EPILEPSY CASE: EVIDENCE BASED MEDICINE

By: Ashley Stafford

Assess	
Directions: ● Identify the patient's therapeutic goals ● Assess the patient-related factors and medication-related factors that might affect your decision to recommend medical cannabis as a treatment option	
Question 1: (1 point) What are the patient's therapeutic goals? You must at least identify the **MAIN** patient problem. The therapeutic goal should be measurable.	The main patient problem for JB is his uncontrolled seizures, including atonic/drop seizures and tonic seizures, despite being on antiepileptic medications and a ketogenic diet. Therapeutic goal: To reduce the frequency of atonic/drop seizures and tonic seizures by at least 50% within the next six months, as measured by seizure diaries maintained by JB's caregivers.
Question 2: (10 points) Identify at least **two patient-related factors** AND **two medication-related factors** that might affect your decision to recommend medical cannabis for this patient. Why are each of these factors important to consider for this patient?	Patient-related factors: 1. Developmental delay: JB's developmental delay may affect his ability to adhere to treatment regimens. It's important to consider how his developmental delay might influence his participation in therapy and accurate reporting of treatment effects. 2. History of hypoxic-ischemic injury: JB's history of hypoxic-ischemic injury may make him more susceptible to certain medications or therapies. Understanding his brain injury history is important when assessing the potential risks and benefits of medical cannabis, as it may impact his response to treatment and ability to tolerate side effects. Medication-related factors:

	1. Current medications (topiramate): JB is currently taking topiramate, an antiepileptic medication. It's essential to consider potential drug interactions between medical cannabis and topiramate. Certain cannabinoids, such as CBD, may interact with the metabolism of other medications, potentially altering their efficacy or increasing the risk of adverse effects. 2. Past medication response (carbamazepine): JB previously took carbamazepine, which was discontinued due to increased staring spells. This suggests that JB may be sensitive to certain antiepileptic medications and may experience adverse effects with new therapies.

Ask

2. **Ask**	
Directions: • Formulate a PICO question	
Question 3: (4 points) What is your final PICO question? Make sure all **FOUR** components of PICO are included in your final question	In children with Lennox-Gastaut Syndrome and developmental delay experiencing uncontrolled atonic/drop seizures and tonic seizures, does adjunctive therapy with CBD compared to standard therapy and ketogenic diet therapy lead to a reduction in seizure frequency by at least 50% within the next six months?

Acquire

3. Acquire

Directions: • Find one interventional trial, which will help you answer your PICO question	
Question 4: (5 points) Select an interventional trial that has a PICO question that most closely aligns with your PICO question. Write the citation in APA/AMA format	Thiele, E. A., Marsh, E. D., French, J. A., Mazurkiewicz-Beldzinska, M., Benbadis, S. R., Joshi, C., Lyons, P. D., Taylor, A., Roberts, C., Sommerville, K., & GWPCARE4 Study Group (2018). Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London, England)*, *391*(10125), 1085–1096. https://doi.org/10.1016/S0140-6736(18)30136-3

Appraise

4. Appraise	
Directions: 1. Appraise the methods in the interventional trial you selected to make an assessment on its internal validity	
Section A: Is the basic study design valid for a randomized controlled trial?	
Question 5: (5 points) What is the PICO question of the experimental trial? Do you think the PICO question is focused and able to assess the outcome of the intervention?	Response: Does the addition of cannabidiol as adjunctive therapy, compared to placebo, lead to a significant percentage change from baseline in the monthly frequency of drop seizures during a 14-week treatment period in patients aged 2-55 years with treatment-resistant Lennox-Gastaut syndrome? The PICO question is focused and able to assess the outcome of the intervention. It clearly defines the population of interest (patients with treatment-resistant Lennox-Gastaut syndrome), specifies the intervention (cannabidiol as add-on

	therapy), identifies the comparison group (placebo), and outlines the outcome of interest (percentage change in monthly frequency of drop seizures during the treatment period). This focused PICO question allows for a comprehensive evaluation of the efficacy and safety of cannabidiol as adjunctive therapy for drop seizures associated with Lennox-Gastaut syndrome.
Question 6: (5 points) What are the results of this experimental trial?	Response: In the experimental trial, the addition of cannabidiol (CBD) led to a significant reduction in monthly drop seizure frequency compared to placebo, with a median reduction of 43.9% in the CBD group versus 21.8% in the placebo group. Adverse events were more common in the CBD group, but most were mild or moderate. Twelve patients in the CBD group and one in the placebo group withdrew due to adverse events. One patient in the CBD group died, but this was considered unrelated to treatment. Overall, add-on cannabidiol was effective and generally well tolerated for treating drop seizures in Lennox-Gastaut syndrome.
Question 7: (10 points) What do you think about the internal validity of this study? (How confident are you about the truthfulness of the results of this study based on its methods?) A study's methods determine its internal validity or "truthfulness of its results." Errors in methods can introduce bias into the study, which skew results. **To receive full credit for this question, you must dissect the study's methods and provide an assessment of if you think they were adequate to minimize bias or if they introduced bias into the study** Methods to focus on include:	Response: **Process of randomization**: The study used a randomized, double-blind, placebo-controlled design, which is a method to minimize selection bias and ensure both treatment groups can be effectively compared. Randomization also helps mitigate potential confounding factors, reducing the risk of systematic differences that could affect outcomes. The use of an interactive voice response system further strengthens the randomization process. **Process of blinding**: The study used double-blinding, where neither patients nor investigators knew which treatment each participant

1. Process of randomization 2. Process of blinding 3. Level of care in both groups of the study (Apart from the experimental intervention, did each study group receive the same level of care) 4. Attrition rates at the conclusion of the study	received. Blinding helps prevent bias in outcome assessment and treatment administration. **Level of care in both groups**: The study ensures that both groups receive similar levels of supportive care to prevent differential treatment effects unrelated to the intervention and reduce potential bias. **Attrition rates**: The attrition rate was relatively low, with 14 patients in the cannabidiol group and one in the placebo group discontinuing study treatment. However, it's essential to consider the reasons for dropout and whether they could introduce bias. Withdrawals due to adverse events were more common in the cannabidiol group, which could potentially impact the interpretation of safety outcomes if adverse events were not evenly distributed between groups. Overall, the study employed methods such as randomization and blinding to minimize bias. I am confident in the study's internal validity.

