AES 2024 ANNUAL MEETING

Behavior Treatment Options: Pharmacologic Approaches

Jay Salpekar, MD, FAES, FANPA, DFAACAP
Director of Neuropsychiatry
Kennedy Krieger Institute
Associate Professor of Psychiatry and Neurology
Johns Hopkins University

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AES AMERICAN EPILEPSY SOCIETY

Child Neurology FOUNDATION
Creating a Community of Support

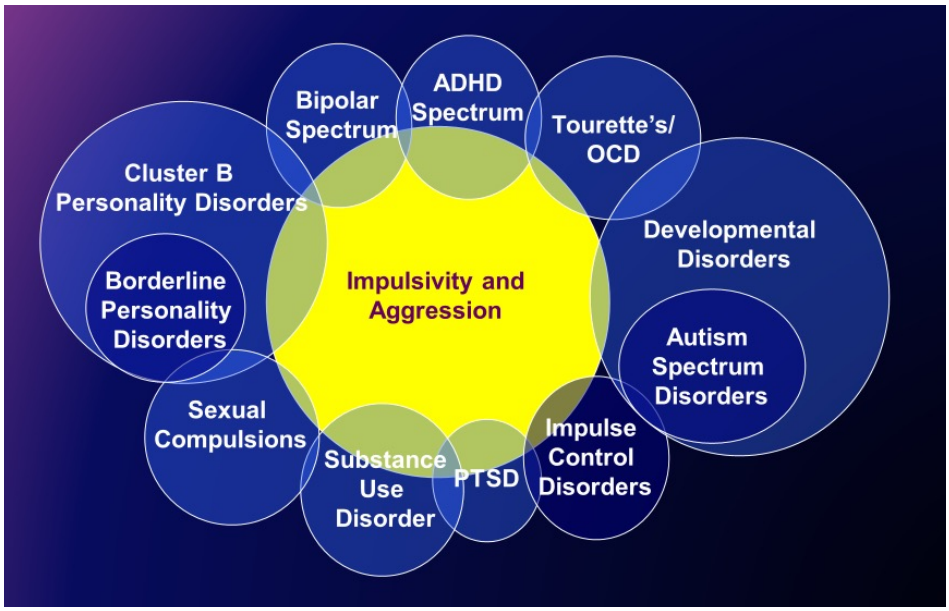
Disclosure

- Jazz Pharmaceuticals: Research funding to institution only
- No marketing or speakers' bureau activities

Learning Objectives

1. Describe a practical way to determine if medications are necessary for psychiatric symptoms associated with epilepsy
2. Identify medications options that may be directed to specific symptoms
3. Name specific steps in antidepressant and antipsychotic treatment plans

Impulsive-Aggressive Spectrum



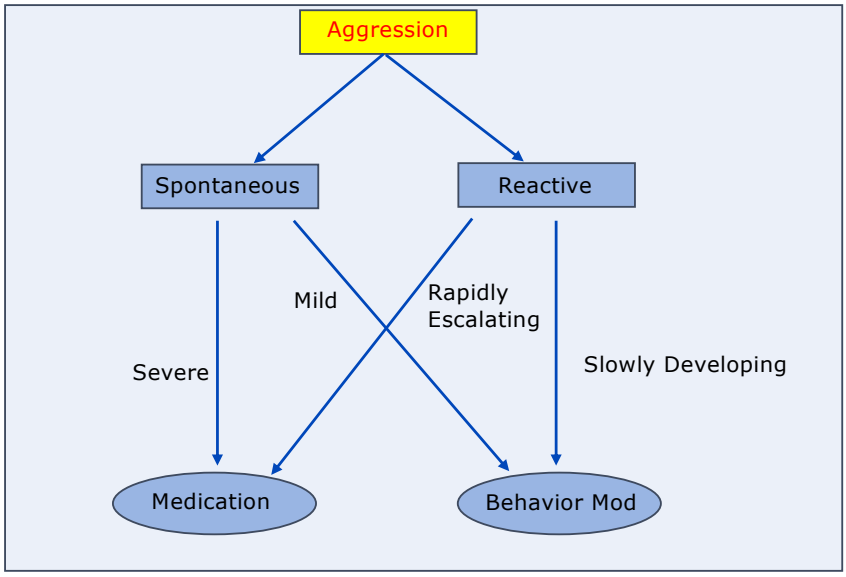
Salpekar J. "Psychiatric Comorbidities of Childhood Epilepsy"; In Pellock's Pediatric Epilepsy 4th ed., eds. J Pellock, DR Nordli, R Sankar, JW Wheless. DemosMedical, pp. 1163-1177, 2017.

