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Randomised controlled monotherapy trials: which comparators to use?*

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ABSTRACT – As approximately 50% of patients with newly diagnosed epilepsy achieve seizure remission after initial monotherapy, the selection of the first-choice drug to be used as the gold standard in randomised clinical trials is critical. Several first and second generation drugs have been used in regulatory and pragmatic monotherapy trials with similar efficacy but differing pharmacokinetic, tolerability, and safety profiles. None of the available compounds has an ideal profile and second generation drugs do not appear to present unequivocal advantages in this regard. Compared to first generation drugs, some newer generation antiepileptic drugs may be preferred as they have similar efficacy but lower potential for idiosyncratic reactions and drug interactions. However, more recent antiepileptic drugs also have limitations, which include lack of superiority and, in some cases, unbearable adverse effects. In this light, there are no standard criteria as a reference for the selection of the best comparator for new monotherapy trials. However, according to the recommendations of evidence-based guidelines, carbamazepine still represents the first-choice drug for patients with partial epilepsy. Ethosuximide may be an option for absence epilepsy. In contrast, for the treatment of patients with other generalised epilepsies, there is no clear indication of preferred drug, as valproate, which has been found to prevail over other compounds, should be withheld in women of childbearing age due to its teratogenic potential, and there is insufficient evidence to choose an alternative drug.

Key words: clinical trial, epilepsy, antiepileptic drugs, monotherapy

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Epilepsy is a complex disorder, determined by several different clinical conditions and characterised by heterogeneous seizure types, some of which respond to different drugs (Stein and Kanner, 2009). Approximately 50% of patients with newly diagnosed epilepsy achieve seizure remission after initial monotherapy (Kwan and Brodie, 2001). For this reason, the choice of the first-line drug for the start of treatment is critical. Several first and second generation drugs have been used in regulatory and pragmatic monotherapy trials. Second generation antiepileptic drugs represent an advance in the development of more manageable products and control of adverse drug reactions of older compounds. However, despite the development of several new antiepileptic drugs, the efficacy and tolerability of drug treatment of epilepsy has not substantially improved in terms of effectiveness, risk-benefit, and cost-benefit profile (Beghi *et al*., 2011). More recent antiepileptic drugs are, at best, equivalent in efficacy to their predecessors, but some of them are more manageable and better tolerated. This background information should direct the choice of comparators for new monotherapy trials, which must be made with reference to a number of variables, among which indicate: efficacy, safety and tolerability, minimal effective dose, pharmacokinetic profile, and ease of use (for treatment of partial or generalised seizures).

To what extent do available drugs match the characteristics of the ideal comparator in monotherapy trials

A drug given as initial monotherapy to a patient with newly diagnosed epilepsy should have unequivocal efficacy, tolerability, and safety, documented by evidence-based reports. The pharmacokinetic profile should be optimal. The drug should not interact with other compounds and have no substantial impact on cognitive functions. Daily administration should be easy and the teratogenic potential should be negligible. In this regard, the available compounds, although varied, are far from ideal (*table 1*). First generation compounds are effective and safe but not always well-tolerated. In addition, a suboptimal pharmacokinetic profile is reflected by hepatic metabolism and microsomal enzyme induction. In this regard, pharmacokinetic interactions may be present and sometimes clinically relevant (Johannessen and Landmark, 2010). In addition, all marketed compounds are teratogenic and there is a documented risk increase with dose and polytherapy (Tomson *et al*., 2011; Harden *et al*., 2009). Second and third generation compounds are effective and fairly safe, however, tolerability is frequently dose-related. The pharmacokinetic profile of new generation drugs is, with some exceptions, better than that of older compounds, but the teratogenic potential is not yet fully elucidated.

