specialists in epilepsy remain apprehensive of what role this option will play in light of its disadvantages including delayed response (2–3 years), and absolute requirement for continued medications compared to anterior medial resection.[34]

Conclusion: *Case Discussion*

Although there are many potential treatment options for the case patient with independent bitemporal seizure foci, unfortunately, there is little data available at this time to suggest that the possibility of his obtaining a seizure-free outcome is >5% to 10%. Due to his seizure frequency, it would be relatively simple to attempt some sequential trials of adjunctive therapy while he considers the option of VNS. Care must be taken that multiple variables are not changed at once (ie, AED dosage change and VNS parameter changes), since it would be difficult to determine which variable resulted in improvement or deterioration of his clinical course. There is also hesitation after an additional AED is added to remove an AED that has been previously maintained. The patient may make this decision easily if he implies a certain AED provided no improvement. Otherwise, there is always the concern that an agent will be removed with a specific mechanism of action (ie, GABA agonist, Na channel blocker) that has provided some seizure control and its removal could result in a seizure exacerbation. The patient always needs to be forewarned of this possibility. Nevertheless, addition of agents without subtraction of others over time will result in an excess "drug load." With too many AEDs taken, agents will compete with each other, alter metabolism, and result in an increased side effect profile and decreased quality of life. As the patient attempts additional medications and considers VNS implantation, the hope is that further progress will be made in providing options that result in a higher percentage of seizure-free outcomes.

