Monotherapy versus Polytherapy in Epilepsy: a Framework for Patient Management

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ABSTRACT: The long-standing debate between proponents of monotherapy and those of polytherapy for treatment of epilepsy has been rekindled by the recent development of several new antiepileptic drugs. The likelihood of improved seizure control on polytherapy must be weighed against the risk of increased side effects, complex drug interactions and cost. Providing maximal seizure control while avoiding over-treatment is a challenge which requires an ongoing critical evaluation of each patient's management. This review provides a framework for decision-making by considering issues affecting the choice between monotherapy and polytherapy in five clinical situations: 1) newly diagnosed epilepsy; 2) seizures on monotherapy; 3) seizures controlled on polytherapy; 4) not controlled on polytherapy; 5) change in medical condition.

RÉSUMÉ: La monothérapie versus la polythérapie dans l'épilepsie: un cadre pour le traitement des patients. Le vieux débat entre les promoteurs de la monothérapie et ceux de la polythérapie dans le traitement de l'épilepsie a été repris à cause du développement récent de plusieurs nouveaux médicaments antiépileptiques. La probabilité d'un meilleur contrôle des crises par une polythérapie doit être évaluée par rapport au risque d'effets secondaires plus importants, d'interactions médicamenteuses complexes et du coût de la médication. C'est un défi que d'arriver à un contrôle maximal des crises tout en évitant de surtraiter, ce qui demande une évaluation critique constante du traitement de chaque patient. Cette revue fournit un cadre pour la prise de décision en considérant les raisons qui influencent le choix entre la monothérapie et la polythérapie dans cinq situations cliniques: 1) un nouveau diagnostic d'épilepsie; 2) des crises sous monothérapie; 3) un contrôle des crises sous polythérapie; 4) une absence de contrôle sous polythérapie; 5) un changement dans l'état médical du patient.

Can. J. Neurol. Sci. 1998; 25: S9-S13

The introduction of five new drugs for the treatment of epilepsy in Canada within the last decade has provided physicians and their patients with new treatment options. However, in some ways this has complicated the management of epilepsy and rekindled the debate concerning the use of monotherapy vs. polytherapy. This review will outline five clinical situations in which the choice between single and multiple drug treatment should be carefully considered. Some of the important issues in each situation will be reviewed in order to provide a framework for clinical decision making.

Newly Diagnosed Epilepsy

Most authorities now agree that monotherapy is the appropriate choice in newly diagnosed epilepsy. Between 70-75% of patients achieve a one year remission (one year seizure-free)[1-3] with a single appropriate antiepileptic drug. Seizures are completely controlled in about forty to fifty percent of newly diagnosed patients.[2-6] Compliance is better and the risk of side effects is reduced with monotherapy.[7,8] Several well controlled trials have now demonstrated that there is no significant difference in efficacy for generalized tonic-clonic seizures among the standard antiepileptic drugs (phenobarbital, primidone, carbamazepine, phenytoin and sodium valproate).[2-4,6] In some studies carbamazepine was superior to other drugs in treating partial seizures[6] but this was not confirmed in other studies.[2,3]

Recent studies indicate that the newer antiepileptic drugs, lamotrigine[9,10] (357 patients), vigabatrin[11,12] (87 patients), gabapentin[13,14] (150 patients) and topiramate[15] (48 patients) are also effective as monotherapy in controlling new onset generalized tonic-clonic seizures and partial seizures with or without secondary generalization in adults and clobazam is effective in children[16] (220 patients). Preliminary evidence suggests that lamotrigine monotherapy is also effective in children with absence seizures.[17] Although only a small number of comparative trials have been carried out, the efficacy of lamotrigine or vigabatrin monotherapy is comparable to carbamazepine.[9,11,12]

Drug selection is based primarily on seizure type or epilepsy syndrome (Table 1) as well as the adverse event profile. For example, phenobarbital and primidone were not as well tolerated as the other standard drugs especially in children.[2-4,6] Side effects were less frequent and severe with lamotrigine or vigabatrin than with carbamazepine.[9,11,12] Individual patient characteristics may also influence the choice of a drug (Table 2).

Patients with more than one seizure type should be treated, if

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Table 1: Choice of antiepileptic drug by seizure type and epilepsy syndrome.

Seizure type	Initial Monotherapy	Alternative monotherapy or Add-on
Partial onset (simple or complex) with or without secondary generalized tonic-clonic seizures	Carbamazepine Phenytoin Valproic acid	Clobazam Gabapentin* Lamotrigine Phenobarbital Primidone Topiramate* Vigabatrin*
Generalized seizures		
Tonic-clonic	Carbamazepine Phenytoin Valproic acid	Clobazam Gabapentin* Lamotrigine Phenobarbital Primidone Topiramate* Vigabatrin*
Absence	Valproic acid Ethosuximide	Clobazam Lamotrigine Topiramate*
Myoclonic Atonic/akinetic Tonic	Valproic acid	Clobazam Lamotrigine Topiramate*
Epilepsy Syndrome		
Juvenile Myoclonic Epilepsy	Valproic acid	Carbamazepine Lamotrigine Phenytoin
Benign Rolandic Epilepsy**	Carbamazepine	Clobazam Phenytoin Valproic acid
Infantile spasms	Vigabatrin	ACTH Corticosteroids

