due to shared abnormalities in GABAergic transmission underlying both epilepsy and ASD, benzodiazepines hold promise for mitigating seizures and managing anxiety symptoms in individuals with ASD. However, risk of tolerance and paradoxical reactions must be considered for children with comorbid epilepsy and ASD.

Other Treatment Strategies

Cannabidiol (CBD) is notable for its therapeutic potential in treating epilepsy [43] as well as ASD [44, 45]. Unlike tetrahydrocannabidiol (THC), CBD acts as a negative allosteric modulator at cannabinoid receptors CB1 and CB2. This modulation can help reduce excitatory neurotransmission, crucial for controlling seizures in epilepsy [46]. CBD also acts on the serotonin receptors in a similar way as antidepressants, particularly 5HT1A, theoretically reducing anxiety and improving mood and and by extension, social interactions, some of the core behavioral issues in ASD [45]. CBD's role in alleviating seizure activity [47, 48], as well as improving behavioral symptoms in children with ASD [49, 50] has been well documented. The FDA approved CBD-based medication, Epidiolex™, has demonstrated significant efficacy in reducing the frequency of seizures in several forms of drug-resistant epilepsy [51, 52].

Behavioral Interventions

As for patients without epilepsy, developmental interventions have shown effectiveness in improving social skills and reducing ASD symptoms. Educational and behavioral interventions focus on enhancing communication, social skills, and adaptive behaviors. Applied Behavioral Analysis (ABA) is a widely used method that involves systematic teaching of skills using reinforcement strategies [53].

Sleep, nutrition, and the environment also impact seizures as well as cognitive functions and behavioral regulation, daily functioning, and severity of autism symptoms. Sleep deprivation has been linked to lower-seizure threshold and

increased risk for epileptic seizures [54, 55]. Establishing consistent bedtime routines, educating families on sleep hygiene, using behavioral and pharmacological treatments, and addressing environmental and sensory sensitivities can enhance sleep quality, raise seizure threshold [56], and alleviate the core symptoms of ASD by improving daytime cognitive and sensory processing [57].

Dietary interventions are increasingly being explored as therapeutic approaches, as nutritional studies highlight the potential of specific diets like the ketogenic diet (KD) and the use of prebiotics and probiotics to improve the symptoms of both conditions. Epilepsy is a metabolic disease, and the KD can mimic fasting by altering substrate metabolism from carbohydrates to fatty acids and ketone bodies (KBs) [58]. KD and its variants have also been shown to reduce epileptogenesis [59]. In ASD, KD may be effective by targeting gut microbiota imbalances and enhancing nutrient absorption [60].

A structured and predictable environment with consistent schedules, clear expectations, and organized physical spaces can help reduce anxiety and increase feelings of security. Sensory-friendly adaptations can help prevent sensory overload and reduce behaviors that are disruptive or harmful [61]. Educating families about ASD and epilepsy, teaching them how to manage seizures, and providing emotional and psychological support are fundamental components of care. Additional wellness and behavioral strategies targeting these can indirectly improve epilepsy, as well as behavioral problems associated with ASD. Continuous monitoring of the effectiveness of the medication regimen and its side effects, regular assessment of developmental progress, and adjustment of educational and behavioral interventions are needed. EEG monitoring of epileptiform activity over time can influence management strategies and outcomes [62].

Conclusion

Ultimately, the overlap of ASD and epilepsy may have a strong physiologic basis that reflects a common underlying developmental process. While it is still difficult to elucidate, a treatment approach that embraces this overlap seems intuitively necessary. The shared pathogenic mechanisms between epilepsy and ASD may offer insight into optimal management strategies. Anti-seizure medicines may provide a "dual role" in treatment and be powerful tools in this population. Other psychotropic medicines may also be used to target specific symptoms, and by and large do not exacerbate seizure thresholds. Effective management necessitates a multidisciplinary team capable of addressing the wide range of symptoms presented by this population, tailored to the individual's specific needs. Understanding an integrated approach that considers the neurobiological, genetic, and clinical complexities of these apparently disparate conditions represents significant advancement in the paradigms of diagnosis and treatment in both neurology and psychiatry.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

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