References

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med.* 2000;342(5):314-319.
2. Schmidt D, Stavem K. Long-term seizure outcome of surgery versus no surgery for drug-resistant partial epilepsy: A review of controlled studies. *Epilepsia.* 2009;50(6):1301-1309.
3. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia.* In press.
4. Engel J Jr. Finally, a randomized controlled trial of epilepsy surgery. *N Engl J Med.* 2001;345(5):365-367.
5. Berg AT, Langfitt J, Shinnar S, et al. How long does it take for partial epilepsy to become intractable? *Neurology.* 2003;60(2):186-190.
6. Morrell F. Secondary epileptogenesis in man. *Arch Neurol.* 1985;42(4):318-335.
7. Lüders HO. Clinical evidence for secondary epileptogenesis. In: Lowenstein DH, ed. *Brain Plasticity and Epilepsy.* San Diego, CA: Academic Press; 2001:469-480.
8. Shorvon SD, Reynolds EH. Reduction in polypharmacy for epilepsy. *Br Med J.* 1979;2(6197):1023-1025.
9. Schmidt D. Reduction of two-drug therapy in intractable epilepsy. *Epilepsia.* 1983;24(3):368-376.
10. French JA, Faught E. Rational polytherapy. *Epilepsia.* 2009;50(suppl. 8);63-68.
11. Ferrendelli JA. Relating pharmacology to clinical practice: the pharmacologic basis of rational polypharmacy. *Neurology.* 1995;45(3 suppl 2);S12-S16.
12. Cramer JA, Ben Menachem E, French J. Review of treatment options for refractory epilepsy: new medications and vagal nerve stimulation. *Epilepsy Res.* 2001;47(1-2):17-25.
13. Ben-Menachem E. Strategy for utilization of new antiepileptic drugs. *Curr Opin Neurol.* 2008;21(2):167-172.
14. White HS, Smith MD, Wilcox KS. Mechanisms of action of antiepileptic drugs. *Int Rev Neurobiol.* 2007;81:85-110.
15. French JA, Gidal BE. Antiepileptic drug interactions. *Epilepsia.* 2000;41(suppl 8):S30-S36.
16. Abou-Khalil BW. Lacosamide: What can be expected from the next new antiepileptic drug? *Epilepsy Curr.* 2009;9(5):133-134.
17. Lacosamide [package insert]. Smyrna, GA: UCB Pharma; 2008.
18. Jung MF, Lippert B, Metcalf BW, Bohlen P, Schechter PJ. gamma-Vinyl GABA (4-amino-hex 5-enoic acid), a new selective irreversible inhibitor of GABA-T:effects on brain GABA metabolism in mice. *J Neurochem.* 1977;29(5):797-802.
19. Vigabatrin [package insert]. Deerfield, IL: Lundbeck; 2009.
20. Michael B, Marson AG. Clobazam as an add-on in the management of refractory epilepsy. *Cochrane Database Syst Rev.* 2008;(2):CD004154.
21. Landmark CJ, Johannesses SI. Pharmacological management of epilepsy; Recent advances and future prospects. *Drugs.* 2008;68(14):1925-1939.
22. Kossoff EH, Rowley H, Sinha SR, Vining EPG. A prospective study of the modified Atkins diet for intractable epilepsy in adults. *Epilepsia.* 2008;49(2):316-319.
23. Sirven JI, Berg AT. Marijuana as a treatment for epilepsy and multiple sclerosis? A "grass roots" movement. *Neurology.* 2004;62(11):1924-1925.
24. Gordon E, Devinsky O. Alcohol and marijuana: effects on epilepsy and use by patients with epilepsy. *Epilepsia.* 2001;42(10):1266-1272.
25. Gross DW, Hamm J, Ashworth NL, Quigley D. Marijuana use and epilepsy; prevalence in patients of a tertiary care epilepsy center. *Neurology.* 2004;62(11):2095-2097.
26. Balabanov A, Rossi MA. Epilepsy surgery and vagal nerve stimulation: what all neurologists should know. *Semin Neurol.* 2008;28(3):355-363.
27. Boon P, Raedt R, de Herdt V, Wyckhuys T, Vonck K. Electrical stimulation for the treatment of epilepsy. *Neurotherapeutics.* 2009;6(2):218-227.
28. Alsaadi TM, Laxer KD, Barbaro NM, Marks Jr WJ, Garcia PA. Vagus nerve stimulation for the treatment of bilateral independent temporal lobe epilepsy. Epilepsia. 2001;42(7):954-956.
29. Fisher RS. Non-pharmacological approach: release of the "Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE)" trial results. Paper presented at: the 62nd Annual Meeting of the American Epilepsy Society; December 5–9, 2008; Seattle, WA.
30. Morrell MJ and the RNS System Pivotal Investigators. Results of a multicenter double blinded randomized controlled pivotal investigation of the RNS System for treatment of intractable partial epilepsy in adults. Abstract presented at: the 63nd Annual Meeting of the American Epilepsy Society; December 6–8, 2009; Boston, MA.
31. Régis J, Rey M, Bartolomei F, et al. Gamma knife surgery for mesial temporal lobe epilepsy. *Epilepsia.* 1999;40(11):1551-1556.
32. Barbaro NM, Quigg M, Broshek DK, et al. A multicenter, prospective pilot study of gamma knife radiosurgery for mesial temporal lobe epilepsy: seizure response, adverse events, and verbal memory. *Ann Neurol.* 2009;65(2):167-175.
33. Behrens E, Schramm J, Zentner J, Konig R. Surgical and neurological complications in a series of 708 epilepsy surgery procedures. *Neurosurgery.* 1997;41(1):1-9.
34. Spencer SS. Gamma knife radiosurgery for refractory medial temporal lobe epilepsy. Too little, too late? *Neurology.* 2008;70(19):1654-1655.

QUESTION-AND-ANSWER SESSION

Q: When would it be appropriate to reconsider the idea of epilepsy surgery for the case patient? Is it possible additional evaluation may point to a single explanation for the apparent bitemporal onsets suggested by the scalp recording?

