Review article

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Rational conversion from antiepileptic polytherapy to monotherapy

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ABSTRACT – For patients with epilepsy, the goal of treatment is to achieve seizure freedom with minimal or no adverse events. Around 60%-70% of newly diagnosed patients will achieve this goal with single antiepileptic drug (AED) therapy, and there is universal agreement that prescription of a single agent constitutes best practice for such patients. For the 30%-40% of patients with poorly controlled epilepsy, treatment options are less clear and many receive add-on therapy with one or more AEDs in an attempt to improve seizure control. Because the therapeutic gain from adjunctive therapy is often marginal and may be complicated by increased drug toxicity, converting individual patients from polytherapy to monotherapy is a common clinical problem facing physicians managing patients with epilepsy today. Evidence from studies with both standard and new AEDs shows that selected patients, including those with previously resistant epilepsy, can be converted successfully from polytherapy to monotherapy without loss of seizure control and in some cases with improved seizure control. Adverse effects can be minimised during the conversion process by slow withdrawal of the first prescribed drug, while increasing the daily dose of the add-on AED to achieve optimal therapeutic doses/levels for continued monotherapy. Deciding which drug(s) to withdraw and which to continue as monotherapy requires adequate consideration of individual patient needs with reference to clinical profiles (seizure type and severity), previous response to individual AEDs and the pharmacokinetic and pharmacodynamic implications of withdrawal.

KEY WORDS: antiepileptic drugs, epilepsy, monotherapy, polytherapy

It is widely accepted that newly diagnosed epilepsy is best managed, whenever possible, with a single antiepileptic drug (AED) [1]. Indeed, AED monotherapy leads to seizure control in approximately 60% to 70% of newly diagnosed patients. These figures include those patients who have required dose adjustments to optimise seizure control as well as those switched to another drug because of poor tolerability of the first AED [2-5]. However, for the 30% to 40% of patients who fail to respond to AED monotherapy, the therapeutic strategies are less clear. While one strategy is to continue monotherapy with alternative AEDs, the other is to combine two drugs thus initiating polytherapy for those patients with persistent seizures. For the most resistant patients further treatment escalation may be needed, often leading to three-drug treatment regimens. By combining drugs with similar, overlapping or different modes of action, AED polytherapy has the potential to improve seizure control and possibly achieve

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higher rates of seizure freedom than monotherapy alone. However, the extent to which AED combinations in practice provide superior seizure control appears variable between different add-on studies, raising concerns that some patients may be over-treated [6].

Furthermore, adverse effects and pharmacokinetic interactions may become more frequent as the drug burden is increased [7, 8]. This can complicate the management of epilepsy and is undoubtedly the most significant drawback to polytherapy. Other drawbacks include difficulties in determining individual drug actions, more complex dosage regimens, poorer treatment compliance and increased treatment costs [9]. For these reasons, polytherapy regimens should always be re-assessed in terms of each drug's contribution to efficacy and the benefit-to-risk ratio of increased drug loads. Whenever possible such regimens should be simplified.

Among the variety of situations in which clinicians consider the reduction or simplification of antiepileptic therapy, the conversion from two AEDs to one is a common procedure. This does not imply, however, that it is always simple and easy to perform, and while there are compelling arguments in favour of converting to monotherapy, it may not prove suitable for all patients. The aim of converting to monotherapy is usually to gain safety and tolerability while maintaining the same level or quality of seizure control. However, conversion to monotherapy can also be used in the design of regulatory trials that aim to demonstrate efficacy in a monotherapy setting, as seen in studies with most new AEDs.

This paper reviews the benefits and the risks of converting to monotherapy as well as the conversion studies published in the literature and their regulatory value. Practical issues such as the criteria for conversion to monotherapy, consideration of which drug to withdraw, how to proceed with conversion therapy and determining the target dosage for monotherapy are also reviewed.

Risks and benefits of conversion to monotherapy

The major risk of converting a patient to monotherapy is losing the benefits of combination therapy. Patients and physicians are often reluctant to consider AED withdrawal to monotherapy for fear of reducing efficacy, such as the loss of seizure freedom if previously obtained, a return to the level of seizure control that had necessitated add-on therapy, or even an exacerbation of seizures. However, the extent to which AED combinations in practice provide superior antiepileptic action is often difficult to evaluate.