Behavioral Dimensions

- Aggression
- Explosive mood
- Irritability
- Impulsivity
- Sleep disruption
- Inattention
- Hyperactivity
- Perseveration/compulsion

https://www.dreamstime.com/illustration/psychomotor.html

Rx Decision Making



Salpekar J. "Recognizing and Treating Psychiatric Comorbidity in Epilepsy", In *Epilepsy: Neurology in Practice*, eds. H. Goodkin, J. Miller, John Wiley & Sons, Ltd., pp 268-274, 2014.

Anti-seizure Medicines are Neuropsychiatric Medicines

- In addition to seizures, treatment targets include impulsivity, rage outbursts, mood lability
- As for epilepsy, low doses of adjunctive ASMs may improve symptoms
- Seizure control and behavior control may go hand in hand
- Some ASMs may have a dual role
  - Retrospective review of 38 pediatric epilepsy cases (30 CPS, 8 PGE) with bipolar spectrum disorder improved for both disorders with carbamazepine, divalproex sodium, lamotrigine, or oxcarbazepine monotherapy
- Treatment of anxiety and epilepsy with clobazam
- Cannabidiol

Salpekar JA, et al. Epilepsy Behav 2006;9(2):327-34

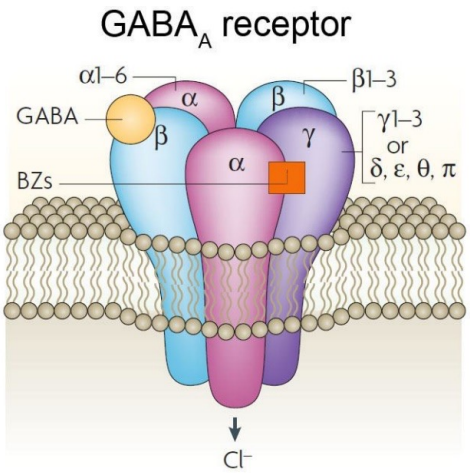
Anxiolytic Versus Hypnotic

- 1, 5-Benzodiazepines
  - bicyclic compounds
    - two N atoms at 1 and 5 positions in a 7-membered ring fused to benzene.
  - some 1,5 compounds have antiviral or anti-inflammatory effects
- Hydroxylated metabolites of diazepam (temazepam and oxazepam) are more hypnotic than anxiolytic, perhaps similar to 1,5 benzodiazepines

(Sankar R. 2012)

GABA

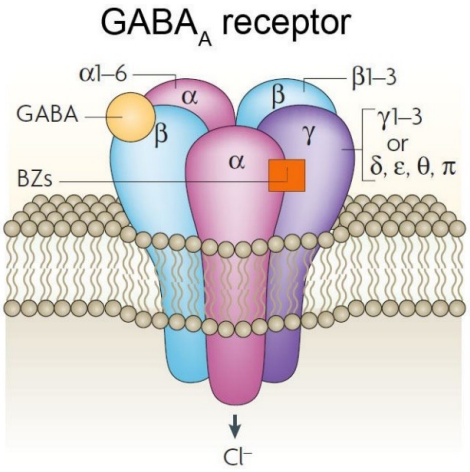
- GABA is everywhere, can't map it like noradrenergic or serotonergic receptors
- GABA –A receptors
  - Inhibitory — opens Chloride channel
  - Most GABA receptors involve five subunits
    - 2 alpha
    - 2 Beta
    - 1 gamma



Jacob et al., Nature Reviews Neuroscience, 2008

GABA

- Alpha 1 - Sedation, Ataxia
  - Target of Zolpidem
- Alpha 2 - Anxiolytic
- Alpha 3 - Anti-seizure
- Alpha 5 - Cognitive effects
  - Mice without Alpha 5 subunits learn mazes better

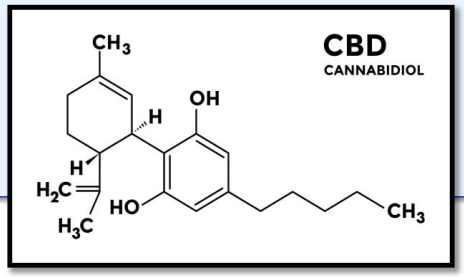


Jacob et al., Nature Reviews Neuroscience, 2008

Sankar R. GABA(A) receptor physiology and its relationship to the mechanism of action of the 1,5-benzodiazepine clobazam. CNS drugs. Mar 1 2012;26(3):229-44.

