

**REVIEW****Pharmacological treatment of attention-deficit/hyperactivity disorder in children with autism spectrum disorder and epilepsy: Current evidence and safety considerations****Zhang Ye, Yuan Yazhen\* and Gou Yanyang**

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**Abstract:** Attention-deficit/hyperactivity disorder (ADHD) symptoms frequently coexist with autism spectrum disorder (ASD) and epilepsy; however, seizure manifestations, antiseizure medication (ASM) effects, sleep disturbances and sensory or emotional factors can complicate diagnosis and treatment. Current evidence on ADHD pharmacotherapy in children with these overlapping conditions was synthesized in a narrative review of English-language clinical studies, reviews and professional guidance published mainly between 2020 and 2025, together with the 2018 International League Against Epilepsy consensus. Interpretation focused on diagnostic differentiation, seizure-related safety, tolerability and functional outcomes. Evidence specifically involving all three conditions remains limited. Methylphenidate has the strongest published support for core ADHD symptoms in children with epilepsy, particularly when seizures are stable and standard therapeutic doses are used. Atomoxetine is an alternative when stimulant treatment is unsuitable or poorly tolerated; alpha-2 adrenergic agonists may address selected symptoms of hyperactivity, impulsivity, or hyperarousal. Antipsychotics can be used for defined ASD-related behavioral indications but should not be regarded as primary ADHD treatments. A proposed clinical pathway links multisource diagnostic confirmation, seizure and ASM baseline assessment, individualized medication selection, gradual titration, seizure diaries, monitoring of sleep, appetite, growth, vital signs and mood and functional feedback from caregivers and schools. The suggested pathway provides an organizational aid rather than a validated risk prediction instrument. Medication decisions should prioritize demonstrable improvements in participation, learning and safety while maintaining neurological follow-up.

**Keywords:** Attention-deficit/hyperactivity disorder; Autism spectrum disorder; Drug safety; Epilepsy; Methylphenidate

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**INTRODUCTION**

Attention-deficit/hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder beginning in childhood and characterized by developmentally inappropriate inattention and/or hyperactivity-impulsivity (National Institute for Health and Care Excellence, 2018). Autism spectrum disorder (ASD) is defined by persistent difficulties in social communication and interaction together with restricted or repetitive behaviors and atypical sensory processing (Zeidan *et al.*, 2022). Epilepsy is a chronic neurological disorder characterized by an enduring predisposition to recurrent unprovoked seizures (Jiao *et al.*, 2025). These conditions frequently co-occur in developmental-behavioral pediatrics, neurology and rehabilitation practice (Bougeard *et al.*, 2021). Reduced joint attention, language-comprehension difficulties, sensory avoidance and impaired task switching in ASD can resemble ADHD. In epilepsy, absence or focal impaired-awareness seizures, nocturnal seizures, postictal fatigue and interictal epileptiform activity may produce staring, slowed responses and reduced learning efficiency; ASMs, antipsychotics and sedative agents may also cause

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drowsiness, irritability, or cognitive slowing (Giambarberi *et al.*, 2025). Accordingly, treatment decisions should begin by asking whether symptoms are persistent, cross-situational and functionally impairing, whether seizure control and the ASM regimen are sufficiently stable to monitor change and whether symptom improvement translates into learning, rehabilitation participation, family functioning and safety (Faraone and Cortese, 2024; Njardvik *et al.*, 2025; Salpekar and Ertenu, 2024).

**Literature search strategy**

A targeted narrative search of PubMed/MEDLINE and Web of Science was undertaken, supplemented by professional guidance and reference-list screening. Search terms covered ADHD, ASD, epilepsy, seizures, methylphenidate, atomoxetine, guanfacine, clonidine, antiseizure medications, pediatric drug safety and related concepts. English-language guidance, clinical studies and reviews published mainly from January 2020 to December 2025 were prioritized. The 2018 International League Against Epilepsy (ILAE) Pediatric Commission consensus was also included because it provides formal evidence grades for ADHD

pharmacotherapy in pediatric epilepsy. Findings from ADHD-only, ASD-ADHD and epilepsy-ADHD populations were compared, with differences in the underlying populations explicitly considered. The search identified 986 records from databases (PubMed/MEDLINE,  $n = 372$ ; Web of Science,  $n = 614$ ). After removal of 251 duplicates, 735 records were screened by title and abstract; 653 were excluded. Eighty-two full-text reports were sought, of which five could not be retrieved. Seventy-seven reports were assessed for eligibility and 47 were excluded: wrong population ( $n=19$ ), no relevant pharmacotherapy ( $n=11$ ), ineligible publication or study type ( $n = 9$ ) and insufficient relevant data ( $n = 8$ ). Eleven additional records were identified through professional guidance and reference-list screening; nine were excluded and two were included. In total, 32 sources were included in the narrative synthesis. The selection process is summarized in figure S1. The aim was interpretive clinical synthesis rather than exhaustive evidence identification or pooled effect estimation. No formal risk-of-bias scoring or quantitative pooling was undertaken. The proposed monitoring categories and clinical pathway are pragmatic organizational aids and have not been prospectively validated.

### **Epidemiological characteristics**

ASD, ADHD and epilepsy have substantial clinical overlap and ADHD symptoms are particularly frequent among children with ASD. Common manifestations include persistent inattention, impulsivity, excessive activity, difficulty waiting and executive-function deficits (Hours *et al.*, 2022). DSM-5 and DSM-5-TR permit concurrent diagnoses of ASD and ADHD, allowing children previously described only as having 'ASD with hyperactivity or poor attention' to receive a more specific functional assessment and targeted treatment (First *et al.*, 2023). ADHD is also more common in children with epilepsy than in the general pediatric population; early seizure onset, frequent seizures, structural brain lesions, intellectual disability, sleep-related epileptiform activity, ASM polytherapy and family-care stress may increase the burden of attention and behavioral problems (Fan *et al.*, 2023; Eaton *et al.*, 2023; Pan *et al.*, 2024).

In a published multicenter cross-sectional study from China (Pan *et al.*, 2024), 395 children with epilepsy aged 6-18 years were evaluated; 189 (47.8%) met criteria for ADHD, only 31 had received ADHD treatment and the inattentive presentation was most frequent. Polytherapy, poor seizure control and interictal epileptiform abnormalities were associated with a higher ADHD burden. These are previously published data cited here for context and are not primary data generated by the present review. Direct Chinese data on the triple comorbidity of ASD, epilepsy and ADHD remain limited; therefore,

clinical interpretation should integrate domestic epilepsy-ADHD evidence with ASD-ADHD studies and individualized developmental assessment rather than extrapolating mechanically from a single-disease population (Martinez *et al.*, 2024; Al Ghamdi and AlMusailhi, 2024).