Improvement in seizure control with combination therapy

A study of the sequential response to carbamazepine and phenytoin in 100 patients with adult-onset seizures found that of the 50% of patients who failed to respond to initial treatment, 17 (34%) became seizure-free when treated with the alternative drug. However, only five (15%) of the 33 patients not completely controlled by monotherapy with either drug became seizure-free when treated with a combination of carbamazepine and phenytoin [10]. In a prospective trial in 30 adult patients with complex partial seizures who had failed first-line therapy, add-on treatment with the most promising combination of drugs produced a 75% reduction in seizure frequency in only four (13%) patients, while the remaining 87% derived no benefit. In three patients, seizure frequency actually increased with polytherapy [11]. More recently, a study of 470 patients with newly diagnosed epilepsy treated with a range of AEDs found that 47% of patients responded to the first AED, and 14% when a second was substituted. By contrast, only 3% became seizure-free following combination therapy with established AED combinations, often administered at maximal dosage [5].

Higher response rates to polytherapy have been observed in a sequential study into the effects of combining carbamazepine with vigabatrin in patients who had failed previous monotherapy with these agents [12]. The 36% seizure-free rate obtained with co-administration of carbamazepine and vigabatrin in the 14 patients who had failed prior monotherapy is mirrored by results from another study in which 35% (6/17) of patients with refractory seizures achieved seizure-free status when treated with a combination of carbamazepine and valproate [13]. Seizure-freedom was obtained in 31% and 39% of patients with partial epilepsy who had failed initial AED monotherapy, when gabapentin and vigabatrin respectively were used as first-line add-on treatments [14].

In more refractory patients, the add-on controlled studies conducted with the new AEDs showed that the gain in seizure control ranged from approximately 20% to 50% of responders at 50% seizure frequency reduction, while the percentage of patients achieving seizure-freedom was low (0% to 8%) [15]. These figures relate to relatively short follow-up periods, often of only 3 months, and these benefits should be evaluated on a longer term [16]. It should be remembered that such studies, conducted with new AEDs in refractory patients, are performed as a regulatory requirement for the initial evaluation of new AEDs.

The advantages of converting patients to monotherapy include not only fewer side effects, lower toxicity, a lower risk of teratogenicity and the avoidance of adverse pharmacokinetic and pharmacodynamic drug interactions but also simpler dosage regimens, easier management, better compliance and often reduced treatment costs [9]. In addition to these well known benefits, some studies suggest that reducing the AED regimen from two drugs to one drug may also result in better seizure control [17, 18].

Table 1. Summary of conversion to monotherapy studies with standard AEDs.

Study	N converted/syndrome	Drugs	Follow-up in months	"Successful" without increase in seizure frequency	Reduction in seizure frequency	"Unsuccessful"
Shorvon, 1979	40 mixed syndromes	PB, PMD, PHT, CBZ, VPA	12	24 (60%)	16 (66% of the 24)	16 (40%) Pre-status in 1
Schmidt, 1983	36 partial epilepsies	PB, PMD, PHT, CBZ	12	30 (83%)	13 (36% of the 30)	6 (17%)
Albright, 1985	90 mixed syndromes	PB, PHT, PMD	16	Reduction in 72 (80%), to one drug in 39	10 (11% of the 72)	18 (20%)

Conversion to monotherapy with standard AEDs

Conversion studies have shown that patients can be successfully converted from polytherapy to monotherapy with carbamazepine without loss of seizure control and indeed, in some cases improved seizure control [19-21]. Among 35 patients on various multi-drug regimens (19, 2-drug regimens; 13, 3-drug regimens and 3, 4-drug regimens) with a mean seizure frequency of 15 per month, conversion to monotherapy resulted in an improvement in seizure control in 54% of patients. Of the 21 patients successfully converted to monotherapy, 13 had previously been on a 2-drug regimen, seven a 3-drug regimen and one on a 4-drug regimen. Conversion to carbamazepine monotherapy was achieved in 19 (54%) patients, while a further two were converted to monotherapy with phenytoin and valproate [19]. Improved seizure control on monotherapy in this study was primarily attributed to the achievement of optimal blood levels of carbamazepine, phenytoin, and valproate during the withdrawal phase.

Schmidt [17], in a prospective study of 36 patients with intractable complex partial seizures receiving two-drug therapy, showed that it was possible to convert 83% of these difficult-to-treat patients to monotherapy without loss of seizure control *(table 1)*.