Cannabidiol (CBD)

- Suspected Mechanisms of Action:
  - G protein mediated inhibition of the enzyme FAAH (fatty acid amide hydrolase), which breaks down anandamide, increasing its availability.
  - Negative Allosteric Modulator: reportedly decreases CB1 and CB2 responsiveness to THC effects.
  - Serotonin 5HT1A Receptors: full agonist, relevant for neuropsychiatric disorders.
- Modulation of serotonin, GABA, and calcium channels may contribute to resultant calming effects.
  - *Navarro D et al. 2022. International journal of molecular sciences, 23(9), 4764.*
  - *Sagar, KA & Gruber, S (2018). International Review of Psychiatry. 1-17.*



Therapeutic Uses of CBD in Epilepsy

- 7/8 improved compared to 1/8 placebo (Cunha et al. 1980)
- Artisanal CBD—(Charlotte's Web®) offshoot of lay public effort to use CBD for refractory epilepsy
- "Pharma grade" CBD—(Epidiolex®)
  - USFDA Indication for treatment of seizures associated with Lennox-Gastaut Syndrome, Dravet's Syndrome, Tuberous sclerosis
    - Abu-Sawwa R, Stehling C, J Pediatr Pharmacol Ther. 2020 Jan-Feb; 25(1): 75–77
  - DBRCT for LGS, 20mg/kg/day, reduced seizures: 44% versus 22%
    - Thiele E et al. Lancet 2018;391:1085-96.
  - DBRCT for LGS, 20mg/kg/day: 42% seizure reduction; 20mg/kg/day: 37%; placebo: 17.2%
    - Devinsky O et al. N Engl J Med 2018;378:1888-97.
- Current clinical trial of Epidiolex® for anxiety in pediatric epilepsy

Drug Class and Theorized Mechanism	Medication	Possible Psychotropic Benefit	Possible Psychotropic Detriment
GABAergic drugs (enhancing inhibitory networks)			Increased Sedation: Fatigue, Depression, Weight Gain, Anti-manic
	Benzodiazepines	Anti-anxiety	Sedation
	Gabapentin	Anti-anxiety, Improves Social Phobia, Chronic Pain	
	Phenobarbital		Depression
	Pregabalin	May be Anti-anxiety	Some Reports of Depression
	Tiagabine		Mood Lability
	Vigabatrin		Hyperactivity
	Clobazam	Improve social anxiety	Confusion, mood lability

Salpekar; Focus 2016; 14:465–472; doi: 10.1176/appi.focus.20160017

ASMs May Cause Agitation

- Any ASM may lead to agitation or irritability, particularly if it causes mild/moderate sedation
  - Levetiracetam associated with irritability
  - Agitation reactions may be associated with perampanel
  - Confusion/agitation may be associated with clobazam, benzodiazepines

Salpekar JA, Mishra G, *Epilepsy & Behavior* 37 (2014), 310-315. Jones JE et al. Pediatr Rev 2008;29:e9-14. Mula M 2008

Drug Class and Theorized Mechanism	Medication	Possible Psychotropic Benefit	Possible Psychotropic Detriment
Anti-glutamatergic drugs (reducing action of excitatory networks)			Associated with increased activation: insomnia, agitation, anxiety, racing thoughts, antidepressant
	Felbamate		possible insomnia
	Lamotrigine	Mood stabilizer, moderate antidepressant effect	May be activating
Mixed, Multiple, or Unknown Mechanisms	Carbamazepine	Mood stabilizer, improves impulsivity and aggression	
	Eslicarbazepine	Mood stabilizer	
	Ethosuximide		Confusion
	Lacosamide	Mood stabilizer	
	Levetiracetam	Improve mood in some cases	Irritability, may be more common in pediatrics

Salpekar; Focus 2016; 14:465–472; doi: 10.1176/appi.focus.20160017

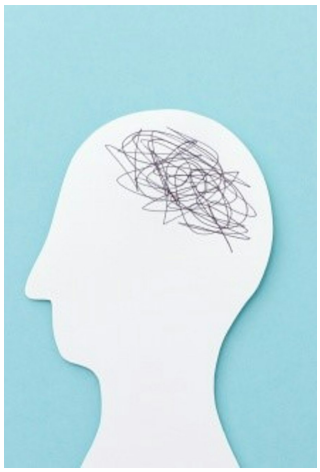
Drug Class and Theorized Mechanism	Medication	Possible Psychotropic Benefit	Possible Psychotropic Detriment
Mixed, Multiple, or Unknown Mechanisms	Oxcarbazepine	Mood stabilizer	
	Rufinamide		Agitation, Depression
	Valproate	Mood stabilizer, improves impulsivity and aggression	May cause irritability especially in context of sedation
	Topiramate	Improve impulsivity	Word finding difficulties, cognitive slowing
	Zonisamide	Improve mood in some cases	Some cases of psychosis, activation

