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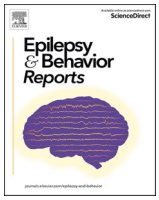

ADHD in Adults with Epilepsy: A Guide for Neurologists☆

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) and epilepsy have one of the lesser known and yet highly debated relationships in neuropsychiatry. Similar to anxiety and depression, ADHD has a bidirectional relationship with epilepsy, in which individuals with epilepsy are more likely than the general population to have ADHD and vice versa. Most importantly, an untreated psychiatric condition can affect quality of life. Although the management of ADHD in PWE has been debated due to perceived seizure risk related to ADHD medications, a consensus has developed based on early pediatric studies that support the treatment of ADHD. However, the management of adults with ADHD, particularly in PWE, remains relatively unexplored. This critical gap in knowledge will be addressed using an illustrative case study followed by practical tips on the identification and pharmacologic management of ADHD in adults with epilepsy. The management of ADHD in PWE should begin with a thorough history, medication assessment for cognitive risk, and the addition of a brief ADHD screening tool, such as the Adult ADHD Self-Report Scale (ASRS). Treatment with stimulants, such as methylphenidate, and non-stimulants, such as atomoxetine, are effective. Caution, however, should be taken for any patients with history of bipolar disorder, as some ADHD medications may exacerbate symptoms of other psychiatric conditions. Patients can also be referred to psychotherapy, such as cognitive behavior therapy (CBT) for ADHD, in addition to or in lieu of medications, thus further minimizing potential pharmacological risk. Patients who have tried and failed multiple ADHD medications and/or who carry a more complex psychiatric history should be referred to a psychiatrist.

1. Illustrative case

A 30-year-old male presents to an outpatient neurology clinic to establish care after a recent move. He was diagnosed with epilepsy in college. He is adherent to 1,500 mg nightly of extended-release divalproex sodium and reports he has been seizure-free for over 5 years.

At the visit, he discloses a history of attention-deficit/hyperactivity disorder (ADHD) diagnosed in childhood and treated with an amphetamine, which was stopped in college by his previous neurologist. Over the past few years since the COVID-19 pandemic, the patient has been working as a freelance programmer from home and taking online graduate courses at night. He has noted worsening difficulty maintaining focus and easy distractibility. He has trouble balancing multiple projects, misses deadlines, and sometimes finds himself "spacing out" during Zoom meetings for work. He had a panic attack for the first time last week and has been having trouble falling asleep for the past few days. His partner is concerned because he has turned down multiple invitations from friends to instead spend time on work, he avoids taking on new projects, and this is all beginning to affect his personal and professional relationships. He denies any substance use, and he has never seen a therapist.

The patient asks his new neurologist about starting treatment for ADHD but worries about how additional medications may affect his seizures.

2. ADHD

2.1. Prevalence and impact

ADHD is typically diagnosed in childhood, and children with epilepsy (CWE) have a considerably higher risk of ADHD (25 % prevalence in CWE, and up to 77 % prevalence in a sample with epileptic encephalopathy) compared to the general population (3–5 % prevalence).[1,2] ADHD can also be found in 2.5 % of adults overall and as many as 1 in 5

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adults with epilepsy. Negative impacts of ADHD can lead to psychosocial morbidity and poor quality of life.[3–6] Despite changes that were implemented in the fifth edition of The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), wherein ADHD criteria for adults now only require five symptoms (compared to 6 symptoms for younger adolescents and children), there remains a stark discrepancy between adult and childhood ADHD rates that some studies believe may have been influenced by genetic or even environmental factors.[7–9]

A systematic review by French et al highlighted barriers to diagnosis, such as a lack of ADHD education in primary care settings and false beliefs that ADHD only occurs in childhood.[10] In fact, however, 15-20 % of children with ADHD continue into adulthood with a full syndrome, and 50 % experience impairment as adults with only subsyndromal symptoms.[7] In comparing inattentive versus hyperactive and impulsivity symptoms, inattentive symptoms tend to persist at higher rates.[7]

Inattentive presentations, which occur predominantly in females with ADHD, may easily go undetected by others because the symptoms may only directly affect the individual.[11,12] Therefore, female adults are at even higher risk for underdiagnosis and referral bias compared to males who often receive much more recognition in childhood because of a hyperactive ADHD presentation that can affect the people around them in school and at home or due to a comorbid conduct disorder (behavior that may include violence and theft).[11,12] Further still, people with high intelligence and ADHD may not manifest with symptom severity or seek treatment until they are faced with the challenges of higher cognitive requirements.[12–14]

2.2. Clinical signs and symptoms of ADHD

The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Text Revision (DSM-5-TR) categorizes ADHD as a neurodevelopmental disorder, thus presenting with several symptoms before age 12. These symptoms lead to impairment in at least two different settings, affect personal, social, academic, and/or occupational functioning, and are not better explained by another disorder.[15] Specifiers include combined inattention and hyperactivity presentation (ADHD-CT), predominantly inattentive presentation (ADHD-IT), or predominantly hyperactive/impulsive presentation (ADHD-HT).