* not yet approved for monotherapy in Canada
** treatment is usually not necessary

possible, with a single broad spectrum agent such as valproate or lamotrigine rather than 2 or more individual drugs specific for each seizure type. Compliance is improved with a single agent while the risks of adverse events and pharmacokinetic interactions are diminished. It may be appropriate to consider discontinuing treatment after one year in children or two years in adults whose seizures are completely controlled. This can be accomplished successfully in approximately 60% of appropriately selected patients.[18,19]

If the seizures are completely controlled with monotherapy, but the patient suffers side effects despite lowering the medication dosage, the patient should be switched to alternative monotherapy. One strategy is to add the second drug and withdraw the first one as soon as the patient has been stabilized. Abrupt discontinuation of the first drug before adequate levels of the second drug have been reached could result in seizure recurrence. Furthermore, if the patients suffer a hypersensitivity reaction to the second drug requiring discontinuation, they may be left without any treatment for their seizures. Patients may be prepared to accept a brief period of side effects on polytherapy rather than run the risk of recurrent seizures. Titrating one drug up while simultaneously withdrawing another drug may confuse patients and lead to medication errors. A written schedule can be very helpful.

Seizures on Monotherapy

The diagnosis should be critically re-evaluated if the seizures are not improved with monotherapy. It is important to ensure that the diagnosis of epilepsy is correct, that the seizure type has been correctly identified and that a thorough search for underlying causes has been carried out. The history and EEG should be reviewed to determine whether the appropriate drug has been chosen for the patient's seizure type (Table 1) and that an adequate dose of the drug has been prescribed. Although drug levels may provide a helpful guide to dosing with some of the standard anti-epileptic drugs (phenytoin, carbamazepine, phenobarbital, valproic acid), they should not be the only consideration. Some patients may not achieve adequate seizure control until their levels are higher than the "therapeutic" range. It may be preferable to increase dosage up to the maximum tolerated dose, rather than adhering too strictly to the drug levels.

One of the most common reasons for failure of anti-epileptic drug therapy is poor patient compliance.[20,21] This is best assessed with a careful history, however, drug levels may also be helpful under these circumstances. Patient education regarding the diagnosis and treatment as well as lifestyle factors, such as sleep deprivation, alcohol and drug abuse, which may interfere with seizure control, may lead to alterations in behaviour which improve seizure control without changing medication.

It is unlikely that a drug which has been ineffective on its own will be effective in combination with other medications. Therefore, patients who do not improve with appropriate monotherapy should be switched to an alternative agent. The situation is more complicated when the first agent significantly reduces the seizures but does not completely control them. A second drug may be added or the patient may be switched to an alternative drug. Unfortunately, there are no controlled clinical trials comparing alternative monotherapy with add-on polytherapy. However, alternative monotherapy may be effective in reducing seizures or even eliminating them in some patients[22,23] while avoiding drug interactions, minimizing side effects and decreasing costs. Establishing an effective dose of the alternate drug may sometimes require considerable time. Discontinuing the first drug while titrating the new agent may result in an increase in seizures. Patients may prematurely conclude that the second drug is ineffective and discontinue it before an adequate trial has been completed.

An alternative approach is to add the second agent. Drug combinations which do not result in significant pharmacokinetic interactions are preferred under these circumstances. Adding a second agent may improve seizure control in 25-50% of patients, but is likely to result in complete control in only 5-10% of patients.[4,7,11] However, if the seizures are completely controlled with combination therapy, consideration should be given to withdrawing the first agent in order to minimize side effects.[7] For example, over 40% of patients whose seizures were completely

https://doi.org/10.1017/S0317167100034909 Published online by Cambridge University Press

Table 2: Some patient characteristics to consider in choosing drugs.

Patient group	Issues	Drugs more likely to cause problem	Drugs less likely to cause problem
Children	Sedation hyperactivity impaired learning	phenobarbital, primidone, benzodiazepines	Valproate carbamazepine lamotrigine
Female	oral contraceptive failure	carbamazepine, phenytoin phenobarbital, topiramate	clobazam, valproate gabapentin, vigabatrin, lamotrigine
	teratogenicity	carbamazepine, phenytoin phenobarbital, valproate	clobazam [lamotrigine, gabapentin, topiramate, vigabatrin not yet known]
Any patient	cosmetic and weight gain	phenytoin valproate, vigabatrin	carbamazepine, clobazam lamotrigine, gabapentin topiramate (weight loss)
Elderly	sedation impaired cognition	phenobarbital, primidone clobazam	lamotrigine gabapentin
Medical conditions	impaired clearance in renal impairment	topiramate, gabapentin vigabatrin	clobazam valproate
	impaired metabolism in hepatic failure	carbamazepine, phenytoin phenobarbital lamotrigine, topiramate	gabapentin vigabatrin
	exacerbate hepatic failure	valproate (in children)	
	cardiac disease	carbamazepine (conduction block)	gabapentin vigabatrin lamotrigine topiramate
	multiple drugs and drug interactions	carbamazepine phenobarbital, phenytoin	gabapentin vigabatrin lamotrigine topiramate
Previous hypersensitivity	cross-reactivity Steven's Johnson Syndrome	carbamazepine, phenytoin phenobarbital, lamotrigine	clobazam, gabapentin topiramate, valproate vigabatrin
Compliance risk	multiple doses	gabapentin valproate carbamazepine	**once daily** clobazam, phenytoin phenobarbital **twice daily** lamotrigine, topiramate vigabatrin, carbamazepine, CR
Cost	patients not covered by insurance society	gabapentin, lamotrigine topiramate, vigabatrin valproate	carbamazepine, clobazam phenytoin, phenobarbital