Salpekar; Focus 2016; 14:465–472; doi: 10.1176/appi.focus.20160017

ASMs May Cause Mood or Anxiety Problems

- High risk: phenobarbital, may not remit spontaneously
- Mild-moderate risk: topiramate, felbamate
- Withdrawal of benzodiazepines may cause depression, anxiety, or disinhibition

Mula M, Sander JW, "Mood" in Behavioral Aspects of Epilepsy, eds. Schachter SC, Holmes GL, Trenite D, 2008.



Clinical Presentation

- Somatic complaints—headaches, GI
- Irritability—in pediatrics, may be equivalent to dysphoria seen in adults
- Externalizing or disruptive behavior may be present, especially in younger, anxious patients
- Sleep—disruption may increase anxiety or irritability
- Substance abuse—in adolescents, "self-medicating"
- Apathy
- Social isolation

Medications for Pediatric Mood Disorders

- FDA indications:
  - **Major Depression**
    - Fluoxetine
  - **Obsessive-Compulsive Disorder**
    - Fluoxetine
    - Sertraline
    - Fluvoxamine
- Evidence even from well-designed research studies *may not* correlate with clinical practice

Fluoxetine

- Prozac, Sarafem (brand names)
  - May be the most robust in terms of widespread response
  - **START LOW!**
    - 10mg may be an adult dose, so start with 5mg (half a tablet) in pediatrics and be patient
  - Long half life, including for the active metabolite
  - Stingy metabolism—CYP2D6 inhibitor (may increase VPA)
  - **Energizing, activating**
  - Nausea (better with food), anxiety/activation, sleep issues
  - Monitor often and increase only if necessary
  - Full response in 3-8 weeks

Citalopram

- May be the mildest
- Sedating, so often helps with initial insomnia
- Start with 10mg QHS
- QTc issue, but may be theoretical
- Short half life, no active metabolites, minimal interactions
- Nausea (better with food)
- Monitor often and increase only if necessary.
- Full response in 2-5 weeks
- (Escitalopram = single isomer product)

For Any Antidepressant Medication

- Side effects emerge in the first 1-2 weeks.
  - Nausea is common with SSRIs
    - Better with food
- Antidepressant "improved mood" effects do not begin until 2-4 weeks.
- The risk for suicide continues to be high in the first weeks of treatment, as the energy level increases but the therapeutic effects for mood have not yet begun.

For Any Antidepressant Medication

- Follow-up early and often.
  - During the initial treatment phase, weekly visits are appropriate. Quarterly visits are not.
- Make safety agreements with patients, contingency plans with caregivers.
- Monitor suicidality at every contact.
- If patients become activated, agitated, or restless, consider discontinuing the medication.

Antipsychotics — May Also Be Mood Stabilizers

- **Risperidone and Aripiprazole** (FDA-approved in pediatrics for irritability associated with autism spectrum disorder)
- **Risperidone:** Similar to typical high potency antipsychotics like haloperidol
- **Aripiprazole:** Agonist-antagonist mechanism, originally reported to be weight neutral

- Class side effects:
  - Metabolic syndrome (dyslipidemia, pre-diabetes)
  - Sedation
  - Dystonia
  - Hormone dysfunction (prolactin)

Risperidone

- Ok to start low, 0.25mg BID. In older patients, once daily dosing possible.
- Increase as tolerated by 0.5mg-1mg every 1-3 days
- EKG
- Labs: lipid, HbA1C, CMP, CBC, prolactin
- Weight gain:
  - Consider metformin if there is any weight gain
- M tabs as a PRN

Aripiprazole

- Ok to start low, 2mg BID, or once daily dosing
- Increase as tolerated by 2mg-5mg every 1-3 days
- Labs: Lipid, HbA1C, CMP, CBC
- Activation may be more of a problem given dopamine agonist mechanism
- May have slight benefit for inattention in those with ADHD-like symptoms

Impact on Clinical Care

- Spontaneous versus reactive distinctions may help determine need for medications and also role of ASMs
- Close monitoring is necessary for antidepressants, but by and large they are very well tolerated
- Risperidone and aripiprazole are reasonable options, but monitoring metabolic status is essential
- Treating co-occurring psychiatric symptoms may markedly improve quality of life