Functional impairment is often greater when these conditions co-occur. ASD with ADHD can reduce engagement in structured learning and behavioral intervention, increase family-care burden and worsen school and peer functioning (The SPARK Consortium, 2022). When epilepsy coexists with ADHD, medication adherence, seizure safety and school performance may also be affected. Sleep disorders, gastrointestinal discomfort, anxiety, depression, aggression and self-injury can further reduce daytime alertness, emotional regulation and executive function (Hyman *et al.*, 2020; Maurer *et al.*, 2023; Spagnoli *et al.*, 2024). These observations support active screening for comorbidity and caution against attributing inattention or hyperactivity solely to ASD or epilepsy.

### **Pathogenesis**

#### *Genetics and neurodevelopmental susceptibility*

ASD, ADHD and epilepsy share genetic and neurodevelopmental vulnerabilities involving synaptogenesis, neuronal migration, ion channels, cell adhesion, mTOR signalling and chromatin regulation (Miller *et al.*, 2025). Genetic syndromes and copy-number variants may increase susceptibility to ASD, epilepsy and attention-behavior problems simultaneously, although the same genetic vulnerability can produce different phenotypes through age-dependent effects on brain-network development, synaptic function and excitation-inhibition balance (Warrier *et al.*, 2022). This helps explain why some children first present with developmental delay and ASD features, later develop seizures or electroencephalographic abnormalities and show more prominent inattention or impulsivity at school age (Marini *et al.*, 2022). Because symptom priorities may change over time, treatment should be based on repeated clinical assessment rather than a single diagnostic label; at different stages, seizure control, sleep disturbance, severe behavior, or core ADHD symptoms may need to be addressed first (Miller *et al.*, 2024).

#### **Neural circuits and neurotransmitter systems**

Core neurobiological models of ADHD involve dysregulation of prefrontal-striatal-thalamic circuits, altered interaction between default-mode and task-positive networks and abnormalities in dopamine (DA) and norepinephrine (NE) signaling (Zhang *et al.*, 2024). Methylphenidate inhibits DA and NE transporters, thereby improving prefrontal signal-to-noise processing, sustained attention, inhibitory control and task persistence (Storebø *et al.*, 2023; Leeman-Markowski and Schachter, 2021).

ASD is also associated with atypical connectivity across prefrontal, temporal, limbic, striatal and cerebellar networks involved in social motivation, sensory processing and cognitive flexibility (Bedford *et al.*, 2025). Epileptic activity can disrupt network synchronization and sleep architecture, with secondary effects on attention and executive function (Uliel-Sibony *et al.*, 2023). In triple comorbidity, similar outward behavior may therefore arise from different mechanisms: prefrontal dysregulation may cause impulsivity, sensory overload may precipitate escape or emotional outbursts, nocturnal seizures may cause daytime fatigue and ASMs may produce sedation or cognitive slowing (Ertenu and Salpekar, 2024). This mechanistic heterogeneity reinforces the need to identify the most likely driver of each target symptom before altering medication.

### **Excitatory-inhibitory balance, neuroinflammation and gut-brain axis**

ASD and epilepsy are both associated with disturbances in excitation-inhibition balance. Reduced gamma-aminobutyric acid (GABA)-mediated inhibition or increased glutamatergic excitability may destabilize neural networks and contribute to sensory hypersensitivity, sleep fragmentation, emotional lability and seizure risk (Ertenu and Salpekar, 2024). Neuroinflammation, oxidative stress, immune activation and gut-microbiota alterations have also been proposed as modulators of neurotransmitter metabolism, vagal signalling and blood-brain-barrier function, although their direct relevance to medication selection remains uncertain (Młynarska *et al.*, 2025). Sleep is a particularly important shared pathway: insufficient or fragmented sleep can reduce prefrontal inhibitory control and worsen hyperactivity, impulsivity and emotional instability, while both ASD and epilepsy are independently associated with sleep disturbance (Estes *et al.*, 2024). ADHD medications can themselves alter sleep. Document baseline sleep before treatment so sleep-related inattention is not misinterpreted as medication non-response and followed by inappropriate dose escalation. Figure 1 summarizes the neurobiological convergence and key clinical decision points.

Clinicians must consider medication effects explicitly during assessment. Valproate may contribute to weight gain, drowsiness and reduced concentration; topiramate may cause word-finding difficulty, slowed thinking and decreased appetite; benzodiazepines may increase daytime somnolence and memory impairment; and levetiracetam may be associated with irritability, aggression, or emotional lability in some children (Besag, 2021). Other ASMs may have fewer cognitive effects but still require monitoring for rash, hepatic dysfunction and clinically relevant interactions. Risperidone and aripiprazole may be used for severe irritability, aggression or self-injury in ASD, but sedation and metabolic adverse effects can obscure the interpretation of attention symptoms (Siafis *et al.*, 2022).

Environmental context can also change symptom expression. Parenting stress, parental anxiety, limited school structure, excessive screen exposure, peer rejection, overly intensive rehabilitation schedules and poor sleep hygiene may worsen ADHD-like behavior (Claussen *et al.*, 2024). Children with ASD may be especially sensitive to environmental demands; in a noisy or visually overwhelming classroom, or when task complexity exceeds language comprehension, leaving the seat, crying, aggression or refusal may reflect distress rather than primary ADHD symptoms (Sibley *et al.*, 2023). Pharmacological management that ignores modifiable environmental factors risks converting support needs into unnecessary polypharmacy.

### **Assessment and diagnosis**

#### **Identification of true ADHD comorbidity**

Diagnosis of ADHD in children with ASD and epilepsy should require symptoms that are persistent, developmentally disproportionate, present across more than one setting and associated with functional impairment (First *et al.*, 2023). Clinical interviews should gather information from family, school and rehabilitation settings about onset, duration, triggers, emotional context and functional consequences. Parents may observe conflict, sleep and eating patterns; teachers can describe classroom behavior, waiting and task completion; rehabilitation therapists can assess instruction following, imitation, turn-taking, reinforcement dependence and transition difficulties (Schachar *et al.*, 2023). Interpret disagreement among informants as contextual information rather than simply averaging it. Structured instruments may include the SNAP-IV, Conners parent/teacher scales, Vanderbilt ADHD scales, locally validated ADHD rating scales, the Childhood Autism Rating Scale, the Autism Behavior Checklist, the Social Responsiveness Scale and adaptive-behavior measures. Assessment should also incorporate seizure diaries, electroencephalography (EEG) findings, neuroimaging when clinically indicated, ASM regimens, sleep and gastrointestinal screening and school/rehabilitation feedback to create a multisource functional profile (Bölte *et al.*, 2014). In children with limited language or intellectual disability, interpret scale scores in relation to developmental level, communication ability and task demands.