Comparative efficacy of antiepileptic drugs

Several first and second generation antiepileptic drugs have been compared for efficacy, safety, and tolerability in randomised regulatory and pragmatic trials. Carbamazepine and lamotrigine have been the object of the majority of the head-to-head comparisons. In most instances, no major differences were found in terms of retention time, time to first seizure, and achievement of prolonged seizure remission (Beghi *et al*., 2011) (*table 2*). Two large randomised, controlled, pragmatic trials (the Standard and New Antiepileptic Drugs [SANAD] trials) in newly diagnosed epilepsy have been conducted mostly in the United Kingdom (Marson *et al*., 2007a; Marson *et al*., 2007b). In the first trial (SANAD A), with enrolled children and adults with partial-onset seizures, lamotrigine was the most effective drug compared to carbamazepine, oxcarbazepine, topiramate, and gabapentin (Marson *et al*., 2007a). Lamotrigine was also found to be superior in efficacy

Table 1. Old and new AEDs and the criteria for an ideal comparator in monotherapy trials.

Parameter	PB	PHT	CBZ	VPA	GBP	LEV	LTG	OXC	TPM	VGB
Efficacy	++	++	++	++	+	++	++	++	++	++
Tolerability & safety	+	+	+	+	++	++	++	++	+	-
Optimal PK profile	+	-	+	+	+	++	++	+	+	++
No interactions	-	-	-	+	++	++	++	+	+	++
No impact on cognition	-	+	+	-	++	++	++	++	-	++
Ease of use	++	-	++	++	+	++	++	++	++	++
Minimal/no teratogenicity	+	+	+	-	?	?	++	?	?	?

CBZ: carbamazepine; GBP: gabapentin; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; TPM: topiramate; VGB: vigabatrin; VPA: valproate; ++: parameter fully met; +: parameter partially met; -: parameter unmet.

Table 2. Comparative efficacy of first and second generation antiepileptic drugs as monotherapy for partial or (^) generalised/unclassified seizures.

Reference	Comparator (daily dose/mg)	HR (95% CI) or % difference for time to treatment withdrawal (*)	HR (95% CI) for time to first seizure
Marson *et al*., 2007a	GBP (1,200) *vs* CBZ (600) †	1.21 (0.99-1.48)	0.75 (0.63-0.90)
Brodie *et al*., 1995	LTG (150) *vs* CBZ (600)	0.74 (0.41-1.34)	1.45 (0.87-2.43)
Brodie *et al*., 1995	LTG (150) *vs* CBZ (600)	0.42 (0.21-0.85)	1.10 (0.69-1.76)
Reunanen *et al*., 1996	LTG (100) *vs* CBZ (600)	NA	1.37 (0.90-2.09)
Reunanen *et al*., 1996	LTG (200) *vs* CBZ (600)	NA	1.07 (0.69-1.64)
Brodie *et al*., 1999	LTG (100) *vs* CBZ (400)$_{§}$	0.31 (0.16-0.60)	0.90 (0.55-1.46)
Nieto-Barrera *et al*., 2001	LTG (200) *vs* CBZ (600) +	0.77 (0.49-1.21)	1.19 (0.83-1.71)
Saetre *et al*., 2007	LTG (93) *vs* CBZ (373)	0.77 (0.45-1.31)	1.50 (0.94-2.40)
Marson *et al*., 2007a	LTG (150) *vs* CBZ (600) †	0.78 (0.63-0.97)	0.91 (0.77-1.09)
Marson *et al*., 2007b	LTG (150) *vs* VPA (1,000) ^†	1.25 (0.94-1.68)	0.76 (0.62-0.94)
Brodie et al., 2007	LEV (1,000) *vs* CBZ (400)	0.2 (-7.8-8.2)*	No difference°
Marson *et al*., 2007a	OXC (900) *vs* CBZ (600) †	1.04 (0.78-1.39)	0.92 (0.73-1.18)
Privitera *et al*., 2003	TPM (100/200) *vs* CBZ (600)/VPA (1,250)	3.0 (-6.1-12.1)	No difference°
Marson *et al*., 2007a	TPM (150) *vs* CBZ (600) †	1.22 (0.99-1.49)	0.86 (0.72-1.03)
Marson *et al*., 2007b	TPM (150) *vs* VPA (1,000) ^†	1.57 (1.19-2.08)	1.93 (0.76-1.15)
Chadwick, 1999	VGB (2,000) *vs* CBZ (600)	0.83 (0.57-1.20)	1.79 (1.33-2.40)

HR: hazard ratio; 95% CI: 95% confidence interval; CBZ: carbamazepine; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PHT: phenytoin; TPM: topiramate; VGB: vigabatrin; VPA: vaproate; †: dose for adults; +: most common dose; $_{§}$: median dose; °: measures of risk unavailable.