To meet the criteria for ADHD-*IT*, a minimum of five symptoms must have persisted for at least six months.[15] These symptoms may include lack of attention to detail, difficulty with sustained attention, the appearance of conversational disengagement, failure to follow through with tasks, difficulty with organization, avoidance of sustained attention activities, misplaced objects, and forgetfulness in daily activities.[15]

To meet the criteria for ADHD-*HT* a minimum of five symptoms must have persisted for at least six months.[15] These symptoms may include fidgeting, frequently leaving one's seat inappropriately, extremely restless activity, frequent inability to engage in leisure activities quietly, discomfort sitting still, talking excessively, blurting out answers, difficulty waiting their turn, or intrusiveness.[15]

This patient reports:

- Childhood onset
- Symptoms that occur in at least two different settings
- More than 6 months of symptoms
- 3 symptoms consistent with ADHD-IT

2.3. Differential diagnosis

2.3.1. Other mental health conditions

Multiple mental health conditions should be considered in the differential diagnosis of ADHD:

Anxiety — Severe anxiety can manifest as inattention or a hyperactive state of agitation that is similar to descriptions of ADHD. However, ADHD *is not* associated with chronic, pervasive worry that defines generalized anxiety disorder, nor is ADHD associated with the paroxysmal physical manifestations of panic attacks (ex. sweating palpitations, "sense of doom"). ***Pearl:*** *Over time, however, patients with untreated ADHD can present with specific worries secondary to the disabling effects of ADHD symptoms.*[16] *When anxiety is secondary to ADHD symptoms, the anxiety resolves with ADHD treatment.*

Bipolar Disorder – Both ADHD and bipolar disorder share similar presentations, such as poor concentration or distractibility and increased impulsivity. In bipolar disorder, however, patients must experience a manic or hypomanic episode, consisting of a distinct period of abnormally elevated or irritable mood lasting *consistently* over 1 week in mania or 4 days in hypomania. ***Pearl:*** *Patients may not always recall their manic episodes. Thus, records, information gathered with patient permission from close family and friends, and family history of bipolar disorder (diagnosed by a psychiatrist) are helpful for diagnostic clarification between ADHD and bipolar disorder.*

Depression – Untreated depression may lead to subjective cognitive changes.[17–19] Depressive cognitive symptoms are caused by changes in processing.[17,18] Therefore, before making changes to the current epilepsy medication regimen in stable epilepsy or adding new medications, it is important to know the symptoms of a treatable underlying psychiatric etiology of cognitive change. A major depressive episode consists of four or more changes in sleep, interest, guilt, energy, concentration, or appetite, with psychomotor retardation/activation, and suicidal ideation can be present. ***Pearl:*** *Untreated ADHD poses a risk of developing depression.*[16] *Therefore, treating ADHD could improve the patient's mood, and some ADHD medications have an additional indication for adjunctive depression treatment.*

Neurocognitive disorders – The sudden, stepwise, and/or degenerative cognitive changes from baseline seen in neurocognitive disorders are unlikely to occur in patients with ADHD. ***Pearl:*** *If there is a specific memory component, patients may be unable to provide an accurate history. With patient permission, gathering collateral information from close friends and family either in person or briefly by phone during a visit can help fill gaps in history.*

Substance use disorders – Substance use can manifest with cognitive changes. For diagnostic clarity and prior to prescribing a potentially habit-forming controlled substance, obtain a substance use history and consider a urine drug screen. ***Pearl:*** *Providing a nonjudgmental, empathetic environment with a neutral affect and body language can help solidify the therapeutic relationship and lead to better outcomes for patients with substance use disorders who might otherwise feel stigmatized. *Those who are resistant to change may benefit from a motivational interviewing approach from addiction specialists (psychiatrists or counselors) and a future trial of non-habit-forming ADHD treatments, such as cognitive behavior therapy for ADHD (with a therapist or psychiatrist) and/or non-stimulant ADHD medications (by a prescriber).*

2.3.2. Other medical conditions

The differential diagnosis also includes other medical factors that can affect cognitive function, such as micronutrient deficiencies (ex. folate and B12), hormone abnormalities (ex. hypothyroid), allergy (ex. uncontrolled environmental triggers) and autoimmune disorders (ex. lupus), or sleep disorders (ex. obstructive sleep apnea).