#### **Identification of pseudo-ADHD factors**

Potential 'pseudo-ADHD' factors should be excluded before medication is started. Absence seizures can present as brief staring or behavioral arrest; focal seizures may cause automatisms, confusion or postictal fatigue; and sleep-related epileptiform activity can impair daytime attention and learning (Pellinen *et al.*, 2024). Reports of sudden blank staring, unexplained behavioral arrest, post-event confusion or stereotyped episodic behavior should prompt neurological reassessment before ADHD symptoms are attributed to a primary attention disorder.

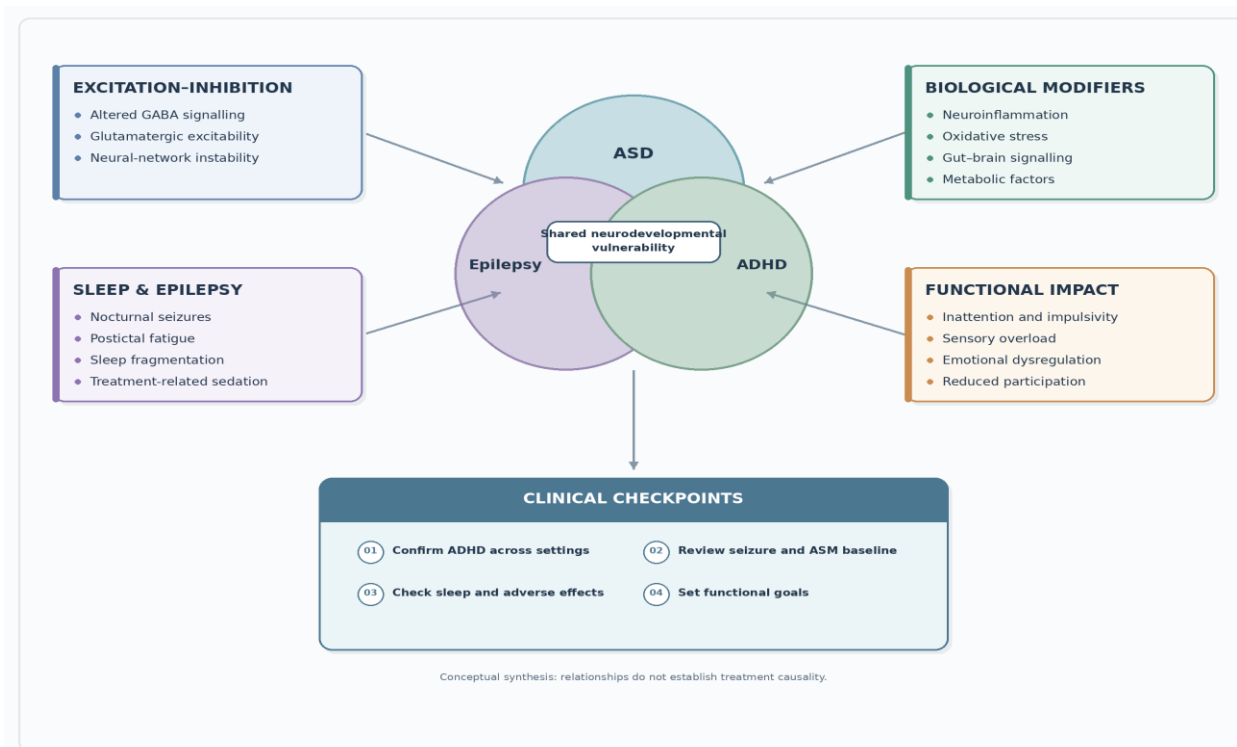


**Fig. 1:** Neurobiological convergence and clinical assessment priorities in ASD–epilepsy–ADHD comorbidity. Redrawn using Python 3 and Matplotlib (<https://matplotlib.org/>); original conceptual synthesis by the authors.

Sleep, gastrointestinal and emotional disorders should also be assessed systematically. Sleep-onset difficulty, night waking, snoring, sleep apnea, constipation, abdominal pain, gastroesophageal reflux, anxiety, depression and sensory overload can cause irritability, task escape and apparent hyperactivity. The medication history should record each ASM, antipsychotic, sedative, melatonin product, nutritional supplement and other relevant treatment, including dose, administration time and recent changes (Moore *et al.*, 2021). If attention worsens after an ASM change, or if seizure control or sleep deteriorates, these factors should be reviewed before concluding that ADHD treatment has failed.

#### **Risk stratification before treatment initiation**

Before initiating ADHD medication, risk assessment should cover four domains. The diagnostic domain asks whether symptoms meet ADHD criteria and are not better explained by ASD core features, seizures or medication effects. The epilepsy domain reviews seizure type, recent seizure frequency, nocturnal events, new seizure patterns, EEG findings and ASM stability (Ertenu *et al.*, 2025). The somatic domain includes height, weight, body mass index, blood pressure, heart rate, appetite, sleep, cardiovascular history, relevant family history, liver status when clinically indicated and allergy history. The care-system domain assesses whether caregivers can maintain seizure and adverse-event records, whether school or rehabilitation staff can provide feedback and whether unsupervised dose changes are likely. For practical communication, clinicians

may describe patients as lower-, intermediate-, or higher-monitoring concern. Examples include stable seizure control with a stable ASM regimen at the lower-concern end and recent seizure escalation, a new seizure type or inability to distinguish seizure events from inattention at the higher-concern end. These categories and time windows are author-proposed pragmatic aids for clinical discussion; they are not validated risk-stratification tools or prescriptive cut-offs and should not replace individualized neurological assessment.

Before prescribing, clinicians should define one or more observable functional goals and document safety red flags. Rather than using the vague target 'better attention', goals can be expressed as classroom sitting duration, completion of a two-step instruction, frequency of leaving the seat, dangerous running, delay in homework initiation, rehabilitation cooperation or family-conflict frequency. Targets should change with the treatment phase: during initiation, priority is tolerability and improvement in one or two high-value behaviors; during titration, the magnitude and duration of functional benefit should be compared with appetite, sleep, cardiovascular and behavioral adverse effects; if seizure control fluctuates, the immediate goal should shift toward safety and attribution of cause before any dose escalation. Red flags include an increase in seizures, new seizure types, persistent severe insomnia, clinically important appetite or weight loss, chest pain, palpitations, syncope, signs of liver injury, severe irritability, self-injury or suicidal ideation.

