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Polytherapy: The Bane and Boon of Refractory Epilepsy

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ABSTRACT:
Epilepsy is a neurological condition, mostly categorised by the recurrence of seizures throughout a person's life. While there are no cures, there are viable treatment options available to those affected by the condition. But when it comes to deciding the type of treatment, factors such as the type of epilepsy and AED interactions become of huge importance, as those are indicators as to whether a treatment plan will be successful or not. This research paper will focus mainly on refractory epilepsy and how different AED interactions can affect the patient's decision of whether to choose monotherapy or polytherapy as their best course of treatment.

INTRODUCTION:
Epilepsy, as we know it today, is one of the most unresolved conditions, with little to no answers on even the possible causes of this lifelong condition. Epilepsy is a neurological condition characterised by recurrent seizures, affecting people of all ages and their daily lives. The probability of a person developing epilepsy is 1 in 26. Estimates also state that 10% of the world's population will have at least 1 seizure in their lifetime. Out of these people, 1/3rd of them will develop epilepsy.

SEIZURE:
The most common sign that someone may have epilepsy is the recurrence of seizures. Seizures are electrical disturbances in the brain that interfere with its normal function. Many scientists and clinicians compare these electrical disturbances to an 'electrical storm in the brain'. This is where the brain cells hypersynchronise in an abnormal pattern, disrupting the delicate brain signal. Epilepsy is a spectrum disorder, meaning the causes, type or extent of severity can differ greatly among those affected by the condition. The four main types of seizures include tonic-clonic seizure (grand-mal), absence(petit-mal), febrile seizures and focal seizures.

THE TYPES OF EPILEPSY:
In general, epilepsy has 3 types, based on its seizure type and underlying cause. Some underlying causes include Brain structural abnormalities, Infectious diseases, stroke or tumours, but nothing is definitive.

1. **Generalised epilepsy:** In this type of epilepsy, both hemispheres of the brain become affected. This results in widespread symptoms such as convulsions or absence of seizures.
2. **Focal epilepsy:** This type of epilepsy is limited to one area of the brain, often causing localised symptoms such as sensory changes or motor disruptions.
3. **Unknown epilepsy:** This type of epilepsy is diagnosed when the root cause of the seizures cannot be determined.

REFRACTORY EPILEPSY:

Quite similar to antibiotic resistance in a way, refractory epilepsy is characterised by the occurrence of persistent seizures despite the use of 2 or more appropriately chosen and tolerated anti epileptic drugs(AEDs) either alone or in combination with. Approximately 30% to 40% of those with epilepsy have seizures that they are unable to control with the help of medication. Patients are considered to have refractory epilepsy if disabling seizures continue, despite appropriate trials of 2 antiseizure drugs, either alone or in combination. In other words, a person can be diagnosed with refractory epilepsy when the AEDs that they are on refuse to work.

At this point, patients should be referred to multidisciplinary centres that perform specialised diagnostic testing. This is done to ensure that the patient is, in fact, pharmacoresistant. And then, if so, offer and find alternative treatments. Pharmacoresistance can result from a variety of situations, including non-compliance, non-epileptic seizures, misdiagnosis of the seizure type or epilepsy syndrome, inappropriate use of medication, and lifestyle issues. While it may seem that people diagnosed with refractory epilepsy will have to struggle their entire lives, all hope is not lost. Research has shown that pharmacoresistant patients have the best opportunities with surgical treatment and, in some cases, even complete freedom from seizures.

CAUSES AND SYMPTOMS OF REFRACTORY EPILEPSY:

While no definitive causes of refractory epilepsy have been identified, researchers and clinicians have stated two possible causes.

Some of the possible known causes include head injuries, infections, fevers, or brain tumours.

1. Some of the possible known causes include head injuries, infections, fevers, or brain tumours.
2. It is possible that the electrical activity in the brain can get so high that the medication may no longer be able to work.

Symptoms of refractory epilepsy may include convulsions or shaking movements, loss of consciousness, confusion, tongue biting, lip smacking, loss of bowel or bladder control, uncontrolled eye movements, staring into space, falling, muscle rigidity, tremors or twitches, and odd behaviour such as yelling or screaming.

TREATMENTS TO MANAGE EPILEPSY:

Since epilepsy has no known cure yet, there are only ways to manage and control the disease. The two main ways of doing so are monotherapy and polytherapy. In the case of refractory epilepsy, polytherapy is more effective and better recommended. Hence, this paper will mainly focus on that.

