AES 2024 ANNUAL MEETING

Assessing Problem Behaviors and Identifying Co-morbidities

Nan Lin, MD
Cincinnati Children's Hospital Medical Center

December 6, 2024

AES AMERICAN EPILEPSY SOCIETY

Child Neurology FOUNDATION Creating a Community of Support

Disclosure

- None

https://www.wordclouds.com/

Learning Objectives

Learners should be able to:

- Identify common co-morbidities of epilepsy with regards to behavior and mood
- Use a multifaceted and nuanced approach to behaviors and mood

Disruptive and Harmful Behaviors in Neurodevelopmental Disorders and Epilepsy

- Disruptive and harmful behaviors:
  - Aggression: Physical or verbal hostility towards others
  - Self-injury: Behaviors such as head-banging, biting, or scratching oneself
  - Tantrums: Intense emotional outbursts characterized by crying, screaming, or physical aggression
  - Hyperactivity: Excessive movement and difficulty staying still
  - Impulsivity: Acting without thinking, which can lead to risky behaviors
  - Repetitive Behaviors: Repeated actions or rituals that can interfere with daily function
- Other behaviors
  - Social withdrawal
  - Anxiety
  - Depression
  - Difficulty-concentrating
  - Negative self-talk

Austin J, Epilepsia 2017 | Dunn DW, Neurology 1999 | Dunn DW, Seizure 1997

Behavioral and Mood Problems are Common!

- 25-45% range of psychosomatic and behavioral challenges in our children with epilepsy (CWE)
- These are **often not recognized** in a clinical visit in the office
- These can **precede** the diagnosis of epilepsy and **persist** after the diagnosis of epilepsy
- There is a **bi-directionality** between mood/behavioral disorders and epilepsy
- Present **independent** of seizure control (but are higher in certain epilepsy syndromes)

Aaberg KM Pediatrics 2016 | Austin JK, Pediatrics 2001 | Hesdorffer DC, Annuals of Neurology 2012 | Oh A, Epilepsy & Behavior 2017

High Incidence of Comorbidities in CWE: Population Study

- Norwegian Patient Registry between 2008-2013
- Children with epilepsy (CWE) were compared to general child population (GCP)
- 6,635 children with epilepsy compared to 1,125,161 children

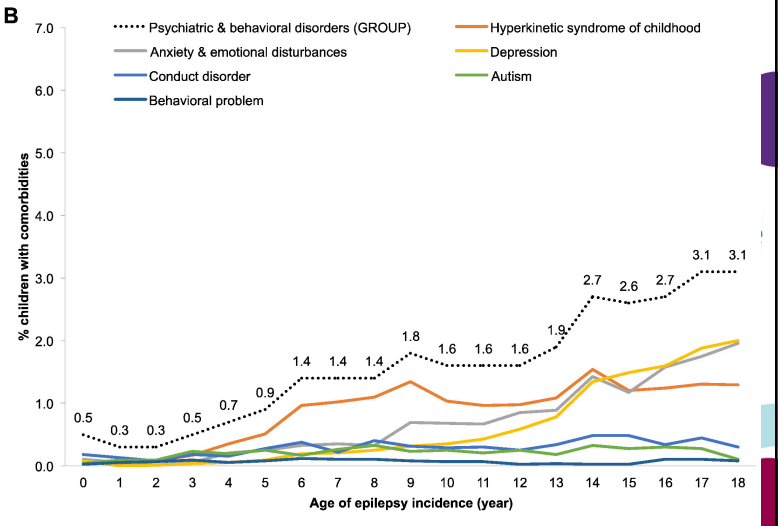
	CWE	GCP
>1 comorbid disorder	78.3%	30.3%
Developmental and/or psychiatric disorder	42.9%	6.6%
Neurologic disorder	41.3	2.5%
Medical disorder	19.1%	5.4%

Category	CWE (N = 6635)		GCP (N = 1 125 161)		CWE vs GCP
Disorders	N	%	N	%	OR (99% CI)
Developmental/psychiatric disorders	2847	42.9	74 086	6.6	9.4 (8.7–10.0)*
Disorders of psychological development (including autism)	1414	21.3	21 787	1.9	11.6 (10.7–12.6)*
Autism	516	7.8	7104	0.6	10.7 (9.5–12.1)*
Intellectual disability	1126	17.0	4583	0.4	41.0 (37.3–45.0)*
ADHD	801	12.1	21 872	1.9	5.4 (4.8–5.9)*
Behavioral/emotional disorders (except ADHD)	698	10.5	28 941	2.6	3.6 (3.2–3.9)*
Unspecified developmental delay	494	7.5	11 834	1.1	8.2 (7.3–9.3)*
Anxiety	99	1.5	5463	0.5	2.3 (1.8–3.0)*
Depression	72	1.1	4873	0.4	1.8 (1.4–2.5)*