to pregabalin in a head-to-head monotherapy trial for the treatment of newly diagnosed epilepsy with partial seizures in adults (Kwan *et al*., 2011). In the second SANAD trial (SANAD B), with enrolled children and adults with primarily generalised or undetermined seizures, valproate was found to be more effective than lamotrigine and topiramate (Marson *et al*., 2007b). In this latter study, the efficacy of valproate was even greater in patients with idiopathic generalised seizures. However, although the results of the SANAD studies give some practical indications on the first-choice treatment for partial and generalised/undetermined seizures, evidence is still insufficient for lamotrigine and valproate as the best comparators for monotherapy trials in patients with partial or generalised seizures, respectively. In the SANAD A trial, carbamazepine, if well-tolerated, was associated with the highest rates of 12-month remission (Bonnett *et al*., 2012). In addition, both SANAD studies have been criticised (French, 2007; Panayiotopoulos, 2007) to have relevant methodological defects, including the enrolment of heterogeneous study populations, a suboptimal diagnosis (which favoured broad-spectrum drugs), unpredicted titration rates, and the inclusion of compounds with high teratogenic potential. As shown in a meta-analysis of randomised trials comparing lamotrigine to carbamazepine (Gamble *et al*., 2006), the purported superiority of lamotrigine might be explained by an inadequate dose of the comparator and the use of standard, rather than slow-release, carbamazepine.

Data on the most effective drug for the treatment of selected epilepsy syndromes are few and mostly supported by poorly designed studies (*see below*). In a recent randomised monotherapy trial comparing ethosuximide, lamotrigine, and valproate in children with absence epilepsy (Glauser *et al*., 2010), the freedom-from-failure rates for ethosuximide and valproate were similar (53 and 58%, respectively) and were higher than the rate for lamotrigine (29%).

Comparative safety and tolerability of antiepileptic drugs

As the comparative efficacy of first and second generation antiepileptic drugs is similar, the tolerability and safety profile of each compound becomes

of paramount importance to direct the physician's choice. Compared to established compounds, the safety of several recently approved drugs has been tested in a limited number of individuals and for a limited period of time. In this regard, long-term toxicity and rare adverse events cannot be documented unless sufficient time has elapsed following treatment and the number of exposed individuals has increased to critical levels. This information is important in the context of monotherapy trials because they may involve large patient cohorts treated for prolonged periods of time. Teratogenicity is also an issue, as there is increasing evidence that even the more recent antiepileptic drugs have a teratogenic potential (Tomson *et al*., 2011), which is documented only after a number of exposures considered sufficient to detect a two to threefold risk.

The large SANAD studies provide a valuable example of the comparative tolerability profiles of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, and topiramate in patients with newly diagnosed partial epilepsies (Marson *et al*., 2007a) and those of valproate, lamotrigine, and topiramate in patients with newly diagnosed generalised and unclassifiable epilepsies (Marson *et al*., 2007b). The overall incidence of adverse events with these drugs and the incidence of selected complaints (drowsiness, rash, memory impairment, vertigo, behaviour abnormalities, and ataxia), as reported in the SANAD studies, is illustrated in *table 3*. In this regard, the proportion of cases reporting adverse events is fairly similar but differences can be found when specific events are considered. In general, lamotrigine carried the lowest adverse event rates and topiramate the highest rates. However, 15% of patients with partial epilepsy and 12% of those with generalised/unclassifiable epilepsy receiving lamotrigine reported rash. Drowsiness peaked with carbamazepine, valproate, and topiramate (33-36%) in patients with partial epilepsy and with topiramate (20%) in those with generalised/unclassifiable epilepsy. Carbamazepine carried the highest risk of rash (32%), gabapentin and topiramate the highest risk of memory complaints (19%), and gabapentin the highest risk of ataxia (12%). In the same studies, the proportion of patients with partial epilepsy discontinuing treatment for adverse events ranged from 7.9% with lamotrigine to 18.0% with topiramate (*table 4*). Treatment discontinuation for adverse events in patients with generalised/unclassifiable epilepsy ranged from 3.8% (lamotrigine) to 9.6% (topiramate). Levetiracetam, which was not used in the SANAD studies, was compared to controlled-release carbamazepine in a recent randomised trial (Brodie *et al*., 2007) which showed identical time to withdrawal and similar tolerability profile, except for depression and insomnia, which were most prevalent with levetiracetam (relative risk [95% confidence interval]: 3.06 [1.23-7.61] and 2.48 [1.04-5.89], respectively).