Apply	
Question 8: (10 points) Can the results be applied to your patient? Include sound logic to defend your answer. **To receive full credit for this question, you must address:** ● You should consider patient-related and medication-related factors that affect your patient and then ask "Are the study participants similar to the patient in your care?" ● Would any differences between your patient and the study participants	When considering the applicability of the study results to the patient JB, several patient-related and medication-related factors should be taken into account: **Patient-related factors**: JB is a 5-year-old boy with Lennox-Gastaut Syndrome and developmental delay, experiencing uncontrolled atonic/drop seizures and tonic seizures. The study included patients aged 2-55 years with treatment-resistant LGS. While JB falls within the age range of the study population, his developmental delay may affect his ability to

alter the outcomes reported in the study? ● Are the outcomes important to your patient? ● Are there any outcomes you would have wanted information on that have not been studied or reported? ● Are there any limitations of the study that would affect your decision?	communicate and adhere to treatment, potentially influencing treatment outcomes. **Medication-related factors**: JB is currently on topiramate and has previously experienced adverse effects with carbamazepine. The study evaluated the efficacy and safety of cannabidiol (CBD) as add-on therapy compared to placebo. It's essential to consider potential interactions between CBD and JB's current medications and whether his past medication response might affect treatment outcomes. In assessing the similarity between JB and the study participants, it's important to consider whether any differences between JB and the study population could alter the outcomes reported in the study. For example, JB's developmental delay and specific medication history may affect his response to CBD differently compared to other participants in the study. The outcomes reported in the study, such as the reduction in monthly drop seizure frequency and safety profile of CBD, are important for JB. However, it's essential to consider whether additional outcomes, such as cognitive or behavioral effects of CBD, were assessed and reported in the study, as these may also be relevant to JB's care. Limitations of the study, such as the potential differences in attrition rates between treatment groups, should also be considered. These limitations could affect the generalizability of the study results to JB and impact decision-making regarding the use of CBD as adjunctive therapy for his seizures.

	In conclusion, while the study results provide valuable insights into the efficacy and safety of CBD for patients with LGS, including JB, careful consideration of patient-specific factors, potential differences between JB and the study population, and limitations of the study is necessary when applying the results to JB's care.

Question 9: (10 points)
Would the experimental intervention provide greater value to your patient than any of the traditional treatment options? Include sound logic to defend your answer.
To receive full credit for this question, you must address:
 	
● You should consider patient-specific and medication-specific factors that affect your patient and then ask "Do you think this patient would be a good candidate for medical cannabis?"
● Describe the benefits and risks of cannabinoid therapy in this patient.
  ● In your assessment, consider:
  ■ Has your patient tried all traditional treatment and non-pharmacological options before trying this therapy?
  ■ What benefit does this experimental intervention have over traditional therapy options?
	When considering whether the experimental intervention of cannabidiol therapy would provide greater value to JB than traditional treatment options, several factors must be evaluated:
	
	Patient-specific factors: Given JB's diagnosis and history of treatment resistance, JB may be considered a candidate for medical cannabis therapy if he has failed to respond adequately to traditional antiepileptic medications and non-pharmacological interventions.
	
	Benefits of cannabinoid therapy: CBD therapy offers the potential for additional seizure control and improved quality of life for patients with treatment-resistant epilepsy, such as JB. Clinical trials have shown promising results in reducing seizure frequency and improving seizure severity in patients with LGS and other forms of epilepsy (Devinsky et al., 2017; Thiele et al., 2018). Additionally, CBD may offer a more favorable side effect profile compared to some traditional antiepileptic medications, which could be particularly beneficial for pediatric patients like JB (Devinsky et al., 2017).
	
	Risks of cannabinoid therapy: While CBD therapy is generally well tolerated, adverse effects such as diarrhea, somnolence, decreased appetite, and vomiting have been reported in clinical trials (Devinsky et al., 2017; Thiele et al., 2018). It's important to weigh the potential

	benefits of CBD therapy against these risks and consider individual patient factors, including JB's developmental delay and past medication history. **Exploration of traditional treatments**: JB has exhausted traditional treatment options and non-pharmacological interventions. This includes trials of multiple antiepileptic medications, ketogenic dietary therapy. In summary, I would recommend a trial of CBD therapy for JB as it may offer additional benefits for patients with treatment-resistant epilepsy including potential seizure reduction and a favorable side effect profile.
What references did you use? Cite in APA or AMA format. (5 points)	Devinsky, O., Marsh, E., Friedman, D., Thiele, E., Laux, L., Sullivan, J., ... & Cannabidiol in Dravet Syndrome Study Group. (2017). Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. The Lancet Neurology, 16(6), 490-499. Thiele, E. A., Marsh, E. D., French, J. A., Mazurkiewicz-Beldzinska, M., Benbadis, S. R., Joshi, C., ... & Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. (2018). The Lancet, 391(10125), 1085-1096.