### **Treatment measures**

#### ***Non-pharmacological intervention as the basis of medication management***

For children with ASD and epilepsy, non-pharmacological intervention should accompany medication rather than being reserved for medication failure. Parent-management training, structured school support, behavior analysis, task decomposition, visual cues, reinforcement strategies, sleep hygiene, exercise and nutrition support can reduce symptom burden and help medication-related gains transfer into daily function (Sibley *et al.*, 2023). Long-term ASD care is best organized around continuous, family-centred and multidisciplinary support (Hyman *et al.*, 2020). If a child leaves the classroom because of language-comprehension difficulty or sensory overload, medication alone is unlikely to normalize participation; environmental adaptation and teaching support remain necessary.

Digital therapeutics, neurofeedback, motor interventions and selected computer-assisted training approaches have been studied in ADHD and ASD, with variable effects on executive function, attention and emotional regulation. Their role should be individualized, particularly in children with epilepsy. Flickering visual stimuli, prolonged screen exposure, immersive environments and sleep-disrupting use patterns may be inappropriate for some patients with seizure susceptibility. Non-pharmacological goals should remain aligned with medication goals: better learning, communication, participation and safe daily living.

#### ***Methylphenidate: Core option and seizure-safety boundary***

Methylphenidate has the most consistent evidence base among pharmacological treatments for core ADHD symptoms in children and adolescents. By inhibiting dopamine and norepinephrine reuptake, it can improve sustained attention, task persistence and inhibitory control. Systematic-review evidence supports reductions in ADHD symptoms compared with placebo or no treatment, while common non-serious adverse effects include reduced appetite, sleep disturbance, abdominal pain, headache and changes in heart rate or blood pressure (Storebø *et al.*, 2023; Liguori *et al.*, 2024).

Epilepsy alone is not an absolute contraindication to methylphenidate. The 2018 ILAE Pediatric Commission consensus concluded that methylphenidate was tolerated and effective in children with epilepsy and comorbid ADHD (Level B), whereas evidence for atomoxetine was more limited (Level C) (Auvin *et al.*, 2018). Evidence published since 2020 has not produced a new formal ILAE grading, but reviews and clinical guidance continue to support cautious stimulant use when epilepsy is stable and follow-up is feasible, without showing a consistent clinically important increase in seizure risk at standard therapeutic doses (Leeman-Markowski and Schachter, 2021; Spagnoli *et al.*, 2024; Ertenu *et al.*, 2025). These later

data reinforce rather than formally upgrade the 2018 evidence level. Greater caution is warranted when seizures are active or changing, because evidence in unstable epilepsy is much thinner and attribution of new events becomes difficult. Initiation should therefore use a low dose and gradual titration, with seizure diaries, sleep review and coordination with pediatric neurology when indicated.

For children with ASD and epilepsy, response to methylphenidate should not be judged simply by whether the child becomes quieter. Reduced activity accompanied by withdrawal, apathy, increased rigidity or reduced social engagement may represent excessive adverse effects, anxiety or mood change rather than improved inhibitory control. Appetite and nutritional status require particular attention in children with selective eating, sensory feeding problems or gastrointestinal comorbidity (Auvin *et al.*, 2018).

#### ***Atomoxetine: Non-stimulant option and precision-use considerations***

Atomoxetine is a selective norepinephrine reuptake inhibitor with a slower onset than stimulants and its benefits may take several weeks to emerge. Its relatively continuous symptom coverage and low misuse potential can make it useful when stimulants are not tolerated or when anxiety, tics or sleep concerns complicate stimulant treatment (Zhang *et al.*, 2024). In children with ASD, it may be considered for persistent inattention and impulsivity when a non-stimulant strategy is preferred, while expectations should reflect the slower onset of action.

Atomoxetine requires a different safety focus from methylphenidate. CYP2D6 genotype and strong CYP2D6 inhibitors can increase exposure and may contribute to somnolence, gastrointestinal symptoms, heart-rate or blood-pressure changes and behavioral adverse effects. Routine CYP2D6 genotyping or therapeutic drug monitoring is not required for every patient; consider it selectively when there is unusual intolerance, an unexpected exposure-response pattern, complex polypharmacy, or clinically relevant hepatic concerns. Rare but important risks include liver injury and suicidal thoughts. Children with ASD and limited language may communicate adverse effects indirectly through crying, refusal, sudden aggression, self-injury, social withdrawal or appetite change. Decisions about testing and monitoring should follow locally available product information and specialist judgement rather than a fixed protocol.

#### ***$\alpha$ 2-Adrenergic receptor agonists***

Alpha-2 adrenergic receptor agonists such as guanfacine and clonidine can reduce hyperactivity, impulsivity and hyperarousal and may also help sleep-onset difficulties in selected patients.

**Table 1:** Safety monitoring and evidence basis for pharmacological management of ADHD in children with ASD and epilepsy.

| Drug/group                     | Target use                                         | Evidence basis                                      | Key risks                                                                        | Monitoring priorities                                                              | References                                                                                     |
|--------------------------------|----------------------------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Methylphenidate                | Core ADHD symptoms; stable epilepsy                | ILAE Level B; supportive subsequent reviews         | Appetite loss, insomnia, growth/BP/HR change; reassess seizure change            | Seizure diary; appetite, sleep, growth, vital signs, function                      | Auvin <i>et al.</i> , 2018; Leeman-Markowski and Schachter, 2021; Storebø <i>et al.</i> , 2023 |
| Atomoxetine                    | Non-stimulant when stimulants are unsuitable       | ILAE Level C; supporting ADHD/ASD evidence          | GI symptoms, mood change, HR/BP change; rare hepatic injury or suicidal ideation | Monitor mood, liver warning signs, BP/HR, sleep; assess CYP2D6 issues as indicated | Auvin <i>et al.</i> , 2018; Zhang <i>et al.</i> , 2024                                         |
| $\alpha$ 2-Adrenergic agonists | Impulsivity, hyperarousal, selected sleep problems | ADHD/ASD evidence; limited epilepsy-specific trials | Sedation, hypotension, bradycardia, rebound hypertension                         | BP/HR, falls, daytime alertness, participation; avoid abrupt discontinuation       | Hyman <i>et al.</i> , 2020; Sifakis <i>et al.</i> , 2022                                       |
| Antipsychotics                 | Severe ASD irritability/aggression; not core ADHD  | Evidence for ASD-related irritability               | Weight gain, metabolic effects, EPS, sedation, prolactin elevation               | Target-behavior review; metabolic and EPS monitoring                               | Sifakis <i>et al.</i> , 2022                                                                   |

Evidence statements in table 1 distinguish formal published grading from narrative synthesis. Only the ILAE Level B and Level C labels are formal evidence levels adopted directly from the 2018 ILAE Pediatric Commission consensus (Auvin *et al.*, 2018). Other entries describe the population and type of supporting evidence and should not be interpreted as newly validated grades. Evidence from ADHD-only, ASD-ADHD and epilepsy-ADHD populations is combined qualitatively because direct trials in children with all three conditions are scarce. ASM: antiseizure medication; BP: blood pressure; HR: heart rate; EPS: extrapyramidal symptoms; TDM: therapeutic drug monitoring.