Aaberg KM, Pediatrics 2016

High Incidence of Comorbidities in CWE: Preceding Medication Initiation

- Large database of commercial claims between 2009-2013 in the US looking at diagnosis codes for newly-diagnosed cases of epilepsy
- 7,654 children had newly diagnosed epilepsy out of a total of 6,107,678 children
- "neurobehavioral comorbidities were significantly more prevalent in children with newly diagnosed epilepsy, **2.5 times the rate of children without epilepsy**" - prior to starting anti-seizure medications



Oh A, Epilepsy & Behavior 2017

High Incidence of Comorbidities in CWE: Preceding Medication Initiation

- Single-center retrospective chart review of 380 youths with epilepsy with completed Behavior Assessment System for Children – Parent Rating Scale (BASC-2:PRS) and Pediatric Epilepsy Side Effect Questionnaire (PESQ)
- Overall baseline elevated symptoms prior to ASM imitation
- Younger age and baseline hyperactivity were associated with increased levels of ASM behavioral side effects
  - Independent of ASM

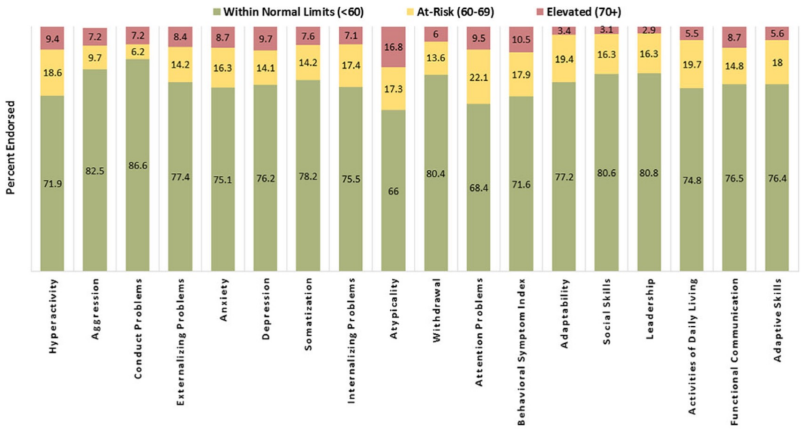


FIGURE 1 Baseline psychological functioning at-risk and clinical elevations (N = 380)

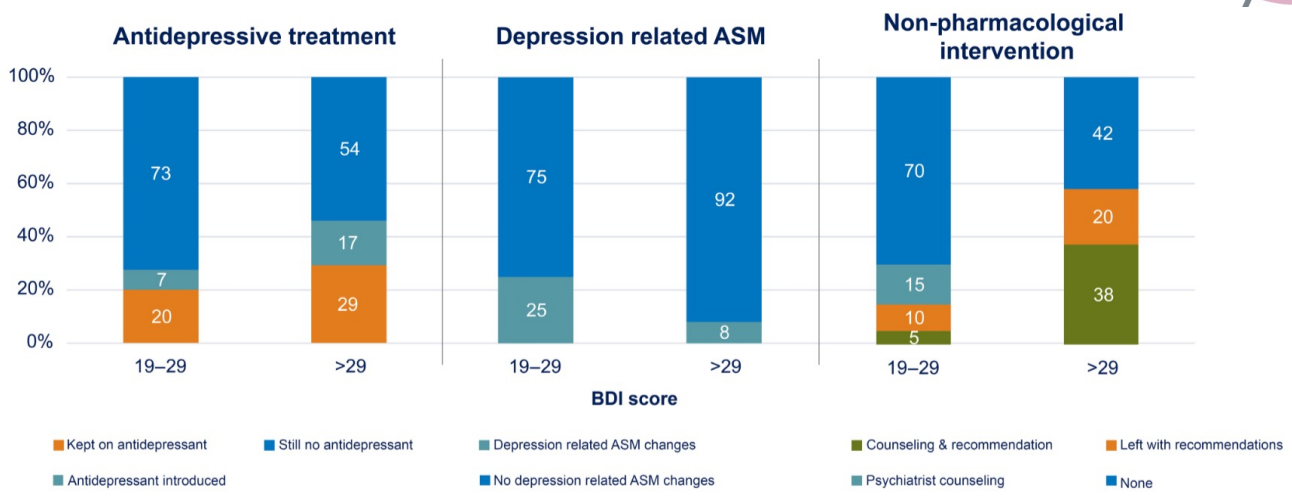
Guilfoyle SM, Epilepsia 2017

Screening is Key!