Interestingly, in 13 patients (36%) seizure control improved on monotherapy, while two became completely seizure-free and one experienced an 87% reduction in seizure frequency. Importantly, the study showed that there was no increase in generalised tonic-clonic seizures or status epilepticus during either the withdrawal or subsequent monotherapy phase. Nystagmus, sedation, ataxia and vertigo were the most common side effects seen and were experienced by patients similarly during both treatment phases *(table 2)*. Albright and Bruni [18] reported a similar level of success in a study of 90 epileptic patients maintained on polytherapy for at least 6 months *(table 1)*. Reduced polytherapy was achieved in 80% of patients, 39 (54%) of whom converted to monotherapy without loss of seizure control and in some cases improved seizure control. Again there was an improvement in tolerability, particularly in the neuropsychological domain [20], as drug burden decreased.

While the notion that seizure control may be improved by reducing drug load is interesting, these studies are difficult to interpret due to the absence of blinding. Many patients had combinations of phenobarbital, phenytoin, or primidone at substantially toxic levels [17], which alone can cause seizure aggravation. Furthermore, some studies may have included patients with generalised epilepsy [18], whose condition could have worsened with phenytoin for example and then improved, simply because of phenytoin withdrawal.

Table 2. Frequency of clinical side effects following conversion from AED polytherapy to monotherapy in patients with intractable complex partial seizures [18].

Side effect	Polytherapy* (*n* = 36)	Monotherapy** (*n* = 36)
Nystagmus	16	13
Sedation	7	5
Ataxia	8	3
Diplopia	3	1
Vertigo	2	3
Nausea	0	2
Anxiety	1	1
Gingival hyperplasia	1	0
Fever	1	0
Exanthema	1	0
Myoclonias	0	1
Myalgia	0	1
Tremor	0	1
Vomiting	1	0
Total	41	31

* Total number of side effects during the polytherapy phase
** Total number of side effects following conversion to monotherapy

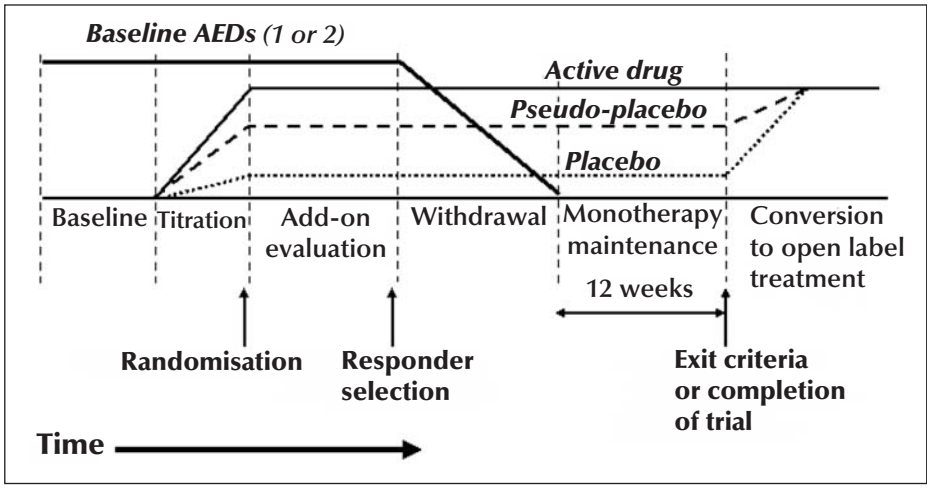

Figure 1. *Typical conversion to monotherapy study design*
Note. A pseudo-placebo arm was employed in most of the studies while a placebo arm was employed in the levetiracetam study.

Overall, the conversion to monotherapy studies with phenobarbital, primidone, phenytoin and carbamazepine, and to a lesser extent valproate, have shown that over a 12 to 16 month follow-up period, 72% to 83% of patients converted without loss of seizure control, while aggravation occurred in between 17% and 28% of patients.

Conversion to monotherapy studies with new AEDs

More recently, most of the new AEDs including lamotrigine, gabapentin, tiagabine, topiramate, felbamate, oxcarbazepine, and levetiracetam have been evaluated in conversion to monotherapy trials, with the aim of assessing evidence of efficacy in a monotherapy setting.

Despite minor variability, these studies had a uniform design, such as that employed with levetiracetam [22], which includes several consecutive phases as shown in *figure 1*. Refractory partial epilepsy patients with several seizures per month are recruited and seizure frequency assessed during the baseline phase. Patients then receive an add-on test drug, followed by a titration phase and subsequent maintenance period. At the end of the maintenance period (add-on evaluation), responders are selected according to a predefined level of response, and first-line drugs gradually withdrawn (withdrawal phase). This leads into the monotherapy maintenance period where efficacy can be evaluated.