In the comparative monotherapy trial on children with absence epilepsy, ethosuximide was discontinued due to adverse events in 24% of cases, lamotrigine in 17%, and valproate in 24% (Glauser *et al*., 2010) (*table 5*). Neurological, behavioural, and psychological adverse events were predominant with valproate (57%), digestive symptoms with ethosuximide (24%), rash with lamotrigine (20%), and fatigue with valproate (14%).

Guidelines for the use of monotherapy in the treatment of newly diagnosed epilepsy

To translate the available evidence into recommendations for the use of monotherapy in clinical practice, the International League Against Epilepsy (ILAE) issued evidence-based guidelines focusing on the efficacy of

Table 3. Selected adverse events in the SANAD studies.

Drug	Total *n* (%)	Drowsy *n* (%)	Rash *n* (%)	Memory *n* (%)	Vertigo *n* (%)	Ataxia *n* (%)
CBZ*	183 (48)	48 (36)	38 (32)	20 (12)	14 (10)	9 (6)
GBP*	178 (47)	46 (34)	13 (4)	22 (19)	23 (15)	24 (12)
LTG*	169 (45)	31 (17)	17 (15)	13 (10)	15 (9)	14 (9)
OXC*	100 (48)	22 (16)	20 (16)	13 (8)	13 (12)	8 (6)
TPM*	200 (53)	43 (33)	17 (8)	26 (19)	15 (8)	9 (3)
LTG**	88 (37)	15 (9)	13 (12)	2 (2)	6 (4)	4 (3)
TPM**	107 (45)	25 (20)	1 (1)	12 (10)	20 (18)	3 (2)
VPA**	85 (36)	18 (12)	2 (0)	3 (0)	4 (4)	2 (2)

CBZ: carbamazepine; GBP: gabapentin; LTG: lamotrigine; OXC: oxcarbazepine; TPM: topiramate; VPA: valproate; *Marson *et al*., 2007a; **Marson *et al*., 2007b.

Table 4. Unacceptable adverse events in the SANAD studies.

Drug	No. cases/exposed (%)	Mean daily dose (SD)	Min/Max
CBZ*	50/37 (13.2)	546 (189)	200-1,000
GBP*	35/377 (9.9)	1,366 (636)	400-3,000
LTG*	30/378 (7.9)	178 (113)	25-550
TPM*	68/378 (18.0)	137 (77)	25-400
OXC*	29/210 (13.8)	895 (351)	300-2,100
LTG**	9/239 (3.8)	119 (99)	25-300
TPM**	23/239 (9.6)	172 (110)	50-500
VPA**	13/238 (5.5)	838 (240)	500-1,200

CBZ: carbamazepine; GBP: gabapentin; LTG: lamotrigine; OXC: oxcarbazepine; TPM: topiramate; VPA: valproate; *Marson *et al*., 2007a; **Marson *et al*., 2007b.

Table 5. Adverse events leading to discontinuation of drugs administered for absence epilepsy.

Event	ESM *n* (%)	LTG *n* (%)	VPA *n* (%)
Total	37/154 (24)	25/146 (17)	35/146 (24)
Neurological Behavioural Psychological	12/37 (32)	9/25 (36)	20/35 (57)
Digestive	9/37 (24)	3/25 (12)	6/35 (17)
Rash	6/37 (16)	5/25 (20)	2/35 (6)
Fatigue	3/37 (8)	2/25 (8)	5/35 (14)
Headache	3/37 (8)	2/25 (8)	2/35 (6)

ESM: ethosuximide; LTG: lamotrigine; VPA: valproate. Source: Glauser *et al*., 2010.