Dr. Smith: The patient may reconsider epilepsy surgery at anytime since he has already fulfilled the criteria for drug resistant epilepsy. Scalp ictal patterns suggesting independent bitemporal onset may be misleading and actually represent a single focus with extratemporal onset and independent bitemporal propagation. Intracranial implantation would be needed to determine ictal origin(s) and potential benefits and risks of focal resection. Some patients who are found to have independent temporal lobe foci may benefit from surgical resection, although which factors result in a positive outcome is still debatable.[1]

Q: Is there any scientific way to determine which combinations of medication have a high likelihood of having a synergistic effect?

Dr. Smith: Animal studies may be utilized to determine which combinations of antiepileptic drugs (AEDs) may have a synergistic effect when a second drug added lowers the effective-dose 50 (EC50). A more complex procedure is the isobolographic method, which combines two drugs in various proportional percentages of their EC50s.[2] If the combination is supra-additive (synergistic) in potency, then lower proportions of both drugs should be effective.[3] Of course, results obtained in animal studies may not correlate with subsequent human experience.

Q: Given the wide therapeutic window for some of the newer drugs, how high a dose should a clinician prescribe before ending the drug's use?

Dr. Smith: With some AEDs, the daily dosage can be increased to amounts higher than the United States Food and Drug Administration-approved maximum dosage with few side effects. Justification of these higher daily dosages will be determined by physician- and patient-based reports on tolerability and improvement with seizure control after

https://doi.org/10.1017/S1092852900000146 Published online by Cambridge University Press

each escalation. The endpoint would be considered a dose beyond which a reasonable change of seizure-freedom is unlikely. To attempt or maintain daily dosages above which there have been clinical trials completed, the patient should be informed of the unknown risks. Restrictions of maximum daily dosages by insurance formularies, or deferred costs to the patient may be the deciding factor.

References

1. Boling W, Aghakhani Y, Andermann F, Sziklas V, Olivier A. Surgical treatment of independent bitemporal lobe epilepsy defined by invasive recordings. *J Neurol Neurosurg Psychiatry*. 2009;80(5):533-538.
2. Jonker DM, Voskuyl RA, Danhof M. Synergistic combinations of anticonvulsant agents. what is the evidence from animal experiments? *Epilepsia*. 2007;48(3):412-434.
3. French JA, Faught E. Rational polytherapy. *Epilepsia*. 2009;50(suppl. 8);63-68

CASE IN POINT: *EVIDENCE-BASED INSIGHTS FOR EPILEPSY MANAGEMENT*

MANAGEMENT OF EPILEPSY IN DRUG-RESISTANT PATIENTS

CME QUESTIONS

1. A patient must fail ≥4 adequate trials of appropriately chosen and used antiepileptic drug (AED) trials before being considered drug resistant, according to an ad hoc Task Force of the International League Against Epilepsy Commission on Therapeutic Strategies.

A. True

B. False

2. Vagus nerve stimulation and the Responsive Neurostimulator System are the only surgical options approved by the United States Food and Drug Administration for epilepsy treatment.

A. True

B. False

3. Among pharmacologic treatment options for epilepsy, which of the following drugs has not been approved by the FDA for epilepsy?

A. Lamotrigine

B. Topiramate

C. Vigabatrin

D. Clobazam

4. A modified Atkins—low carbohydrate, high protein—diet has been shown to benefit patients with epilepsy, although also caused increased cholesterol among other side effects.

A. True

B. False

5. There are no clinical trials addressing the usefulness of AED combinations, despite clinicians beliefs about the utility of combination therapy.

A. True

B. False

6. It has been shown that patients with epilepsy are not referred for potential surgical intervention how many years following symptom onset?

A. 2

B. 13

C. 15

D. 22

7. Drug resistant epilepsy patients have been shown to often achieve freedom from seizures without side effects on available and approved AEDs.

A. True

B. False

8. As more states in the US allow an exemption from criminal penalties for defined patients who possess and use medical marijuana under physician supervision, use of marijuana for treatment of epilepsy has gained increased attention among researchers.

A. True

B. False

https://doi.org/10.1017/S1092852900000146 Published online by Cambridge University Press