Common adverse effects include somnolence, fatigue, dizziness, hypotension, bradycardia and rebound hypertension after abrupt discontinuation. Concurrent sedating ASMs can further reduce daytime alertness. Because availability, approved indications and formulations vary by country, clinicians should follow local labeling. Assess blood pressure and heart rate at baseline and during titration and review daytime alertness, falls and school participation through caregiver and teacher feedback.

#### **Antipsychotics, ASMs and combination therapy**

Risperidone and aripiprazole can be used for severe irritability, aggression or self-injury associated with ASD, but they are not first-line treatments for core ADHD symptoms (Sifakis *et al.*, 2022). Important adverse effects include weight gain, hyperglycemia, dyslipidemia, hyperprolactinemia, extrapyramidal symptoms, sedation and cognitive slowing. Interpreting 'calmness' as improved

attention can therefore overestimate benefit. In combination regimens, each drug should have a clearly defined target symptom, observation period and monitoring plan. When feasible, major ASM changes and ADHD-medication titration should not occur simultaneously, because new inattention, irritability or sedation may otherwise be difficult to attribute. Children with worsening or newly changing seizures should undergo neurological reassessment before an ADHD medication is initiated or escalated.

#### **Safety considerations**

##### *Principle of drug initiation*

Pharmacological treatment should follow a sequence of diagnostic confirmation, individualized risk review, stabilization of major competing problems and target-based titration. Diagnostic confirmation requires cross-setting ADHD symptoms with clear functional impairment. Risk review considers seizure stability, EEG

findings in clinical context, ASM polytherapy, communication limitations and the reliability of follow-up. Whenever feasible, major sleep or gastrointestinal problems and recent ASM changes should be addressed before ADHD medication is escalated. Document functional targets and criteria for urgent review before prescribing. Dosing should be cautious: begin low, titrate gradually and avoid introducing multiple medication changes at the same time. Children with low body weight, limited language, uncertain seizure control, antipsychotic exposure or ASM polytherapy may require slower titration and closer observation. The aim is not simply symptom suppression, but improved learning, communication, safety and family functioning.

### ***Dynamic monitoring content***

Safety monitoring should cover four domains: seizures, physical status, mood/behavior and function. Seizure monitoring should record timing, duration, possible triggers, semiology, postictal state and missed ASM doses. Physical monitoring should include sleep, appetite, height, weight, body mass index, blood pressure, heart rate, gastrointestinal symptoms and clinically indicated signs of hepatic dysfunction. Behavioural monitoring should include anxiety, irritability, aggression, self-harm, social withdrawal, depressed mood and suicidal ideation. Functional monitoring should include target-behavior feedback from parents, teachers and rehabilitation therapists. During initiation, review should focus on tolerability and early functional change; during titration, clinicians should compare benefit duration with adverse effects and seizure stability; during maintenance, growth, cardiovascular measures, sleep, adherence and sustained function become increasingly important. If seizure control worsens, the treatment target should temporarily shift toward event characterization and safety before further ADHD dose escalation. Follow-up timing should be individualized to clinical risk and local practice rather than fixed to a universal interval. Table 1 summarizes the evidence basis and monitoring priorities for commonly used drug groups; it aids case review, not a substitute for product labeling or professional judgment.

### ***Treatment of special clinical situations***

When seizures are active, newly changing or diagnostically uncertain, ADHD medication initiation or escalation should generally be deferred until neurological reassessment clarifies seizure control and the ASM plan. EEG abnormalities without clinical seizures should not automatically trigger an ASM solely to improve attention; management of interictal discharges depends on seizure risk, cognitive regression, sleep-related discharge burden and specialist assessment. The examples used in this review (such as 'recent seizure increase' or 'stable over several months') are pragmatic prompts for closer review, not validated temporal thresholds.