- Meta-analysis of 27 studies looking at anxiety and depression in people with epilepsy found:
  - A pooled prevalence of anxiety and depression was at 20.2% and 22.9%, respectively
  - Unstructured clinical assessment **yielded 8.1% versus prevalence of 27.3%** compared in a structured clinical interview for **diagnosis of anxiety**
  - Epilepsy duration, polypharmacy of ASM and presence of medication-resistant epilepsy **did not have bearing on the** diagnosis rates of anxiety and depression

Scott AJ, Epilepsia 2017

Important to Not Only Screen But Follow Up!

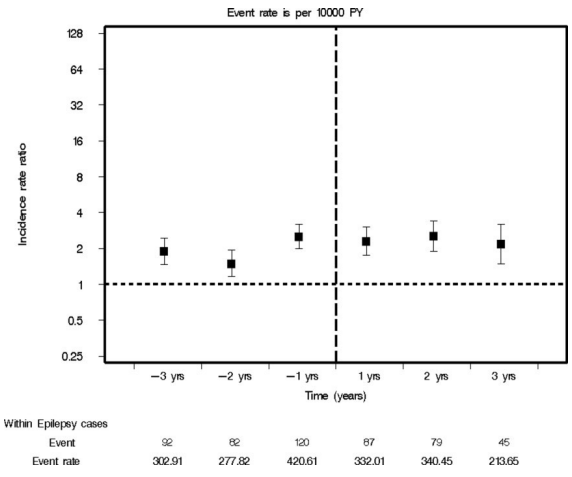


BDI - Beck Depression Index
Moderate Depression score 19-20 Severe Depression score >29

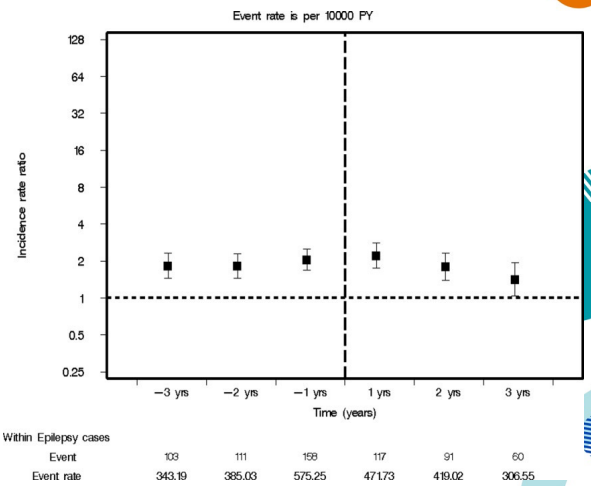
von Wrede R, Epilepsia 2024

Bi-directionality of Epilepsy and Psychiatric Disorders

Depression



Anxiety



Hesdorffer DC, Annals of Neurology 2012

Social Context Matters - Adverse Childhood Experiences

Five of the nine ACE exposures were associated with an increased risk of epilepsy diagnosis – **even when ADHD, mental health diagnosis, behavioral/emotional difficulties were considered**

- Food and housing insecurity
- Domestic violence
- Community violence
- Incarcerated household member
- Household member with mental illness

Table 5 Association of Current Epilepsy or Seizure Disorder Diagnosis With Current ADD/ADHD; Taking Medication for ADD/ADHD, Autism/ASD or Other Emotional/Behavioral Difficulties; and Mental, Emotional, Developmental, or Behavioral Problems

Demographic variable	Odds ratio [95% CI]	*p* Value
Current ADD/ADHD	3.07 [2.39, 3.94]	<0.001
Taking medication for ADD/ADHD, autism/ASD, or other emotional/behavioral difficulties	3.32 [2.60, 4.24]	<0.001
Mental, emotional, developmental, or behavioral problems	9.22 [7.22, 11.77]	<0.001

Table 6 Association of Current Epilepsy or Seizure Disorder Diagnosis With Cumulative ACE Score When Controlling for These[a] (n = 59,963)

Demographic variable	Odds ratio [95% CI]	*p* Value
Cumulative ACE score when controlling for		
Current ADD/ADHD	1.14 [1.07, 1.22]	<0.001
Taking medication for ADD/ADHD, autism/ASD, or other emotional/behavioral difficulties	1.14 [1.07, 1.21]	<0.001
Mental, emotional, developmental, or behavioral problems	1.14 [1.06, 1.21]	<0.001

[a] Adjusted for age by year, race, income level, insurance status, and sex.