POLYTHERAPY:

Polytherapy or combination therapy is the use of more than one intervention concurrently to treat a single symptom or multiple symptoms. Polytherapy aims to achieve better treatment outcomes by combining various therapies with different mechanisms of action, which could potentially lead to synergistic effects and increased efficacy. Some common applications include epilepsy and cancer. In the case of epilepsy, it is used when a patient has drug-resistant epilepsy(DRE), meaning they haven't achieved freedom with 2 or more appropriately chosen and tolerated anti-epileptic drugs.

BENEFITS OF POLYTHERAPY:

The benefits of polytherapy in the management of drug-resistant epilepsy could be related to the recent introduction of many new AEDs. Studies have shown that polytherapy has a higher rate of efficacy in treating refractory epilepsy. The overall cost of polytherapy may be more affordable than treating the recurrence of seizures. Newer Autism spectrum disorders(ASDs) are better tolerated and ideal for polytherapy. They also have a more diverse mechanism of action and favourable pharmacokinetics. There are also more specific benefits of polytherapy.

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1. **Improved seizure control:** In some individuals, polytherapy can achieve better seizure control than monotherapy, especially when seizures are resistant to a single drug.
2. **Targeting multiple seizure types:** Different anti-seizure medications(ASMs) may be effective against different types of seizures. Combining them can also provide broader seizure control.
3. **Reduced individual drug doses:** By combining drugs, lower doses of each medication may be used, potentially minimising side effects associated with higher doses of a single drug.
4. **Synergistic effects:** Some combinations of ASMs may have synergistic effects, meaning that their combined effect is greater than the sum of their individual effects.

DIFFICULTIES OF POLYTHERAPY:

The choice of optimal polytherapy poses a difficulty for several reasons. First and foremost, there is limited data regarding favourable or unfavourable combinations. Although there are a few exceptions, there is little systematic evidence that any 2 combinations are any more or less effective than any other.

The reason to start polytherapy begins with the clinician's comfort with the AEDs chosen first for monotherapy. This may result in combinations of AEDs that are idiosyncratic for each practitioner and not necessarily optimally selected for the patient requiring polytherapy. Patients may end up on a specific polytherapy because of the order of introduction of the AEDs to the market, or in some countries, by funding mechanisms or government subsidies.

It may also be governed by the relative ease or difficulty of establishing a specific combination of drugs. For example, the addition of Valproic acid(VPA) to Lamotrigine(LTG) is a challenging task for physicians because of the pharmacokinetic interactions necessitating careful reduction in the reduction of the LTG dose.

In comparison, the addition of Levetiracetam(LEV) or Gabapentin(GBP) to LTG is simple due to the lack of any drug-drug interactions. Even when the desired combination of efficacy and side effect profile is suboptimal, ease of administration may dictate the individual components of polytherapy.

Lastly, medication side effects are less thoroughly addressed than the effectiveness of medications during the patient follow-up visit. When the patient fails 2 or more trials of monotherapy and the physician prepares to combine medications, the efficacy of any AED will be of even greater importance than the medication side effects, even though AED polytherapy is the strongest indicator for patients experiencing subjective side effects in some studies. Once an effective combination is found, it becomes difficult to reduce medication to act upon side effect complaints, even if they are persistent, debilitating or are known to cause severe chronic side effects such as osteoporosis.

Patients and their doctors do not always agree on the need for these adjustments, especially when the AED reduction leads to physician advice to refrain from driving due to concern for possible seizure recurrence.

Furthermore, it is quite probable, and likely, that more optimal AED combinations that are both effective and tolerable may not have been found yet.

TYPES OF AED INTERACTIONS:

One of the main difficulties that comes with polytherapy is the AED interactions. While there are multiple AED interactions, this paper will focus on the main: Enzyme inhibition or induction, Pharmacokinetic interactions and Medical or Pharmacodynamic interactions.

1. **Enzyme inhibition/induction:** Enzyme inhibition is a process where the activity of an enzyme is reduced or blocked by the presence of an inhibitor. Inhibitors are compounds that convert the enzymes into inactive substances and thus adversely affect the rate of enzymatically catalysed reactions. There are 5 types of enzyme inhibition:

A. **Reversible competitive inhibition**: This is where the inhibition of enzymic activity is done by the competitive inhibitors at the active site.

B. **Reversible non-competitive inhibition:** This is where the inhibition of enzymatic activity by the binding of inhibitors occurs at the allosteric site and not the active site.

C. **R-uncompetitive inhibition:** This is where the binding of the inhibitor occurs at the allosteric site, just like in the case of non-competitive inhibition, but instead the binding takes place with the enzyme-substrate (ES) complex and not with the free enzyme molecule.