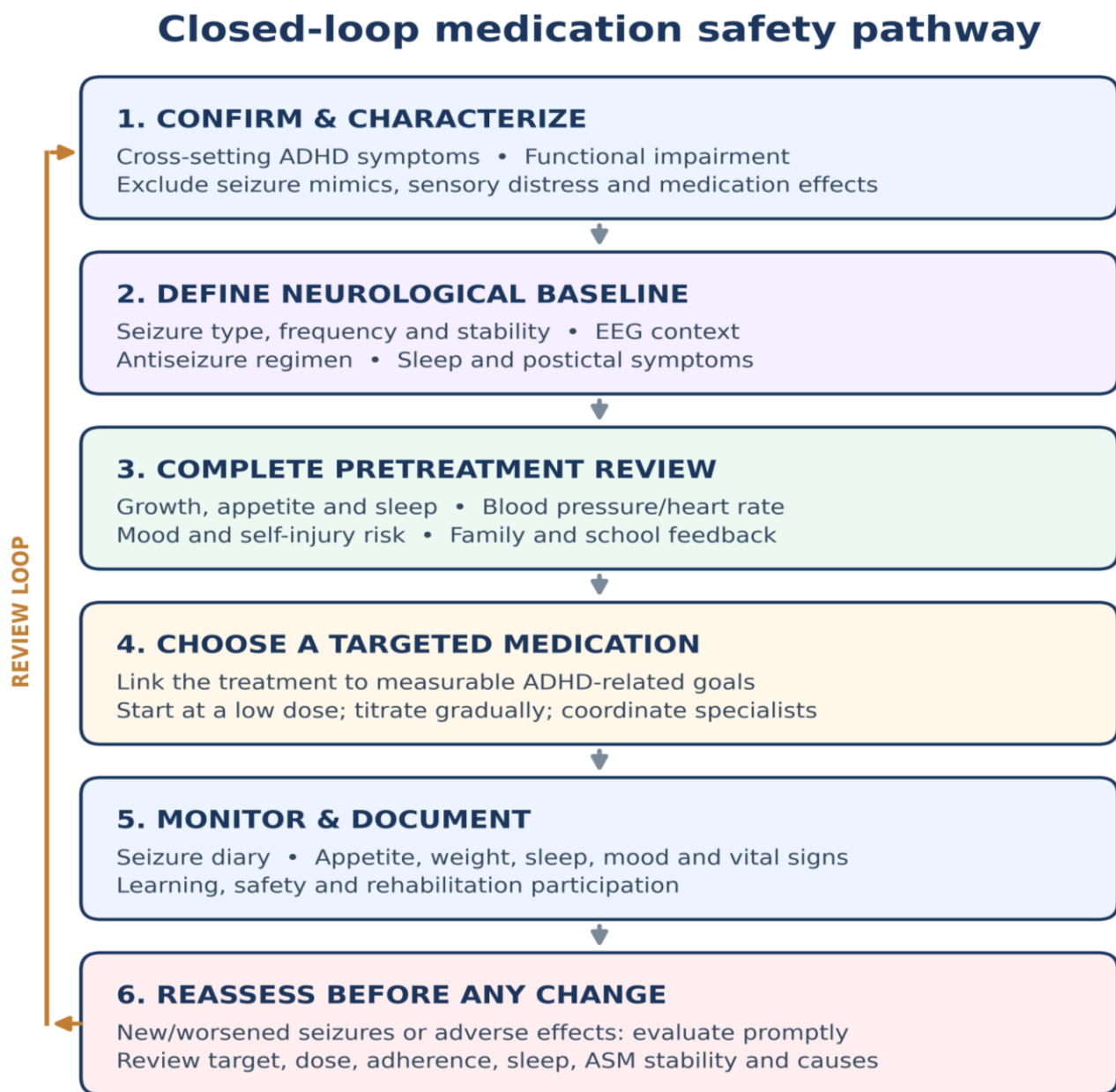
Adverse effects in children with ASD and limited language may present primarily as behavioral change. Caregivers can record food intake, sleep-onset time, night waking, stool pattern, seizure-like events, crying, scratching, self-injury, refusal to learn and aggression. Apparent improvement in attention accompanied by marked withdrawal or unusual quietness should prompt consideration of anxiety, depressed mood or excessive medication effect. When sleep disorder, constipation, or malnutrition is prominent, optimize these conditions before judging medication response. In multi-drug regimens, document each change with dose, administration time, clinical purpose, observation period and stopping or reassessment criteria.

### ***Closed-loop management path***

Figure 2 presents an author-proposed closed-loop pathway for outpatient and multidisciplinary management. It is intended as a clinical organization framework rather than a validated decision rule. Step 1 confirms ADHD using cross-setting symptoms, functional impairment and exclusion of major mimics. Step 2 reviews the seizure baseline, recent seizure pattern and ASM stability. Step 3 reassesses other contributors to inattention, including sleep disturbance, anxiety, postictal states, medication effects, pain and environmental demands. Step 4 completes a pretreatment safety review; step 5 links drug choice to the dominant target symptom and comorbidity profile; and step 6 obtains functional and safety feedback from caregivers, school or rehabilitation staff and clinicians. If treatment is ineffective or poorly tolerated, clinicians should first revisit the target, seizure and sleep stability, adherence, dose and duration and alternative explanations for difficulty before adding further medication.

### ***Evidence gaps and future research directions***

Evidence remains limited for children with the full combination of ASD, epilepsy and ADHD. Most data derive from ADHD-only cohorts, epilepsy-ADHD studies or ASD-ADHD studies and extrapolation is constrained by heterogeneity in seizure type, seizure control, intellectual and language ability, ASD severity and ASM combinations. China also lacks prospective cohorts and randomized trials specifically evaluating ADHD pharmacotherapy in this triple-comorbidity population. Future studies should therefore stratify participants by epilepsy syndrome, seizure stability, EEG characteristics, ASM monotherapy versus polytherapy, developmental level, ASD severity and sleep or gastrointestinal comorbidity. Although the formal ILAE evidence grading dates from 2018, more recent reviews generally reinforce cautious methylphenidate use in stable epilepsy; prospective data in active or unstable epilepsy are still needed before stronger evidence statements can be made (Auvin *et al.*, 2018; Leeman-Markowski and Schachter, 2021; Ertenu *et al.*, 2025).



Author-proposed organizational pathway; not a validated clinical prediction rule.

**Fig. 2:** Closed-loop safety pathway for ADHD pharmacotherapy in children with ASD and epilepsy. Redrawn using Python 3 and Matplotlib (<https://matplotlib.org/>); author-proposed framework, not a validated prediction rule.

Future efficacy evaluation should move beyond total ADHD symptom scores. Clinically meaningful outcomes for children with ASD and epilepsy include rehabilitation participation, classroom safety, risk behavior, sleep quality, seizure stability, caregiver burden, school adaptation and quality of life. Multisource assessment should include parents, teachers, rehabilitation therapists and clinicians and, where feasible, objective or semi-

objective indicators such as frequency of leaving the seat, dangerous running events, completion of two-step instructions and concordance of seizure diaries.

Long-term safety also requires stronger evidence. Follow-up should be sufficient to assess growth, appetite, weight and metabolic change, cardiovascular status, behavior, suicidal ideation, seizure patterns and adherence.

Precision-pharmacotherapy research should clarify when CYP2D6 genotype or atomoxetine exposure measurement is clinically useful, whether methylphenidate formulations differ meaningfully in patients receiving ASMs and how drug-drug interactions, sleep and other biological modifiers affect tolerability. Such questions should be tested prospectively rather than converted prematurely into universal monitoring rules.

Implementation research in Chinese hospitals should evaluate whether structured assessment packages, pragmatic risk-communication tools, electronic seizure/adverse-event diaries, school-rehabilitation feedback forms and scheduled multidisciplinary review improve safety and function. Any proposed three-level risk framework should undergo prospective validation before it is used as a predictive instrument. Ethical safeguards should emphasize caregiver education, age-appropriate assent when possible, independent adverse-event assessment and avoiding equating medication-induced quietness with functional improvement.

## CONCLUSION

Pharmacological treatment of ADHD symptoms in children with ASD and epilepsy can be appropriate, but the evidence base is uneven and clinical attribution is complex. Methylphenidate remains the best-supported option for core ADHD symptoms and recent literature generally reinforces its cautious use when epilepsy is stable. Atomoxetine is a reasonable non-stimulant alternative when stimulants are unsuitable or poorly tolerated, while alpha-2 adrenergic agonists may be useful for selected hyperarousal, impulsivity or sleep-onset problems. Antipsychotics and ASMs should retain clearly defined non-ADHD targets and sedation should never be equated with ADHD improvement. The practical risk categories and closed-loop pathway proposed here are organizational aids, not validated prediction tools. Safe prescribing requires diagnostic reconfirmation, review of seizure and medication baselines, low-dose initiation, gradual titration, phase-specific functional goals, seizure diaries, multisource feedback and multidisciplinary reassessment whenever seizure control, sleep or behavior changes.