Anto M, Neurology Clinical Practice 2023

Hypothesized Behavior Mechanism in Neurodevelopmental Disorders

- Up to 40% of children with autism spectrum disorder have aggressive or self-injurious behavior
- Proposed mechanisms:
  - Operant conditioning: Antecedent > Behavior > Consequence(s)
  - Provoking factor: Setting event > Antecedent > Behavior > Consequence
  - Interoception: Dysregulated processing of sensations such as pain/discomfort, hunger, thirst

Setting Event		Antecedent		Behavior		Consequence
Stomach Pain	>	Math task	>	Aggression	>	Escapes working on task

Setting Event		Interoceptive Responsivity		Antecedent		Behavior		Consequence
Stomach pain	>	High	>	Math task	>	Aggression	>	Escapes working on math task
Stomach pain	>	Low	>	Math task	>	No aggression	>	Works on math task
Stomach pain	>	Unable to locate pain	>	Math task	>	Aggression	>	Escapes working on math task
Stomach pain	>	Not impaired	>	Math task	>	No aggression	>	Works on math task

Edelson SM, Journal of Personalized Medicine 2022

Common Co-morbid Conditions – Identify to Treat!

Medical	Neurological	Developmental/psychiatric
Gastrointestinal disorders	Cerebral palsy	Autism spectrum disorder
Nutritional and bone health	Headache and migraines	Intellectual disability
Hearing and vision impairment	Neuropathic pain	ADHD
Sleep		Anxiety
Metabolic disorders		Depression
Infectious causes		Sensory processing disorders
Dental		

Aaberg KM, Pediatrics 2016 | Oh A, Epilepsy & Behavior 2017

Migraines are Common in CWE

- Peri or post-ictal phenomenon in seizures
- Seen in up to ¼ of children with epilepsy
  - "Only 50% of patients with weekly or greater migraines had documented discussions regarding headaches with their neurologist" (Kelley et al, Neurology 2012)
- Risk factors – older age (>10 years), certain epilepsy types
- Not more common in those with intractable epilepsy
- More common after epilepsy diagnosis

Kelley SA, Neurology 2012 | Oakley CB, Current Pain and Headache Reports 2014

Bi-directional Impact Between Sleep and Epilepsy

- Sleep apnea, periodic limb movement disorder, and other sleep disorders are more common in people with epilepsy
- Poor quality or insufficient quantity sleep can increase seizures, impact mood and behavior, daytime fatigue, cognition and significantly impact quality of life
- Interictal EEG and its role on sleep
- Certain epilepsy syndromes are characterized by seizures arising from sleep
- Addressing sleep is key for both epilepsy and sleep optimization
- Consider sleep medicine referral early in epilepsy course

https://epilepsysociety.org.uk/sites/default/files/2020-08/Chapter18Eriksson2015_0.pdf

Anti-seizure Medications Can Impact Sleep

Table 1. Effect of antiepileptic drugs on sleep.

	Effect on sleep						Effects on sleep disorders	
	Sleep efficiency	Sleep latency	Stage I	Stage II	Stage III	REM	Improves/ treats	Worsens
Phenobarbitone	↑	↓	-	↑	0	↓	Sleep onset insomnia	OSA
Phenytoin	0	↓	↑	↑	↓	0 or ↓	None known	None known
Carbamazepine	0	0	0	0	0	0	RLS	RLS
Valproate	-	0	↑	↓	0	0	None known	OSA*
Ethosuximide	-	-	↑	-	↓	-	None known	None known
Gabapentin	0	0	0	0	↑	↑	RLS	OSA*
Lamotrigine	0	0†	0	↑	↓	↑	None known	None known
Topiramate	0	↓	0	0	0	0	OSA*	None known
Tiagabine	-	-	-	-	↑	-	Insomnia	None known
Levetiracetam	-	-	-	-	↑	-	None known	None known
Pregabalin	↑	-	-	-	↑	-	None known	OSA*