There are several problems with this type of study design. The main difficulties arise from the necessity to demonstrate the statistical superiority of the study drug in one arm of the trial against the control arm. In the levetiracetam conversion to monotherapy study, a placebo arm was used as a control [22]. In all the other studies, patients randomised to the control arm received either a low dose of an established AED or a low dose of the test drug. At the sub-optimal doses used, treatment was considered ineffective enough to allow for statistical superiority of "active treatment" to be demonstrated [23]. However, treating outpatients with severe epilepsy with a voluntarily sub-optimal dosage of a single drug, even when the sub-optimal treatment is intended to prevent severe seizure worsening, raises ethical issues. One way to address these problems is to select patients carefully, avoiding those at risk of severe complications. Escape criteria can also be used to prevent too much deterioration in seizure control. They often include a doubling of the highest 2-day seizure rate calculated from the baseline, a doubling of the highest monthly seizure rate, pre-status epilepticus or status, and emergence of a more severe seizure type, particularly a generalised tonic clonic seizure when absent at baseline [24]. In the levetiracetam study, where the control group received placebo, certain measures (respecting blinding), were taken to limit the number of placebo-responders who were actually converted to placebo alone at the end of the add-on period [22].

Another difficulty is that not all these studies have been successful. The outcome measures generally consisted of a comparative analysis of the completer rate, or time to exit, or both, taking as reference the population actually selected for the conversion phase at the end of the add-on period. Whereas studies such as the felbamate 3 600 mg/day *versus* valproate 15 mg/kg/day [25, 26], lamotrigine 500 mg/day *versus* valproate 1 000 mg/day [27], oxcarbazepine 2 400 mg/day *versus* 300 mg/day [28,29], topiramate 1 000 mg/day *versus* 100 mg/day [30] showed superiority, others have failed to do so. These include the gabapentin 600 mg *versus* 1 200 mg *versus* 1 800 mg [31] and the tiagabine 36 mg *versus* 6 mg [32], studies.

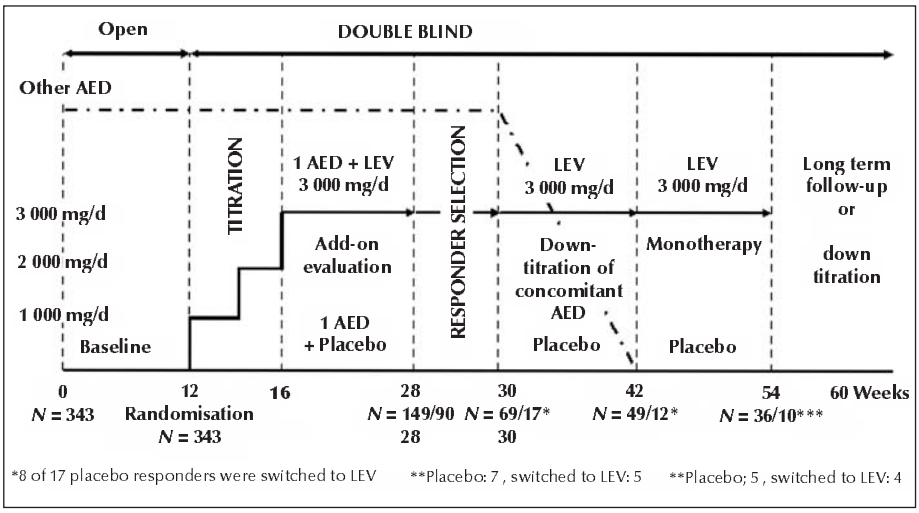

Figure 2. *Placebo-controlled conversion to monotherapy with levetiracetam: Patient disposition (reproduced with permission from Ben-Menachem* et al.*, Epilepsia* 2000 [22]).

One reason for these difficulties in demonstrating efficacy is the marked reduction in the study population at each successive phase of the study, which can leave the study statistically under-powered. It was notable that the percentage of patients who met exit criteria and dropped out of the pseudo-placebo arm in these studies was very high, ranging from 69% to 93% [24]. The percentages of patients exiting the study were also high among the patients in the active or high dosage groups, ranging from 19 to 82% [33].