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## Authors' contributions

Zhang Ye: Contributed to conceptualization, literature review and drafting of the manuscript; Yuan Yazhen: Contributed to methodology, supervision, interpretation of the evidence and critical revision; Gou Yanyang: Contributed to the literature review, reference checking and preparation of the figures and tables. All authors reviewed and approved the revised manuscript. The authors used an AI-based language-editing tool during

revision to improve grammar and clarity. All scientific statements, citations and final wording were independently reviewed and approved by the authors.

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## Data availability statement

All information analyzed in this narrative review is contained in the published literature cited in the article. No new primary dataset was generated.

## Ethical approval

Not applicable. This narrative review did not involve human participants, identifiable patient data or animal experiments.

## Conflicts of interest

The authors declare no conflict of interest.

## REFERENCES

- Al Ghamdi K and AlMusailhi J (2024). Attention-deficit hyperactivity disorder and autism spectrum disorder: Towards better diagnosis and management. *Med. Arch.*, **78**(2): 159-163.
- Auvin S, Wirrell E, Donald KA, Berl M, Hartmann H, Valente KD, Van Bogaert P, Cross JH, Osawa M, Kanemura H, Aihara M, Guerreiro MM, Samia P, Vinayan KP, Smith ML, Carmant L, Kerr M, Hermann B, Dunn D and Wilmschurst JM (2018). Systematic review of the screening, diagnosis and management of ADHD in children with epilepsy: Consensus paper of the Task Force on Comorbidities of the ILAE Pediatric Commission. *Epilepsia*, **59**(10): 1867-1880.
- Bedford SA, Lai MC, Lombardo MV, Chakrabarti B, Ruigrok A, Suckling J, Anagnostou E, Lerch JP, Taylor M, Nicolson R, Stelios G, Crosbie J, Schachar R, Kelley E, Jones J, Arnold PD, Courchesne E, Pierce K, Eyler LT, Campbell K, Barnes CC, Seidlitz J, Alexander-Bloch AF, Bullmore ET, Baron-Cohen S and Bethlehem RAI (2025). Brain-charting autism and attention-deficit/hyperactivity disorder reveals distinct and overlapping neurobiology. *Biol. Psychiatry*, **97**(5): 517-530.
- Besag FMC (2021). Behavioural adverse effects of antiseizure medications in children. *CNS Drugs*, **35**(9): 901-916.
- Bougard C, Picarel-Blanchot F, Schmid R, Campbell R and Buitelaar J (2021). Prevalence of autism spectrum disorder and co-morbidities in children and adolescents: A systematic literature review. *Front. Psychiatry*, **12**: 744709.

- Bölte S, de Schipper E, Holtmann M, Karande S, de Vries PJ, Selb M and Tannock R (2014). Development of ICF Core Sets to standardize assessment of functioning and impairment in ADHD: The path ahead. *Eur. Child Adolesc. Psychiatry*, **23**(12): 1139-1148.
- Claussen AH, Holbrook JR, Hutchins HJ, Robinson LR, Bloomfield J, Meng L, Bitsko RH, O'Masta B, Cerles A, Maher B, Rush M and Kaminski JW (2024). All in the family? A systematic review and meta-analysis of parenting and family environment as risk factors for attention-deficit/hyperactivity disorder (ADHD) in children. *Prev. Sci.*, **25**(Suppl 2): 249-271.
- Duong KL, Yang BR, Yun HY and Chae JW (2024). Effect of methylphenidate on height in pediatric attention-deficit hyperactivity disorder patients: A systematic review and meta-analysis. *Eur. Child Adolesc. Psychiatry*, **33**(6): 1755-1770.
- Eaton C, Roarty K, Doval N, Shetty S, Goodall K and Rhodes SM (2023). The prevalence of attention deficit/hyperactivity disorder symptoms in children and adolescents with autism spectrum disorder without intellectual disability: A systematic review. *J. Atten. Disord.*, **27**(12): 1360-1376.
- Ertenu DD and Salpekar JA (2025). Treating neuropsychiatric conditions in pediatric epilepsy: Practical considerations. *Epilepsy Curr.*, **26**(4): 273-279.
- Ertenu DD, Sohn J and Salpekar JA (2024). Key treatment issues for epilepsy in the context of autism spectrum disorder. *Curr. Treat. Options Neurol.*, **26**(11): 417-432.
- Estes A, Hillman A and Chen ML (2024). Sleep and autism: Current research, clinical assessment and treatment strategies. *Focus (Am. Psychiatr. Publ.)*, **22**(2): 162-169.
- Fan HC, Chiang KL, Chang KH, Chen CM and Tsai JD (2023). Epilepsy and attention deficit hyperactivity disorder: Connection, chance and challenges. *Int. J. Mol. Sci.*, **24**(6): 5270.
- Faraone S V and Cortese S (2024). The neurobiology and genetics of attention-deficit/hyperactivity disorder. *Nat Rev Neurosci*, **25**(7): 446-464.
- First MB, Clarke DE, Yousif L, Eng AM, Gogtay N and Appelbaum PS (2023). DSM-5-TR: Rationale, process and overview of changes. *Psychiatr. Serv.*, **74**(8): 869-875.
- Giamballeri L, Alexander HB and Munger Clary H (2025). ADHD in adults with epilepsy: A guide for neurologists. *Epilepsy Behav. Rep.*, **29**: 100739.
- He Z, Yang X, Li Y, Zhao X, Li J and Li B (2024). Attention-deficit/hyperactivity disorder in children with epilepsy: A systematic review and meta-analysis of prevalence and risk factors. *Epilepsia Open*, **9**(4): 1148-1165.
- Hours C, Recasens C and Baleyte J M (2022). ASD and ADHD comorbidity: What are we talking about?. *Front Psychiatry*, **13**: 837424.
- Hyman SL, Levy SE and Myers SM (2020). Identification, evaluation and management of children with autism spectrum disorder. *Pediatrics*, **145**(1): e20193447.
- Jiao D, Xu L, Gu Z, Yan H, Shen D and Gu X (2025). Pathogenesis, diagnosis and treatment of epilepsy: Electromagnetic stimulation-mediated neuromodulation therapy and new technologies. *Neural Regen. Res.*, **20**(4): 917-935.
- Leeman-Markowski B A and Schachter S C (2021). Methylphenidate for attention problems in epilepsy patients: Safety and efficacy. *Epilepsy Behav.*, **115**: 107623.
- Liguori S, De Crescenzo F and Cortese S (2024). What are the benefits and harms of methylphenidate in children and adolescents with attention-deficit/hyperactivity disorder? A Cochrane Review summary with commentary. *Dev Med Child Neurol*, **66**(10): 1289-1291.
- Marini C and Giardino M (2022). Novel treatments in epilepsy guided by genetic diagnosis. *Br. J. Clin. Pharmacol.*, **88**(6): 2539-2551.
- Martinez S, Stoyanov K and Carcache L (2024). Unraveling the spectrum: Overlap, distinctions and nuances of ADHD and ASD in children. *Front Psychiatry*, **15**: 1387179.
- Maurer JJ, Choi A, An I, Sathi N and Chung S (2023). Sleep disturbances in autism spectrum disorder: Animal models, neural mechanisms and therapeutics. *Neurobiol. Sleep Circadian Rhythms*, **14**: 100095.
- Miller CJ, Golovina E, Gokuladhas S, Wicker JS, Jacobsen JC and O'Sullivan JM (2025). Unraveling ADHD: Genes, co-occurring traits and developmental dynamics. *Life Sci. Alliance*, **8**(5): e202403029.
- Miller DJ, DeGrauw TJ and Lovell AM (2024). Comorbidity of attention deficit hyperactivity disorder in pediatric epilepsy. *Pediatr Neurol Briefs*, **38**: 6.
- Moore JL, Carvalho DZ, St Louis EK and Bazil C (2021). Sleep and epilepsy: A focused review of pathophysiology, clinical syndromes, co-morbidities and therapy. *Neurotherapeutics*, **18**(1): 170-180.
- Młynarska E, Barszcz E, Budny E, Gajewska A, Kopeć K, Wasiak J, Rysz J and Franczyk B (2025). The gut-brain-microbiota connection and its role in autism spectrum disorders. *Nutrients*, **17**(7): 1135.
- National Institute for Health and Care Excellence (2018). Attention deficit hyperactivity disorder: Diagnosis and management (NG87). last reviewed 2025-05-07.
- Njardvik U, Wergeland GJ, Riise EN, Hannesdottir DK and Öst LG (2025). Psychiatric comorbidity in children and adolescents with ADHD: A systematic review and meta-analysis. *Clin. Psychol. Rev.*, **118**: 102571.
- Pan G, Han Y, Wang TC, Chen ZY, Wang XQ, Sun HB, Liu YH, Wang Q, Lin WH, Li JM, Zhou SZ and Zhang YH (2024). Attention deficit hyperactivity disorder in children with epilepsy: A multicenter cross-sectional analysis in China. *World J. Pediatr.*, **20**(10): 1070-1078.