0, no change; -, not reported; ↑, increase; ↓, reduction; OSA, obstructive sleep apnoea; REM, rapid eye movement; RLS, restless leg syndrome

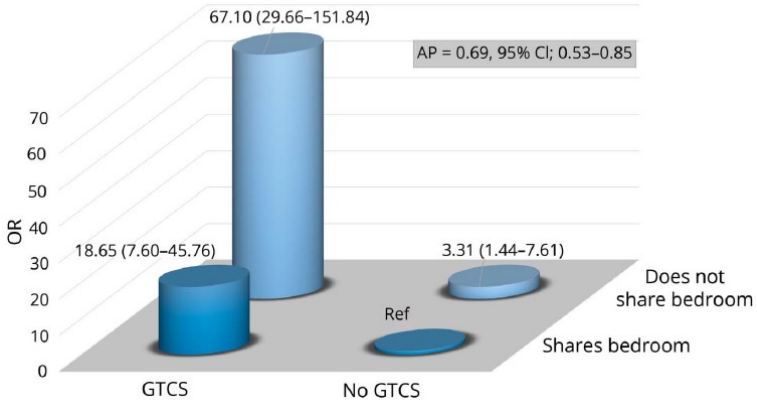
*Due to change in weight

†Lamotrigine may be associated with insomnia (clinical observation but rarely reported in the literature)

https://epilepsysociety.org.uk/sites/default/files/2020-08/Chapter18Eriksson2015_0.pdf

Sudden Unexpected Death in Epilepsy Patients (SUDEP)

- Motor convulsive seizures arising from sleep are the most significant risk factor for SUDEP – with OR of 67 if sleeping alone



Sveinnson O, Neurology 2020

Epilepsy and its Role in Behavioral and Mood Changes

- Type of epilepsy matters!
  - Etiology of epilepsy
    - Structural | Genetic | Metabolic | Auto-immune
  - Epilepsy syndromes
    - Developmental and epileptic encephalopathies | Self-limited epilepsies | Variable age
  - Focal epilepsies - Temporal lobe epilepsy can have peri-ictal psychosis and interictal psychosis
- Early referral to epilepsy surgery or consideration of ketogenic/modified Atkins diet after 2 or more ASM are not efficacious

Scheffer IE, Epilepsia 2018

Epilepsy Syndromes and Associated Cognitive and Psychiatric Impairments

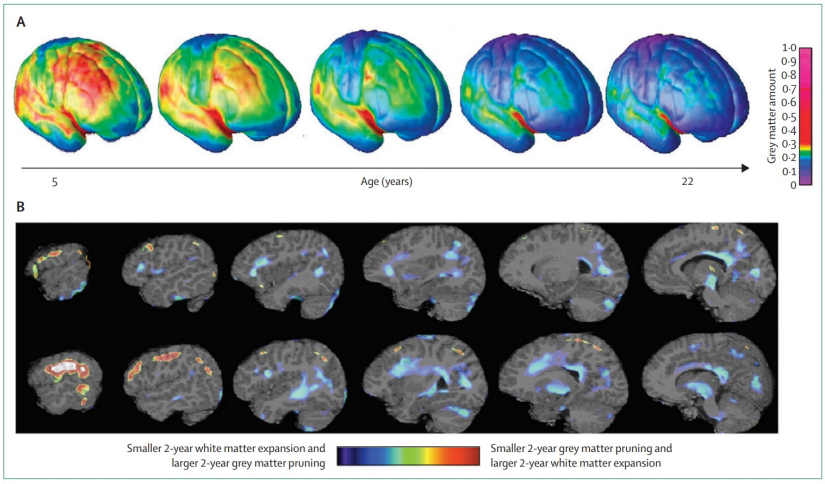
	Core pathophysiology	Core cognitive deficit	Core psychiatric deficit
Temporal lobe epilepsy	Hippocampus and mesial temporal lobe	Anterograde memory	Depression and anxiety
Frontal lobe epilepsy	Frontal lobe	Executive functions	Personality disorders
Benign epilepsy with centrotemporal spikes	Sylvian and Rolandic regions	Language abilities	Unknown
Absence epilepsy	Thalamocortical network	Attention	Unknown
Juvenile myoclonic epilepsy	Frontothalamic network	Executive functions	Personality disorders

Table 3: **Epilepsy syndromes and anticipated cognitive and psychiatric complications**

