

Management: Monotherapy vs Polytherapy

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I. Learning Objectives

At the end of this activity, the fellow will be able to:

1. State the overall goal of therapy with anti-epileptic drugs (AEDs).
2. Describe the evidence in support of substituting another AED in monotherapy in a patient who has failed their first monotherapy regimen due to inadequate seizure control.
3. Describe the evidence in support of adding another AED (polytherapy) to a drug regimen for a patient who has failed their first monotherapy regimen due to inadequate seizure control.
4. Explain how knowledge of *AED mechanisms of actions* can be used to optimize polytherapy drug choices in the treatment of patients with epilepsy.
5. Explain how knowledge of *potential drug-drug interactions* can be used to optimize polytherapy drug choices in the treatment of patients with epilepsy.
6. Explain how knowledge of *potential drug-related adverse events* can be used to optimize polytherapy drug choices in the treatment of patients with epilepsy.

II. Key Definitions and Concepts:

Monotherapy: Use of a single drug at a time to treat a disease, symptom or condition.

Polytherapy: Use of more than one drug or therapy at a time to treat a disease, symptom or condition.

Overall goal of therapy with AEDs: The use of AEDs in such a way to achieve the highest possible degree of seizure control with the lowest possible degree of drug-related adverse effects. (Note: This definition does not stipulate the use of drugs in monotherapy or in combination).

Potential advantages of monotherapy, compared to polytherapy:

- Monotherapy avoids potentially dangerous drug-drug interactions
- Monotherapy lessens the chance of drug-related adverse effects

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- Monotherapy provides simpler regimens to improve compliance
 - Monotherapy often costs less

III. Important Clinical Questions in the Literature:

1. Is there an advantage for monotherapy or polytherapy in the INITIAL treatment of epilepsy?

No. There is no proven advantage for monotherapy or polytherapy in the initial treatment of epilepsy in terms of seizure control, although there are non-seizure-related advantages to monotherapy regimens (see above). Here's the evidence:

- In a double-blind, randomized study, adult patients with untreated “generalized tonic-clonic and/or partial seizures” were randomized to receive either carbamazepine (CBZ) monotherapy or carbamazepine/valproate (CBZ/VPA) polytherapy at standardized drug loads (Decker, et al., 2001).
- In this study, drug load was defined as the prescribed daily dose of drug divided by the WHO defined daily dose.
- The authors then followed patients for 12 months.
- Overall, no statistical differences were found between the two treatments with respect to three different outcomes: (1) the reduction of seizure frequencies (self-reported by patients); (2) overall neurotoxicity; and (3) overall systemic toxicity.
- When adverse effects were analyzed individually, the authors found a significantly greater incidence of sedation in the monotherapy group and a significantly greater incidence of weight gain in the polytherapy group.

2. Is there an advantage to choosing an alternate monotherapy vs. adding a second AED after one (or multiple) AEDs in monotherapy has failed to control an individual's seizures?

No. There is no clear clinical advantage in terms of seizure control to prescribing an alternate monotherapy to a patient who has incomplete seizure control on a single AED, compared to the addition of a second, adjunctive AED. As stated above, however, there are non-seizure-related advantages to monotherapy regimens. Here is some of the evidence to support this:

- Kwan and Brodie (Seizure, 2000) published an observational study that followed a cohort of newly-diagnosed epilepsy patients (ages 9-89) after they had failed one AED due to incomplete seizure control.
- These patients then received either an alternate monotherapy or an add-on drug (polytherapy) per treating physician preference.

- The rates of seizure freedom in the two groups were similar (17% in the group receiving an alternate monotherapy and 26% in the group receiving two drugs).
- The incidence of intolerable side effects was also similar in the two groups (26% in the group receiving an alternate monotherapy and 12% in the two-drug group).
- Interestingly, the authors found that “more patients became seizure-free [for at least one year] when the combination involved a sodium-channel blocker and a drug with multiple mechanisms of action”.
- In a later, multicenter, randomized, pragmatic controlled trial, patients (aged 2 to 70) with a diagnosis of cryptogenic or remote symptomatic partial epilepsy with incompletely-controlled seizures after single or sequential AED monotherapies were randomized to receive either monotherapy with an alternate AED or adjunctive therapy with a second AED. All AED choices were made by the patients’ treating physicians (Beghi, et al., 2003).
- There was no significant difference in the 12-month cumulative probability of remaining on the assigned treatment between the two groups.
- There was no significant difference in the percentage of patients who became seizure-free with assigned treatment between the two groups.
- The incidence of adverse effects was similar in the two groups.
- Caution: Only 157 patients were studied.

3. How do you make the best polytherapy drug choices for a specific patient?

Polytherapy drug choices can be guided by:

- A. AED mechanisms of action
- B. Potential for drug-drug interaction
- C. Potential drug-related adverse events.

A. AED Mechanisms of Action:

According to Stephen and Brodie (2012), “evidence is slowly accumulating to support the strategy of combining AEDs with differing mechanisms of action, as opposed to using agents that have similar pharmacological properties”. For examples:

- Deckers, et al. (2000) suggests that there may be specific benefit, in terms of seizure control, to combining a sodium channel blocker with a GABAergic drug.
- In addition, as mentioned above, Kwan and Brodie (2000) found that “more patients became seizure-free [for at least one year] when the combination involved a sodium-channel blocker and a drug with multiple mechanisms of action”.
- Both Brodie et al. (1997) and Pisani et al. (1999) published data that suggested that the particular combination of lamotrigine and valproate may be synergistic,

yielding better seizure control than when the drugs were used alone or in combination with other AEDs.

B. Potential for Drug-Drug Interaction:

Drug-drug interactions are prevalent. Although the individual mechanisms of action of AEDs are covered elsewhere, when choosing a polytherapy combination, avoiding combinations of drugs with high potential for drug-drug interactions is advised.

C. Potential for Drug-Related Adverse Events:

Drug-related adverse events are also prevalent. Again, specific drug-related adverse events for individual AEDs are covered elsewhere, but a basic rule of thumb is pertinent to this section: Avoid choosing a polytherapy combination in which both drugs have similar negative drug-related adverse events. In this case, polytherapy may lead to improved seizure control, but at a price of double the toxicity.

LITERATURE REFERENCES

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