D. **Irreversible inhibition:** It is the inhibition of enzymic activity by the irreversible change in the structure caused due to the binding of the inhibitor to the enzyme, or by destroying some functional group that is essential for its activity.

E. **End-product inhibition:** It is the cellular control mechanism in which the activity of enzymes is inhibited by the enzyme's end product. It is also referred to as feedback inhibition.

In the case of AEDs, enzyme inhibition is bound to happen. Since they are widely used as long-term adjunctive therapy or as monotherapy and for other indications, as well as considered a group of drugs, they are highly susceptible to drug interactions. Older AEDs such as Carbamazepine, Phenobarbital, Phenytoin, and Primidone all cause enzyme induction. This means that there will be an increase in the synthesis of enzymes in response to specific substances, leading to enhanced chemical activity. Valproic acid, on the other hand, causes enzyme inhibition, resulting in a decrease or increase, respectively, in the serum concentration of other AEDs. They are also known to affect other drug classes such as anti-coagulants, oral contraceptives, antidepressants, antipsychotics, antimicrobial drugs, antineoplastic drugs and immunosuppressants. Conversely, the serum concentration of AEDs may be increased by enzyme inhibitors among antidepressants, antipsychotic drugs and antimicrobial drugs(as Macrolides and Isoniazid) and decreased absorption or excretion(as oral contraceptives, Cimetidine, Probencid and Antacids)

2. Pharmacokinetic interactions: In general, pharmacokinetic interactions may alter absorption, protein binding, metabolism and the excretion of any drug. They are usually related to alterations in metabolism by enzyme inducers or inhibitors and are often well described in clinical models. Most drug interactions in the past were discovered due to unexpected changes in the clinical status of a patient after the addition or withdrawal of a drug from existing medication. Enzyme induction, as previously mentioned, involves the synthesis of a new enzyme, requiring protein synthesis and may take many days before it is completed. This thus increases metabolism, decreases serum concentrations, and the pharmacological effect (if no active metabolites are present) of the affected drug, and possibly leads to loss of seizure control.

The process is reversed when the inducer is withdrawn, increasing serum concentration and potential for toxic side effects of the affected drug. Enzyme inhibition results from the competition between drugs for the same active site on the enzyme and results in a decreased metabolism of the affected drug. Circulating concentrations of the inhibited drug increase to a new steady rate about 5 half-lives after the interaction. Consequently, pharmacological potentiation will occur quickly if the drug has a short half-life and slowly if it has a long half-life. Conversely, if the inhibitor is withdrawn, drug concentrations will decrease the risk of seizures. If the drug is a substrate, in vitro and in vivo inhibition is enzyme-specific and substrate-independent. All the drugs that are metabolised to a significant degree by the same enzyme are inhibited by inhibitors of that enzyme. Therefore, they exhibit the same spectrum of interactions. For any given drug, the knowledge of the isoform(s) that catalyse(s) its metabolism is important.

Pharmacokinetic interactions involving newer AEDs include enzyme inhibitors such as Felbamate, Rufinamide and Stripentol and inducers like Oxcarbamazepine and Topiramate. Lamotrigine is affected by these drugs, older AEDs and other drug classes such as oral contraceptives. Individual AED interactions may be divided into 3 levels depending on the clinical consequences of alterations in serum concentrations. This approach may point to interactions of specific importance, although it should be implemented with caution as it is not to oversimplify factual matters.

A. **Level 1 interactions:** These may result in potentially serious clinical consequences, and the combination should be avoided.
B. **Level 2 interactions:** These usually imply caution and possible dosage adjustments, as the combinations may not be possible to avoid.
C. **Level 3 interactions:** These refer to interactions where dosage adjustments are not necessary and clinically relevant changes in serum concentrations are not expected.

Furthermore, updated knowledge regarding drug interactions is important to predict any potential harmful or lacking effects involving AEDs.

Since several of the older AEDs are well-known enzyme inducers(Carbamazepine, Phenytoin, Phenobarbital and Primidone) or inhibitors(Valproic acid), interactions with AEDs are commonly occurring and often have potentially serious clinical implications(Level 1 and Level 2 interactions). In various instances, the knowledge of the possibility of a given interaction may help in better rationalising the therapeutic approach in avoiding unnecessary risk to patients. The clinical significance of some of the reported interactions with AEDs may, however, be questioned if the alterations in the serum concentrations are minor(Level 3 interactions). It should also be noted that the enzyme-inducing AEDs affect endogenous biochemical pathways, as the metabolism of sex hormones, vitamin D homeostasis, bone metabolism and cholesterol synthesis.