Lin JJ, Lancet 2012

Proposed Pathophysiology of Mood/Behavior and Epilepsy

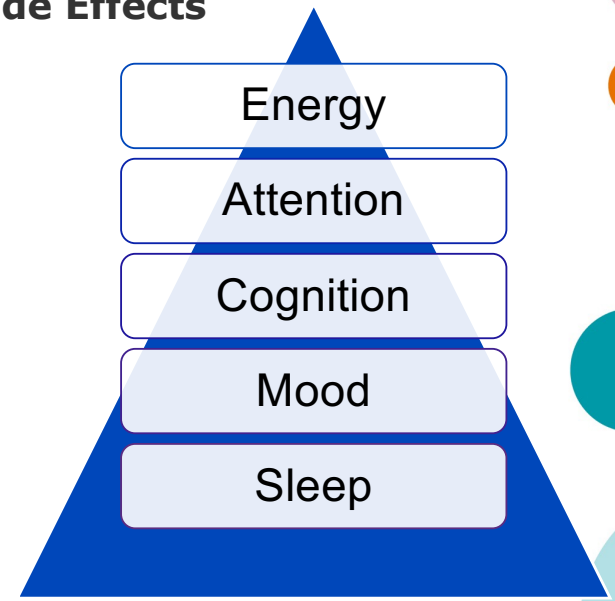
- Synaptic development
- Limbic system
- Neurotransmitters
- Interictal/ictal epileptic network
- GABA receptors
- ASM impact
- Pathophysiology may be different in those without epilepsy compared to those with epilepsy but research is lacking



Lin JJ, Lancet 2012

Anti-Seizure Medication Side Effects

- 1/6-1/7 develop side effects
- Medication and mechanism-specific – GABAergic
- Individuals with underlying psychiatric disorders may be at more risk
- Distinguishing between medication side effects, underlying neurodevelopment features, and behavior can be challenging!



Chen B, Epilepsy & Behavior 2017 | Glauser T, Epilepsia 2006 | Weintraub D, Epilepsy & Behavior 2007

Drug	Psychiatric side effects
Barbiturates (primidone and phenobarbital)	Depression In children and individuals with intellectual disabilities: hyperactivity, irritability, aggression
Benzodiazepines	In children, older adults, and individuals with intellectual disabilities: hyperactivity, irritability, aggression
Brivaracetam	Aggressive behavior, depression, psychosis, but better tolerated than levetiracetam
Carbamazepine	Not reported
Eslicarbazepine	Not reported
Ethosuximide	Psychosis
Felbamate	Anxiety, psychosis
Gabapentin	In children and individuals with intellectual disabilities: hyperactivity, aggression, irritability
Lacosamide	Not reported
Lamotrigine	In individuals with intellectual disabilities: hyperactivity, irritability, aggression
Levetiracetam	Irritability, aggression, anxiety, depression, psychosis
Oxcarbazepine	Not reported
Phenytoin	Psychosis (particularly at high serum levels)
Pregabalin	Depression
Rufinamide	Not reported
Stiripentol	Hyperactivity, irritability, aggression
Tiagabine	Irritability
Topiramate	Depression, psychosis, irritability
Valproate	Not reported
Vigabatrin	Psychosis, depression In children and individuals with intellectual disabilities: hyperactivity, aggression, agitation
Zonisamide	Psychosis, depression, irritability

Mula M, Continuum 2022

A Holistic and Comprehensive Approach to a CWE is Key in Working with Behavioral and Mood Changes

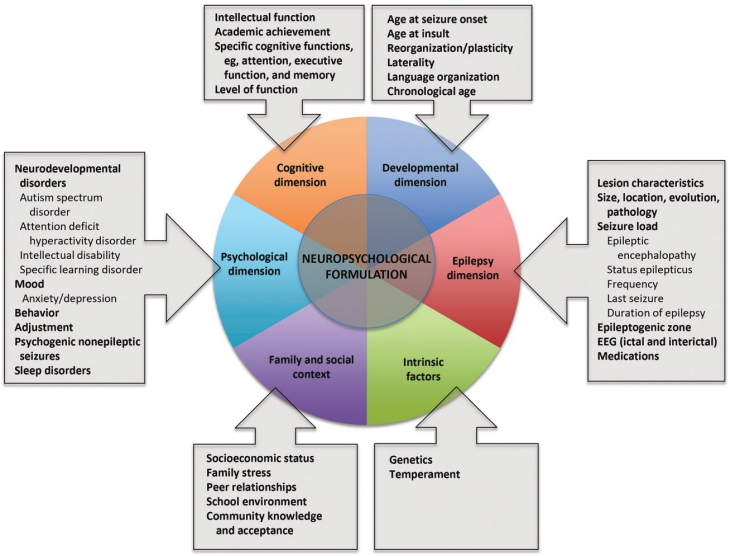


FIGURE 8-1
An overview of the process of neuropsychological formulation, taking into consideration not only neurophysiologic factors (epilepsy dimension) but also developmental, intrinsic, cognitive, psychological, and social factors.
EEG = electroencephalogram.