2.3.3. Iatrogenic causes

Sedating medications (ex. opioids and sleep aids), anticholinergic medications (ex. antihistamines and certain psychiatric medications, such as tricyclic anti-depressants), and antiseizure medications (ASMs) may all affect cognition. People with epilepsy (PWE) are particularly at risk for cognitive changes because of uncontrolled seizures, postoperative complications, and/or ASMs themselves. The iatrogenic effects of ASMs should be considered by all prescribers and providers managing PWE. Inattention is linked to higher doses of ASMs and polytherapy.[20] In this special issue, Miller et. al summarize the effects of ASM on ADHD symptoms, with only three ASMs (carbamazepine, clobazam, and lamotrigine) having positive effects on ADHD

symptoms.[21,22] Numerous other ASMs* were found to have negative effects, while others have a neutral effect or the effect is unknown due to lack of relevant data.[21–23].

***Pearl:** *If possible, consider avoiding levetiracetam, perampanel, phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide.*

2.4. ADHD assessments

Once a patient has met DSM-5-TR criteria for ADHD, there are several screening tools used to further characterize symptoms. Conners' Adult ADHD Rating Scale (CAARS) measures both the presence of symptoms and their severity.[24] CAARS short and long versions are available for purchase and are usually administered by professionals.[24] Neurologists could consider using a brief tool that is freely available, such as the Adult ADHD Self-Report Scale (ASRS).[4,25–27] The World Health Organization assisted in developing the ASRS, which is a standardized self-report assessment consisting of a 6-item screener (Part A) and an 18-item symptom checklist (Part B).[4,25–27] Frequency of symptoms range from never to rarely, sometimes, often, and very often. The first 3 screener items address symptoms of difficulty completing final project details, organizing a task, and remembering obligations, with ratings of sometimes or higher considered significant, and the final 3 items address avoidance of starting a cognitively demanding task, fidgeting, and feeling overly active, as if driven by a motor, with ratings of often or higher considered significant. Four or more symptoms with significant ratings in Part A typically warrant further investigation and intervention. Dunbar et al found utility in using the ASRS in patients with seizures who were admitted to an epilepsy monitoring unit.[28]

3. Pharmacologic treatment of ADHD

These may be divided into two groups, stimulants and non-stimulants. Although some may experience effects sooner or require early termination of the trial due to side effects, a starting dose should be trialed minimally for 1 week before increasing the dose. This is a much quicker titration compared to other psychiatric medication trials, which recommend at least 4–6 weeks. Symptoms can be tracked for improvement by revisiting the initial ASRS and assessing for any decrease in the frequency of symptoms, as well as general impact on day-to-day activities. For example, if the patient was having difficulty at work, you may ask if their supervisor noticed any changes.

3.1. Stimulants

Methylphenidate and amphetamines are gold standard pharmacologic treatments for ADHD. In a systematic review and network meta-analysis by Cortese et al, amphetamines were found to be most efficacious and tolerable in adults with ADHD, while methylphenidate was most efficacious and tolerable in children with ADHD.[29] However, this study did not focus on epilepsy. In 2018, the International League Against Epilepsy (ILAE) assigned methylphenidate a level B for probable efficacy and tolerability in children with epilepsy (CWE) specifically due to seizure exacerbation risk.[30] Amphetamine tolerability in CWE was undefined and received a Level U; therefore, rendering its effects on seizures less favorable compared to methylphenidate.[30]

Immediate release methylphenidate has a maximum 4 h duration. It may be dosed orally twice daily, 5 mg in the morning and 5 mg in the afternoon. Doses may be titrated by 5–10 mg each week for a total of 20–30 mg orally in 2 or 3 divided doses: a maximum of 60 mg per day. In order to avoid appetite suppression, immediate release amphetamine should be taken about 30 min. before meals. To also avoid stimulant-induced sleep issues, the last dose of the day should be before 6 PM.

Sustained release methylphenidate has a maximum 12 h duration. It may be dosed orally once daily every morning. The dose may be increased at weekly intervals in 18 mg increments: a maximum of 72 mg per day.

***Pearl:** *Consider low dose sustained release formulations first, as these may provide less fluctuation or "crashing" throughout the day. If insomnia cannot be resolved with earlier dosing, consider switching to immediate release for more precise titrations. At times, certain formulations may be cost-prohibitive.*

3.2. Non-stimulants

Atomoxetine is FDA-approved for ADHD and received a level C from the ILAE for its limited evidence of tolerability in CWE.[30] However, in the general population, non-stimulants may be tolerated better than stimulants, thus warranting consideration for use in adult PWE. The starting dose of atomoxetine is 40 mg orally daily. It may be titrated to a target dose of 80 mg daily as a single daily dose in the morning or as 2 divided doses of 40 mg in the morning and 40 mg in the late afternoon/early evening: a maximum of 100 mg per day. Other FDA-approved non-stimulants for ADHD, such as viloxazine and guanfacine, do not have adequate trials in PWE and may be considered in the future.