While newer AEDs are less susceptible to causing pharmacokinetic interactions than older drugs, they may still be affected by other AEDs or drug classes. Recently, out of 4 new AEDs(Eslicarzepine acetate, Lacosamide, Rufanamide and Stiripentol), 2(Rufanamide and Stiripentol) have been observed to have pharmacokinetic interactions, with Stiripentol having a greater interaction potential than Rufanamide. However, it should be noted that the use of Rufanamide and Stiripentol is limited to special pediatric populations.

3. Medication interactions: Interactions between AEDs and other drugs may result in alterations in serum concentrations of the actual AEDs or other drugs, often caused by the induction or inhibition. Another example of medication interactions is pharmacodynamic interactions. These interactions occur at the site

of action of the drugs and may not involve synergistic or antagonistic alterations. They are also not possible to measure and elevate, as no alterations in serum concentration have been observed to date.

Although pharmacodynamic interactions may affect efficacy and tolerability in most central nervous system(CNS) active drugs. Synergistic pharmacodynamic interactions between Lamotrigine and Valproic acid have been demonstrated in an open crossover study with 20 adult patients with refractory complex partial seizures. However, the dose of both drugs may need to be reduced to minimise the risk of intolerable side effects. Some preclinical studies have suggested a supra-additive or synergistic pharmacodynamic effect. For example: Levetiracetam with Carbamazepine, Felbamate, Oxcarbamazepine or Topiramate. Similarly with Gabapentin and Vigabatrin, as demonstrated in the maximal electroshock-induced seizure model in mice. On the other hand, Lamotrigine in combination with Carbamazepine or Oxcarbamazepine results in an antagonistic effect. Other combinations of AEDs may give rise to excessive adverse reactions, which may be explained as pharmacodynamic interactions. There is also common usage of psychotropic drugs in epilepsy, and they may affect seizure threshold and contribute to CNS-related adverse events.

WHEN TO SIMPLIFY TREATMENT:

To prevent adverse effects of AED interactions, a clinician should titrate slowly from low doses and maintain the lowest possible dose while still achieving effective treatment. They may adapt to the adverse effects of the AED over time, or the effect of the AED may go away on its own. Therefore, if the adverse effect is tolerable, it may be considered optimal to maintain the AED at its current dosage; if the adverse effects include weight gain and the loss of bone mineral density, a replacement of the AED may be required to eliminate these effects. An AED may also cause cognitive dysfunction. Adverse effects that require an immediate cessation of AED treatment include rash, Stevens-Johnson Syndrome, hepatic dysfunction, aplastic anaemia and agranulocytosis. Such cases require a detailed patient evaluation and appropriate treatment changes.

If the AED treatments are not working, then physicians may consider and recommend the concept of rational polytherapy. This treatment includes:

1. Setting the optimal doses of the ongoing AEDS.
2. Avoiding AEDs with a similar action mechanism.
3. Avoiding the increase in the number of prescribed AEDs
4. Changing the dosage if needed, by titrating or tapering off slowly.
5. Considering drug-drug interactions to achieve synergy and avoid adverse effects.
6. In case a new AED is suboptimal, replace it with another.
7. If a newer AED is effective, withdraw the previous one.

In the end, the goal of AED treatments is remission without any adverse effects. Resolved epilepsy might not be a possible goal for all patients, and decisions about whether or not to continue the AEDs should be made keeping the patient's best interest in mind. While there may be no definitive strategy for withdrawing AED treatment, tapering off is recommended as a sudden withdrawal of an AED can cause withdrawal seizures. A tapering period of around 6 months is usually recommended.

CONCLUSION:

While polytherapy has shown great results in helping manage refractory epilepsy, it is most definitely not a cure. Polytherapy is still known to have side effects, especially with the various pharmacokinetic and pharmacodynamic interactions that could occur. But that doesn't mean that all hope is lost. Scientists and

researchers are working around the clock to find better and more viable treatments as well as potential cures for epilepsy as a whole. Organisations such as the Epilepsy Foundation (USA), Epilepsy Foundation Indian, Indian Epilepsy Association and epilepsy smart Australia(national epilepsy support service) all help to provide useful and important information regarding the neurological condition, as well as how to take care of yourself if you have epilepsy or take care of your loved ones if they have it. In the end, whether the treatment chosen is monotherapy or polytherapy, it is always important that the patient's best interest be kept in mind, because to scientists and researchers, it's a discovery. But, to a patient, it's a second chance at life.

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