



## How long would it take to try all the antiepileptic drugs available?

Drug resistant epilepsy is defined as epilepsy that persists despite adequate trials of two tolerated and appropriately chosen antiepileptic drugs (AED), whether as monotherapies or in combination (Kwan et al., 2010). Although many new AED became available in the last decades, the outcome of epilepsy has not improved (Kwok et al., 2017), and approximately one third of patients still have drug resistant epilepsy. Most patients who achieve complete seizure control do so with the first or second antiepileptic drug (Chen et al., 2018).

Epilepsy surgery is markedly superior to continued AED treatment for appropriate surgical candidates, both adult and pediatric (Engel et al., 2012; Wiebe et al., 2001), with a number needed to treat of  $< 2$  in order to render a person seizure-free after suffering from chronic epilepsy. Furthermore, it usually takes only a short time to determine that a patient is drug-resistant. Yet the average duration of epilepsy at the time of referral for consideration of epilepsy surgery is just over 2 decades (Engel et al., 2012). At least part of this delay is due to referring neurologists' mentality that they will first "try one more AED", or try the most recently approved one in case that is the magic bullet for the patient.

In order to establish how long it would take to try all the available AEDs (or at least a significant number) in the treatment of drug resistant epilepsy, we considered: a) twenty different AEDs; b) time to establish that the AED was ineffective (6 months); c) every possible combination of AED.

To calculate the time necessary for an exhaustive series of experiments (with mono, duo, or triple therapy); firstly, we calculated the time  $T$  it takes to complete a set of therapy tests. For this purpose, we denote the number of drugs to be tested by  $n$ , the number of months used for each individual test by  $m$ , and the type of therapy by  $p$ , i.e.,  $p = 1$  for monotherapy,  $p = 2$  for duotherapy and  $p = 3$  for triple therapy.

In the  $p$  therapy trials, we want to test every possible combination of  $p$  drugs. As the drugs cannot be repeated, this is equivalent to the number of possible permutations of  $n$  samples where  $p$  and  $(n - p)$  samples are indistinguishable. Therefore, we can use the formula:

$$C_n^p = \frac{n!}{p!(n-p)!}$$

However, this value must be multiplied by the number of months ( $m$ ) used for each individual test. Thus, we have:

$$T = m \cdot C_n^p.$$

Summarizing, the time required for each trial for the three explicit cases is given by:

- Monotherapy:  $T = m \cdot n$
- Duotherapy:  $T = m \cdot \frac{n(n-1)}{2}$
- Triple therapy:  $T = m \cdot \frac{n(n-1)(n-2)}{6}$

**Table 1**

Time required for AED trials.

# AEDs trialed	Duration of each trial, months	Monotherapy, duotherapy, or triple therapy	Time required for all trials
20	6	mono	10 years
20	6	duo	95 years
20	6	triple	570 years
6	6	mono	3 years
6	6	duo	7 years, 6 months
6	6	triple	10 years

AED: antiepileptic drug.

We found that it would take 10 years to try all the 20 AEDs in monotherapy; 95 years to try every possible combination of two AEDs, and 570 years to try every possible combination of three AEDs.

Secondly, we considered a more realistic approach of using only six AEDs. We found that it would take 3 years to try all six AEDs in monotherapy; 7 years and 6 months to try every possible combination of two AEDs, and 10 years to try every possible combination of three AEDs (Table 1).

We conclude that it would take far too long to try every possible AED combination prior to referring for epilepsy surgery, even if only trying 6 medications. We hope this simple mathematical exercise will help prevent clinicians from thinking they should "try one more AED" before referring.

As guidelines suggest, patients should be referred for video/EEG monitoring to confirm the diagnosis and begin consideration of epilepsy surgery after the failure of two adequate AED trials of any kind.

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