- Pellinen J, Foster EC, Wilmshurst JM, Zuberi SM and French J (2024). Improving epilepsy diagnosis across the lifespan: Approaches and innovations. *Lancet Neurol.*, **23**(5): 511-521.
- Salpekar JA and Ertenu DD (2024). Common ground: We can comprehensively treat pediatric epilepsy and psychiatric comorbidities. *Epilepsy Curr.*, **24**(6): 381-386.
- Schachar RJ, Dupuis A, Arnold PD, Anagnostou E, Kelley E, Georgiades S, Nicolson R, Townes P, Burton CL and Crosbie J (2023). Autism spectrum disorder and attention-deficit/hyperactivity disorder: Shared or unique neurocognitive profiles? *Res. Child Adolesc. Psychopathol.*, **51**(1): 17-31.
- Siafis S, Ciray O, Wu H, Schneider-Thoma J, Bighelli I, Krause M, Rodolico A, Ceraso A, Deste G, Huhn M, Fraguas D, San Jose Caceres A, Mavridis D, Charman T, Murphy DG, Parellada M, Arango C and Leucht S (2022). Pharmacological and dietary-supplement treatments for autism spectrum disorder: A systematic review and network meta-analysis. *Mol. Autism*, **13**(1): 10.
- Sibley MH, Bruton AM, Zhao X, Johnstone JM, Mitchell J, Hatsu I, Arnold LE, Basu HH, Levy L, Vyas P, Macphree F, Schoenfelder Gonzalez E, Kelley M, Jusko ML, Bolden CR, Zulauf-McCurdy C, Manzano M and Torres G (2023). Non-pharmacological interventions for attention-deficit hyperactivity disorder in children and adolescents. *Lancet Child Adolesc. Health*, **7**(6): 415-428.
- Spagnoli C, Ioppi A, Di Santo F, Rollo D and Pisani F (2024). Comorbidity between ADHD and epilepsy: A narrative review. *Acta Biomed.*, **95**(4): e2024136.
- Storebø OJ, Storm MRO, Pereira Ribeiro J, Skoog M, Groth C, Callesen HE, Schaug JP, Darling Rasmussen P, Huus CL, Zwi M, Kirubakaran R, Simonsen E and Gluud C (2023). Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database Syst. Rev.*, **3**(3): CD009885.
- The SPARK consortium (2022). Co-occurring attention-deficit/hyperactivity disorder and anxiety disorders differentially affect males and females with autism. *Clin Neuropsychol*, **36**(5): 1069-1093.
- Uliel-Sibony S, Chernuha V, Tokatly Latzer I and Leitner Y (2023). Epilepsy and attention-deficit/hyperactivity disorder in children and adolescents: An overview of etiology, prevalence and treatment. *Front. Hum. Neurosci.*, **17**: 1021605.
- Warrier V, Zhang X, Reed P, Havdahl A, Moore TM, Cliquet F, Leblond CS, Rolland T, Rosengren A, Rowitch DH, Hurles ME, Geschwind DH, Børglum AD, Robinson EB, Grove J, Martin HC, Bourgeron T and Baron-Cohen S (2022). Genetic correlates of phenotypic heterogeneity in autism. *Nat. Genet.*, **54**(9): 1293-1304.
- Zeidan J, Fombonne E, Scora J, Ibrahim A, Durkin MS, Saxena S, Yusuf A, Shih A and Elsabbagh M (2022). Global prevalence of autism: A systematic review update. *Autism Res.*, **15**(5): 778-790.
- Zhang Y, Yin L, You C, Liu C, Dong P, Xu X and Zhang K (2024). Efficacy and safety of methylphenidate and atomoxetine in medication-naïve children with attention-deficit hyperactivity disorder in a real-world setting. *Paediatr. Drugs*, **24**(1): 29-39.