Mula M, Continuum 2022

Received: 19 March 2021 | Revised: 16 November 2021 | Accepted: 19 November 2021
DOI: 10.1111/epi.17140

Epilepsia

SPECIAL REPORT

Consensus-Based Standards for the Diagnosis and Treatment of Anxiety and Depression in Children and Adolescents with Epilepsy: A Report from the Psychiatric Pediatric Issues Task Force of the International League Against Epilepsy

[1,2,3]Kette D Valente
[4,5,6]Colin Reilly
[1,3]Rachel M Carvalho
[7,8]Mary Lou Smith
[9]Marco Mula
[10]Elaine C Wirrell
[11]Jo M Wilmshurst
[12]Nathalie Jetté
[13]Francesco Brigo
[14,15,16]Symon Kariuki
[17]Choong Yi Fong
[3]Wang Pang
[3]Guilherme Polanczky
[18]Viviane Castanho
[19]Izabel G. Demarchi
[20,21,22]Stéphane Auvin
[23]Mike Kerr

Stephane Auvin and Mike Kerr are co-senior authors of this manuscript.

ILAE clinical practic
treatment of depress

Marco Mula[1] | Martin J Bre
Hrvoje Hecimovic[5,6] | Kousul

Received: 6 June 2018 | Revised: 28 July 2018 | Accepted: 3
DOI: 10.1111/epi.14549

SPECIAL REPORT

Systematic review of the
of ADHD in children with
Task Force on Comorbid

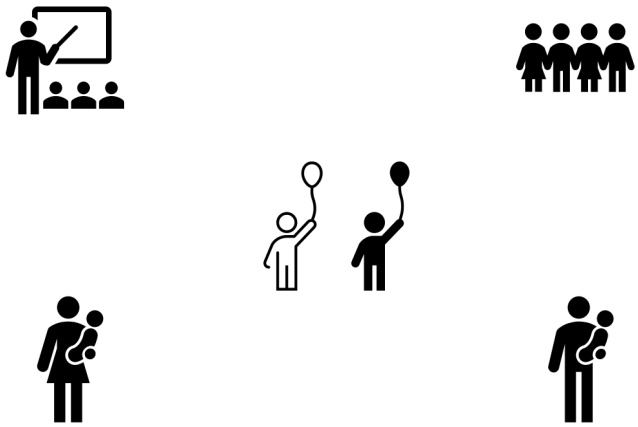
Stéphane Auvin[1] | Elaine Wirrell[2] |
Hans Hartmann[5] | Kette D. Valente[6] |
Makiko Osawa[9] | Hideaki Kanemura[10]
Pauline Samia[13] | Kollencheri Puthenv
Michael Kerr[17] | Bruce Hermann[18] |

Mula M, Epilepsia 2022 | Auvin S, Epilepsia 2018 | Valente, Draft Epilepsia

Structured Tools for Assessing Disruptive Behaviors

1. Aberrant Behavior Checklist (ABC):	2. Child Behavior Checklist (CBCL):	3. Conners Rating Scale for ADHD:	4. Vineland Adaptive Behavior Scales:
Measures irritability, lethargy, stereotypic behavior.	Comprehensive assessment of behavioral and emotional problems in children.	Evaluates ADHD symptoms and related behaviors.	Assesses personal and social skills needed for everyday living.