antiepileptic drugs given as monotherapy in patients with newly diagnosed or previously untreated epilepsy (Glauser *et al*., 2006). In a critical appraisal of 50 randomised clinical trials and seven meta-analyses, the most effective drugs for the treatment of partial-onset seizures were carbamazepine and phenytoin in adults, oxcarbazepine in children, and gabapentin and lamotrigine in the elderly. In contrast, no high-quality trials were available to identify the first-choice drug for adults with generalised tonic-clonic seizures and for patients with benign childhood epilepsy with centro-temporal spikes or juvenile myoclonic epilepsy. The authors concluded that, based on the paucity of well-designed and properly conducted trials and the absence of rigorous comprehensive adverse effect data, it was impossible to develop evidence-based guidelines aimed at recommending a drug for initial monotherapy. In keeping with the ILAE, the ultimate drug choice for a patient with newly diagnosed or untreated epilepsy should consider a number of variables, including: efficacy, safety and tolerability profile, pharmacokinetic properties, formulations, and cost.

When comparing the ILAE guidelines for the use of monotherapy in newly diagnosed patients to other evidence-based guidelines issued in the United Kingdom and in the United States, the recommendations were barely consistent, with the exception of carbamazepine (*table 6*). The UK National Institute for Clinical Excellence (2004) recommends the preferential use of older agents. Newer antiepileptic drugs, within their licensed indications, are recommended for the management of epilepsy in people who have not benefited from treatment with the older antiepileptic drugs, such as carbamazepine or valproate, or for whom the older antiepileptic drugs are unsuitable because: there are contraindications to the drugs, possible interaction with other drugs, they are already known to be poorly tolerated, or the person is a woman of childbearing potential. The Scottish Intercollegiate Guidelines and Network (2005) identifies specifically carbamazepine, valproate, lamotrigine, and oxcarbazepine as first-line agents. The side effect and interaction profiles should direct the choice of drug for the individual patient. In contrast, the US panelists recommend patients with newly diagnosed and previously untreated epilepsy to be treated with an older drug or with a new drug among lamotrigine, gabapentin, oxcarbazepine, or topiramate, depending on individual patient characteristics (French *et al*., 2004). In this light, except for carbamazepine for the

Table 6. Antiepileptic drugs recommended as first-line treatment for partial seizures.

	AAN*	NICE†	SIGN‡	ILAE§
Carbamazepine	Yes	Yes	Yes	Yes (level A)
Gabapentin	Yes	-	-	Yes (level C)
Lamotrigine	Yes	Yes	Yes	Yes (level C)
Levetiracetam	-	-	-	-
Oxcarbazepine	Yes	Yes	Yes	Yes (level C)
Phenobarbital	Yes	-	-	Yes (level C)
Phenytoin	Yes	-	Yes	Yes (level A)
Topiramate	Yes	Yes	-	Yes (level C)
Valproate	Yes	Yes	Yes	Yes (level B)

Level A: drug established as efficacious or effective as initial monotherapy; level B: drug probably efficacious or effective as initial monotherapy; level C: drug possibly efficacious or effective as initial monotherapy. Source: Perucca and Tomson, 2011.
*: American Academy of Neurology; †: National Institute for Clinical Excellence; ‡: Scottish Intercollegiate Guidelines Network; §: International League Against Epilepsy.

treatment of partial seizures, there are no standard recommendations for the selection of the best comparator for new monotherapy trials.

Drug daily dose

The decision to use a classic (first generation) or a newer antiepileptic drug as comparator in a randomised monotherapy trial should be considered, among others, in light of the target dose with the best risk: benefit profile. Several reports have unequivocally documented that successful seizure control in epilepsy can be obtained with low drug daily doses (Dogan *et al*., 2008; Brodie *et al*., 2007; Brodie *et al*., 2002; Kwan and Brodie, 2001). In these instances, the probability of drug-related adverse events is minimised, even for first generation drugs with suboptimal tolerability profile.

Conclusions

When comparing the recommendations of evidence-based guidelines (*see table 6*), carbamazepine still represents the first-choice drug for patients with partial epilepsy. Ethosuximide might be an option for absence epilepsy based on the results of a single well-designed comparative trial. In contrast, for the treatment of patients with other generalised epilepsies, there is no clear indication of preferred drug, as valproate, which has been found to prevail over other compounds, should be withheld due to its teratogenic potential, and there is insufficient evidence to choose an alternative drug. □

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