The progressive enrichment of the population can be well appreciated in the levetiracetam study. Of the 181 and 105 patients randomised to add-on levetiracetam 3000 mg/day or placebo respectively, 36 (19.9%) and 10 (9.5%) completed the trial ($P = 0.029$) *(figure 2)* [22]. The analysis was however different from the other studies, as the reference was the population initially randomised to the add-on phase and therefore evaluation was performed simultaneously on both the add-on response and the conversion to monotherapy success. The quality of control may be very satisfactory in this highly selected subgroup of patients. Compared with baseline, the 49 patients on levetiracetam monotherapy achieved a median reduction in seizure frequency of 74%, while the responder rate was 59%. Additionally, some of these patients remained seizure-free, suggesting that monotherapy with new drugs may be a realistic objective for certain patients who are initially difficult to control.

From a regulatory point of view these conversion to monotherapy trials have several disadvantages. At around 12 weeks, the maintenance period is too short to be of relevance to clinicians considering AED treatment for newly diagnosed patients. Efficacy parameters tend to assess a predefined level of aggravation, which allows completers to have some degree of deterioration. Study completers represent an enriched fraction of the randomised population at each successive phase of the study, which leads to an irrelevant intent to treat (ITT) analysis. Results may also be partly confounded by withdrawal phenomena, in which the baseline drug being discontinued is possibly more relevant to the result than the effects of the new drug which is maintained. Finally, the doses tested in the add-on phase and continued in conversion to monotherapy are often high daily dosages and may not always represent the dose range that will be used in the wider monotherapy setting.

In spite of these difficulties, these conversion to monotherapy studies have the advantage of reproducing real clinical practice. When positive, they do represent a first level of unequivocal efficacy in a monotherapy setting [33]. However, it is important to bear in mind that they do not provide information about the effectiveness of the drug in the patient populations most suited to monotherapy (*i.e.*, patients with less severe epilepsy than the difficult-to-treat patients usually enrolled in these studies). The fact that results for all the pseudo-placebo groups were similar for the different studies has led to suggestions that a meta analysis from these figures could be used as historical control in future studies. This suggestion, currently in discussion, would eliminate most of the ethical concerns associated with studies of this design [24].

Clinical situations and practical issues

Selecting patients for conversion to monotherapy

Many patients currently receiving two-drug treatment are potential candidates for conversion to monotherapy. A recent survey showed that of 1617 patients on AED therapy who had been seizure-free for at least 12 months,

Table 3. AED combinations with potentially positive pharmacodynamic interactions [38].

Combination	Seizure type	Level of evidence
Valproate-carbamazepine	Partial	Extensive clinical experience but few controlled studies
Valproate - ethosuximide	Absence	Well documented
Valproate - lamotrigine	Various	Well documented
Carbamazepine - vigabatrin	Partial	Speculative
Lamotrigine - vigabatrin	Partial	Controversial
Tiagabine - vigabatrin	Partial	Anecdotal
Gabapentin - lamotrigine	Partial	Anecdotal
Lamotrigine - topiramate	Partial	Anecdotal

21% were taking two or more AEDs; 287 on two (86%), 42 on three (13%), three on four (1%) [34]. Patients who have achieved seizure-free status on combination therapy are first line candidates for drug simplification. Other potential candidates include patients who have failed several attempts at add-on therapy when priority should be given to tolerability if the persisting seizures are not too severe [35].

In selecting patients for conversion from polytherapy to monotherapy, the history of response to add-on therapy is important. It is also important that when considering conversion to monotherapy patients should be fully informed and counselled of the objectives of such a treatment change and of the potential outcomes and risks. The decision to attempt monotherapy should then be made by the physician only with the patient's understanding and agreement, essential factors for a successful outcome. Those in whom seizure control is relatively easily obtained and whose seizures are not too severe are good candidates for attempting monotherapy, while those with a history of fluctuating symptoms may find polytherapy beneficial during exacerbations but monotherapy preferable during periods of remission. Patients with poor tolerance to polytherapy due to systemic adverse events from one of the combination of drugs or adverse neurological effects from both are also candidates for conversion to monotherapy. Life-style factors should be taken into account. Conversion to monotherapy should be systematically considered for those entering school or university, for people whose work involves driving, for women planning a pregnancy and for those with cognitive impairment or other handicaps. The latter are often at high risk of being over-treated [36].