Assessing for Behavioral and Mood Changes



Management Strategies

- Obtain baseline cognition, behavior and habits
- Use formal screening tools for accurate and timely diagnosis and for surveillance over time
- Identify externalizing and internalizing behaviors and associated triggers
- Identify and treat any reversible medical causes of behavioral worsening such as presence of migraines or difficulties with sleep
- Identify the epilepsy syndrome and/or the etiology for the epilepsy which may have associated behavioral or cognitive differences
- Behavioral therapy, cognitive-behavioral therapy (CBT), and family counseling (parent-child interactive therapy) can be very helpful for managing behavior

Take Away Messages

- Behavioral and psychiatric co-morbidities are common!
- Use a multi-disciplinary approach to screen and appropriately diagnose behavioral and dysregulated emotions are key
  - Treat any co-morbid conditions found that can exacerbate behaviors and seizures
- Behavioral interventions and supportive therapies can help manage comorbidities
- Medications for behaviors should be considered only if necessary

References

- Aaberg KM, Bakken IJ, Lossius MI, et al. Comorbidity and childhood epilepsy: a nationwide registry study. Pediatrics 2016. 138(3):e20160921.
- Anto M, Shipley SC, Massey S, Szperka C. Adverse childhood experiences are associated with seizures in children. Neurology Clinical Practice 2023. 13(2): e200136.
- Austin J, Harezlak J, Dunn D, et al. Behavior problems in children before first recognized seizures. Pediatrics 2001. 107: 115–22.
- Berg AT, Altalib HH, Devinsky O. Psychiatric and behavioral comorbidities in epilepsy: a critical reappraisal. *Epilepsia* 2017. 58(7):1123-1130.
- Chen B, Choi H, Hirsch LJ et al. Psychiatric and behavioral side effects of antiepileptic drugs in adults with epilepsy. Epilepsy Behavior 2017. 27:24-31.
- Dunn DW, Austin JK. Behavioral issues in pediatric epilepsy. Neurology. 1999.53:S96-100.
- Dunn D, Austin J, Huster G. Behaviour problems in children with new onset epilepsy. Seizure 1997. 6: 283–7.
- Edelson SM. Understanding challenging behaviors in autism spectrum disorder: a multi-component, interdisciplinary model. Journal of Personalized Medicine 2022: 12(7).1127.
- https://epilepsysociety.org.uk/sites/default/files/2020-08/Chapter18Eriksson2015_0.pdf
- Guilfoyle SM, Follansbee-Junger KF, Smith AW. Antiepileptic drug behavioral side effects and baseline hyperactivity in children and adolescents with new onset epilepsy. Epilepsia 2017. 59(1): 145-154.
- Hesdorffer DC, Ishihara L, Mynepalli L et al. Epilepsy, suicidality, and psychiatric disorders: A bidirectional association. Annals of Neurology 2012. 72(2):184-91.
- Kelley SA, Hartman AL, Kossoff EH. Comorbidity of migraine in children presenting with epilepsy to a tertiary care center. Neurology 2012.79(5):468-73.
- Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. Lancet 2012. 380. 1180-1192.
- Mula M, Coleman H, Wilson SJ. Neuropsychiatric and cognitive comorbidities in epilepsy. Continuum 2022. 28(2):457-482.
- Oakley CB, Kossof EH. Migraine and epilepsy in the pediatric population. Current Pain and Headache Reports 2014.18(3):402.
- Oh A, Thurman DJ, Kim H. Comorbidities and risk factors associated with newly diagnosed epilepsy in the U.S. pediatric population. Epilepsy & Behavior 2017. 75:230-236.
- Ott D, Siddarth P, Gurbani S et al. Behavioral disorders in pediatric epilepsy: unmet psychiatric need. Epilepsia 2003. 44(4):591-7.
- Oyegbile-Chidi T, Harvey D, Eisner J et al. The relationship between sleep, cognition, and behavior in children with newly diagnosed epilepsy over 36 months. Frontiers in Neurology 2022.13:903137.
- Reilly C, Atkinson P, Das KB, et al. Neurobehavioral comorbidities in children with active epilepsy: a population-based study. Pediatrics 2014. 133(6):e1586-93.
- Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies position paper of the ILAE commission for classification and terminology. Epilepsia 2018. 58(4):512-521.
- Scott AJ, Sharpe L, Hunt C, Gandy M. Anxiety and depressive disorders in people with epilepsy: a meta-analysis. Epilepsia 2017. 58(6):973-982.
- Sveinnson O, Andersson T, Mattsson P et al. Clinical risk factors in SUDEP: A nationwide population-based case-control study. Neurology 2020;94:e419-e429.
- von Wrede R, Witt JA, Jessen N et al. Screening for depression in patients with epilepsy: What are the benefits for physicians and patients in the real-life setting. Epilepsia 2024. 00:1-7.
- Watkins LV, Pickrell WO, Kerr MP. Treatment of psychiatric comorbidities in patients with epilepsy and intellectual disabilities: Is there a role for the neurologist? Epilepsy & Behavior 2019. 98:322-327.