controlled when lamotrigine was added to valproate, phenytoin or carbamazepine, remained seizure-free on lamotrigine monotherapy.[7] The first drug can be re-instituted if the seizures recur. However, sufficiently long observation periods are required to ensure that seizure recurrences do not simply represent the natural fluctuation in seizure frequency.

There may be a tendency to add 3rd or 4th agents when add-on therapy results in an apparent improvement, but not complete seizure control. However, there are no controlled trials to support this practice. It is probably preferable to proceed to alternative add-on agents rather than continuing to add to the polypharmacy which increases the risk of side effects with little if any improvement in seizure control. Under these circumstances, the first add-on drug can be stopped abruptly and an alternative add-on agent tried. It is again imperative that the patient be carefully re-evaluated to ensure correct diagnosis and treatment. Surgical treatment should be considered in refractory patients with partial-onset seizures. Alternative therapies such as ketogenic diet might be considered in some children.[24]

Similarly, patients who do not improve with the first add-on

https://doi.org/10.1017/S0317167100034909 Published online by Cambridge University Press

drug should be re-evaluated, tried on alternative add-on agents, or considered for surgery.

Controlled on Polytherapy

Patients whose seizures are controlled on polytherapy should be re-evaluated periodically to determine the need for multiple drug therapy. Although the polytherapy may be responsible for seizure control, it is also possible that the second drug alone might be effective.[7] Side effects are increased on polytherapy,[8] however, it is not clear whether this is due to the number of medications or to the total drug load.[25] Patients may not have obvious side effects, however, there may be subtle cognitive problems that become apparent in retrospect only after one of the drugs is discontinued. The ongoing cost of multiple medications may also be a significant issue. Continued polytherapy may also increase the risk of teratogenicity in women of childbearing age.[26-29] However, patients may be reluctant to consider a switch to monotherapy with the second agent because of uncertainty regarding seizure recurrence. The critical issue is often the ability to continue driving. If patients are switched to monotherapy under these circumstances, they should be warned not to drive until it is reasonably clear that this strategy is successful. They may have to be reported to the Ministry of Transportation in some jurisdictions.

Withdrawing medications in patients on polytherapy can produce complex drug interactions. For example, discontinuing enzyme-inducing agents such as phenytoin or phenobarbital may increase the plasma levels of drugs such as lamotrigine[30] or topiramate.[31] This might partially compensate for the antiepileptic effects of the drug being withdrawn, however, it could also cause side effects from the remaining drugs. Conversely, stopping valproate in a patient taking lamotrigine could result in sub-optimal lamotrigine levels.[30,32] An increase in seizures under these conditions could be managed by increasing the lamotrigine dose rather than re-introducing valproate.

Not Controlled on Polytherapy

Patients whose seizures are not controlled on multiple medications should have their diagnosis and treatment critically re-evaluated. A careful history will usually identify which, if any, of the medications significantly reduced the frequency or severity of the seizures. In some cases it may become clear that none of the drugs were effective. A gradual reduction in the number of medications may simplify management, reduce side effects and cost and improve the patient's quality of life even if the seizures are unaltered.

Change in Medical Condition

A significant change in the patient's general medical condition or pregnancy should also prompt a re-evaluation of their treatment. For example, the risk of fetal malformations increases with polypharmacy.[26-29] Side effects may increase during pregnancy, particularly with multiple medications. In addition, drug pharmacokinetics become more complex during pregnancy.[33-35] For all of these reasons, patients who are contemplating pregnancy should have their medication carefully reviewed and simplified if possible.

Severe hepatic, renal or cardiac disease may alter anti-epileptic drug pharmacokinetics.[36-41] In addition, these patients are frequently treated with multiple other medications which may interact with the anti-epileptic drugs.[42-44] This may also result in pharmacodynamic interactions which lead to side effects or seizures.[41] Drug toxicity may become more difficult to evaluate and manage under these circumstances. Similar considerations may apply in some elderly patients.[45] Under these circumstances, it is appropriate to try to reduce the number of anti-epileptic drugs.

The framework described above is intended to provide a guide for clinical decision making, however, successful management requires individualization of drug therapy for each patient (Table 2).

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