Avoiding interactions may be the primary objective, and elderly patients are frequent candidates, as many are on co-medications with the potential to interact with AEDs. The patient's perception of their illness is an important factor and account should be taken of patient concerns about having treatment reduced as well as their willingness to accept the implications of a change in treatment.

Deciding which drug to withdraw

Deciding which drugs to withdraw and which to continue as monotherapy is obviously essential for successful conversion therapy. The patient's previous experience of and response to each drug in the regimen and the long-term evolution of this response are important criteria. A correlation between a given adverse effect and one drug in the polytherapy regimen drug may be a clear indication. Other essential criteria include the spectrum of drug activity in relation to clinical syndrome, and seizure type. Is there a rational way to simplify AED treatment, analogous to rational combination therapy? [37]. It is difficult to see how drugs suitable for conversion to monotherapy can be selected as a function of their mode of action. Certainly, there is no evidence-base for preferring, for instance, a sodium channel blocker to drugs with alternative mechanisms of action, provided the spectrum of activity is appropriate. The potential pharmacodynamic interactions of the combination regimen should nevertheless be taken into account. Certain combinations may be additive (but respective contributions may be unequal), certain may be supra-additive (synergistic), while others may display adverse pharmacodynamic interactions *(table 3)* [38].

This is nicely illustrated in a study in which patients not fully controlled with sodium valproate (n = 117), carbamazepine (n = 129), phenytoin (n = 92) or phenobarbital (n = 9) monotherapy were recruited into a conversion to lamotrigine monotherapy study [39]. If 50% or more seizure reduction occurred (responders) following the addition of lamotrigine to ongoing baseline therapy, an attempt was made to withdraw the original AED. If successful, patients continued with 12 weeks of lamotrigine monotherapy. Interestingly, patients on valproate-lamotrigine combination therapy behaved differently from those under other combinations in that they reached a higher level of seizure control during the combination phase, but showed a tendency to aggravate after withdrawal of valproate. This was in spite of the higher lamotrigine concentrations obtained during the withdrawal phase. The synergism between valproate and lamotrigine, which has been de-

scribed in other studies [40], illustrates that in certain situations conversion to monotherapy may give less satisfactory results.

As a general rule adverse effects can be minimised during the conversion process by slow withdrawal of the first-line drug, while at the same time increasing the daily dose of the add-on AED to raise plasma concentrations to optimal therapeutic levels for continued monotherapy.

Determining target dosage in conversion to monotherapy

Because pharmacokinetic interactions are common when two or more AEDs are given concomitantly, dosage adjustment is frequently needed during conversion to monotherapy. This is illustrated in a conversion to monotherapy study in which 156 patients with partial seizures receiving first-line carbamazepine or phenytoin monotherapy subsequently received add-on therapy with either lamotrigine or valproate [27]. In the lamotrigine arm of the study, carbamazepine or phenytoin was gradually withdrawn (20% decrements per week) from the 76 patients once a target dose of lamotrigine 500 mg/day had been reached. Carbamazepine and phenytoin are enzyme inducers and can increase the rate of lamotrigine clearance and so influence attainable levels in serum. A subsequent analysis of the time course of de-induction following the step-wise withdrawal of carbamazepine or phenytoin indicated that lamotrigine concentrations would not start to increase until the concomitant enzyme inducer had almost completely disappeared [41].

In another study, Sachedo *et al*. [42] have shown that the addition of topiramate to phenytoin generally does not cause clinically significant pharmacokinetic interaction. Phenytoin, however, induces the metabolism of topiramate, causing increased topiramate clearance, which may require dose adjustments when phenytoin is discontinued from a regimen containing topiramate.

Clearly, dosages should be adapted and increased if necessary in conversion to monotherapy but it is important this is not done at the risk of reaching toxic levels of the single drug. In the study by Schmidt [17] described earlier, the dosages of phenytoin used after conversion were too high and caused toxicity by themselves, in spite of the treatment simplification. Moderate daily dosages of two drugs may sometimes be better tolerated than very high dosages of a single drug.

Conclusions

Monotherapy has many advantages over polytherapy and, because the risk of drug-induced side effects is lower, the risk-to-benefit ratio generally favours monotherapy for the majority of patients. As this review illustrates, many patients well controlled on two or more AEDs can be successfully converted from polytherapy to monotherapy without loss of seizure control using both standard AEDs and newer AEDs. Importantly, reduced toxicity with monotherapy generally leads to improved tolerability, while improvements in neuropsychological status may be an additional benefit and can lead to improvements in patient well being. □

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