3.3. Adverse effects of ADHD medications

Some of the most common adverse effects of stimulant use are decreased appetite, headache, or insomnia. While meta-analyses of placebo-controlled trials in children and adolescents did not support an association of ADHD medications with anxiety and/ or worsening tics, little evidence exists for the effects specifically in adult PWE.[31,32] Therefore, each patient should be assessed individually if new or worsening anxiety or tics arise after introducing a stimulant. Additionally, stimulants may result in unmasking manic symptoms*.[33,34] Therefore, providers should always obtain a personal and family history of bipolar disorder prior to starting ADHD medications. Due to the risk of serotonin syndrome, stimulants are contraindicated during the use of monoamine oxidase inhibitors (MAOIs) or within 14 days of discontinuing MAOIs. Stimulants also hold a black box warning for high abuse potential and should be avoided in patients with a substance use disorder.

***Pearl:** *ASMs, such as carbamazepine, lamotrigine, oxcarbazepine, and valproic acid are often used as mood stabilizers to treat bipolar disorder. Therefore, proceed with caution when tapering ASMs in a patient with known bipolar disorder taking a stimulant and consider a psychiatry referral to help manage psychiatric symptoms.*

3.3.1. Safety for use in epilepsy

ADHD medication use in PWE has a controversial history because of concern for lowering the seizure threshold. However, evidence, as summarized in more detail in this special issue by Gopaul et al. has shown that ADHD medications do not increase risk of seizures in PWE.[30,35 36–39] Even so, prior to starting a new medication, seizures should be stable, and the patient should continue to be monitored closely with regular follow up to assess for any side effects.

3.3.2. Potential pharmacokinetic and pharmacodynamic interactions with antiseizure medications that can result in iatrogenic and /or therapeutic phenomena

When treating patients with epilepsy and co-occurring ADHD, there are some pharmacological interactions to consider with certain antiseizure medications, but none are a contraindication to use. Methylphenidate may block the metabolism of phenobarbital, phenytoin, and primidone, which may result in higher levels of the anti-seizure medications and therefore higher risk of side effects.[23] Concurrent use of carbamazepine and methylphenidate may result in decreased effect of the methylphenidate, while concurrent use of cannabidiol and methylphenidate may increase the methylphenidate exposure.[40,41]

Amphetamine concentrations may be increased in the presence of CYP2D6 inhibitors, such as clobazam. [40–44] Carbonic anhydrase inhibitors, such as acetazolamide, topiramate, and zonisamide, may also

increase amphetamine concentrations due to the potential for alkalinizing the urine, thus resulting in decreased excretion of amphetamine.[40–44]

It is important to keep these considerations in mind not only when starting new medications, but also when discontinuing medications that are known to have potential interactions.

4. Other ADHD treatments: Psychotherapy

While there is stronger efficacy data for treating ADHD with medication, psychotherapy, in particular cognitive behavior therapy (CBT), may be used in conjunction with or instead of medications to treat ADHD.[45–49] If a patient is not a good candidate for immediate medication changes, has experienced side effects, or has a strong personal preference to avoid further medications, a referral can be placed for psychotherapy.

5. Case recommendations

While valproic acid has been implicated as negatively affecting patient cognition, the above patient had been seizure free for years on his extended-release divalproex sodium. Additionally, his ADHD complaints presented in the context of stressors and without any mental health interventions. Therefore, instead of a potential cross-titration to another ASM with a better cognitive profile, the provider may opt to

1) Consider a low and slow trial of controlled release methylphenidate, which is a stimulant and, therefore, a first-line treatment for ADHD. Controlled released allows for even release throughout the day. Methylphenidate is effective and a better tolerated stimulant. If there is a major concern for potentially worsening anxiety, a non-stimulant, such as atomoxetine, may be a better medication to trial first.
2) Refer the patient to psychotherapy for CBT or other techniques to help with ADHD, sleep, and stress.

5.1. Mental health referral recommendations

There should be a low threshold for referring to mental health specialists when

1) There is any concern for suicidality.
2) The patient has failed one trial of a psychiatric medication for ADHD.
3) There is a family history or patient history of bipolar disorder.
4) The patient may benefit from additional mental health services, such as specialized psychotherapy or neuropsychological testing for further diagnostic clarity and/or treatment-resistant cognitive deficits.

CRediT authorship contribution statement

Luciana Giambarberi: Writing – original draft. **Halley B. Alexander:** Writing – review & editing. **Heidi Munger Clary:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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