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Prospective audits with newer antiepileptic drugs in focal epilepsy: Insights into population responses?

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ABSTRACT

Despite the availability of a wide range of new antiepileptic drugs (AEDs), there is little evidence that their introduction has substantially altered outcomes. This paper reviews data from 5 consecutive prospective audits with new AEDs using similar methodology. Prospective audits with topiramate (TPM; n = 135), levetiracetam (LEV; n = 136), zonisamide (ZNS; n = 141), pregabalin (PGB; n = 135), and lacosamide (LCM; n = 160) were undertaken in treated patients with uncontrolled partial-onset seizures. Follow-up continued until one of four endpoints was reached: seizure freedom for ≥6 months on unchanged dosing; ≥50% reduction (responder) in seizure frequency on the highest tolerated dose compared with baseline; <50% seizure frequency reduction (marginal response) compared with baseline in patients wishing to continue treatment with the new AED; or withdrawal due to lack of efficacy, side effects, or both. A greater proportion of seizure-free patients occurred with LEV (23.5%), LCM (21.9%), and TPM (20.7%) than with ZNS (12.8%) and PGB (10.4%). A higher percentage discontinued treatment with ZNS (41.8%) and PGB (50.4%) than with LEV (32.4%), TPM (31.1%), and LCM (22.5%). Most seizure-free patients responded to the new agent as first or second add-on (TPM 96%; LEV 97%; ZNS 89%; PGB 86%; LCM 97%) often at modest or moderate dosing (TPM 68%, ≤200 mg/day; LEV 63%, ≤1000 mg/day; ZNS 61%, ≤100 mg/day; PGB 86%, ≤300 mg/day; LCM 74%, ≤200 mg/day). With <10% of patients discontinuing all AEDs due to lack of efficacy, tolerability was the major factor influencing the number of patients remaining on treatment. Lacosamide was the best (77% patients continued treatment), while PGB was the worst (50% continued treatment) tolerated AED. Overall, seizure freedom was achieved in <25% of patients in each audit, mainly as a first or second add-on, with best tolerated AEDs producing a higher number of good outcomes. Seizures in very few patients with drug-resistant epilepsy, as defined by the International League Against Epilepsy task force, responded to any of the 5 newer AEDs. These data support the suggestion that the introduction of modern agents has not importantly impacted the outcomes in refractory epilepsy.

1. Introduction

Over the last 20 years, more than a dozen new antiepileptic drugs (AEDs) possessing a variety of mechanisms of action have been introduced into everyday clinical practice around the world as adjunctive treatment for uncontrolled partial-onset seizures [1]. Despite this plethora of novel agents, this common seizure type in over 30% of patients remains uncontrolled [2]. A recent analysis of patients attending the epilepsy clinic at the Western Infirmary, who remained seizure-free for at least the previous year on more than one AED, hinted at the likelihood of a modest impact of their introduction on outcomes in this population [3]. Results from placebo-controlled dose-ranging, adjunctive regulatory trials over this period have paralleled this relatively disappointing situation [4] with very few patients remaining seizure-free for even the short duration of the studies [5]. In the last two decades, we have undertaken a series of similar pragmatic prospective audits with topiramate (TPM), levetiracetam (LEV), zonisamide (ZNS), pregabalin (PGB), and lacosamide (LCM) following their approval for use by the Scottish Medicines Consortium [6–10]. These data have allowed us to compare the patterns of response to 5 newly introduced AEDs used as adjunctive treatment in patients with uncontrolled localization-related epilepsies and to tentatively explore population responses.

2. Methods

Audits were instituted in the weeks following the approval of each of TPM, LEV, PGB, ZNS, and LCM for the adjunctive treatment of partial-onset seizures by the local regulatory body. Patients aged 12 years and over with uncontrolled epilepsy taking one or more AEDs were recruited into each audit if they had partial seizures with or without secondary generalization. The audits with TPM, LEV, and ZNS also included some patients with idiopathic generalized epilepsies, who were excluded from this analysis. Exclusion criteria for all the audits included patients who were intermittently noncompliant with their treatment or clinic attendances and those who did not document their seizures appropriately. This population had less severe epilepsy than those recruited

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Table 1
Characteristics of patients with localization-related epilepsies receiving adjunctive topiramate, levetiracetam, zonisamide, pregabalin, and lacosamide in prospective audits.

Audit	Number of patients	Gender (male:female)	Median (range) age (years)	Median (range) monthly baseline seizure frequency	Median (range) number of current antiepileptic drugs	Median (range) number of previous antiepileptic drugs
Topiramate	135	65:70	42 (18–75)	4 (2–120)	1 (1–3)	No data
Levetiracetam	136	65:71	40 (16–78)	4 (1–120)	1 (1–3)	2 (0–9)
Zonisamide	141	63:78	42 (15–80)	4 (1–210)	2 (1–4)	2 (0–12)
Pregabalin	135	73:62	44 (18–76)	12 (1–480)	2 (1–4)	2 (0–14)
Lacosamide	160	74:86	42 (14–74)	4 (1–300)	1 (1–4)	1 (0–12)

into the regulatory trial programs with these agents [11]. Each patient recorded baseline seizure frequency for 12 weeks on an unchanged regimen. Thereafter, the new AED was introduced and the dose titrated according to efficacy and tolerability. Seizures, adverse effects, and weight were recorded at 4–6 weekly visits to the Epilepsy Unit at the Western Infirmary in Glasgow. Reduction in dosing of other AEDs was undertaken as necessary. Adverse effects were inquired about by the question "Are you having any problems with your new medication?". To facilitate optimal management, patients were given telephone numbers to allow direct contact if they had problems with their treatment or seizure control.

Patients were kept under observation until one of the following endpoints was reached: no seizures (seizure freedom) for at least 6 months on unchanged dosage; ≥50% reduction (responder) in seizure frequency on the highest tolerated dose compared with baseline; <50% seizure frequency reduction (marginal response) compared with baseline in patients wishing to continue treatment with the new AED; or withdrawal of treatment due to lack of efficacy, side effects, or both.

Demographics of patients with partial seizures with or without secondary generalization recruited to each audit are summarized in Table 1. In the TPM audit, dosing was incremented as follows: week 1, 25 mg daily; week 2, 25 mg twice daily; weeks 3–4, 25 mg in the morning and 50 mg at night; and weeks 4–5, 50 mg twice daily [6]. Thereafter, upward and downward adjustments in dosing were made by 25- to 50-mg daily increments according to clinical response or the development of adverse effects. With LEV, the initial starting dose varied between 250 mg once daily, 500 mg once daily, and 500 mg twice daily depending on patient preference and seizure density [7]. Dosage modifications were made in increments of 250–500 mg daily every 2–4 weeks. The schedule with adjunctive ZNS depended on whether or not the patient was receiving hepatic enzyme-inducing AEDs [8]. This group took ZNS 25 mg twice daily in week 1, increasing to 50 mg twice daily in week 2. Thereafter, dosing was adjusted as clinically indicated in 2 weekly increments of up to 100 mg, with initial target dosing of 150 to 250 mg twice daily. Patients not taking enzyme-inducing AEDs were started on 25 mg twice daily in weeks 1 and 2, increasing to 50 mg twice daily in weeks 3 and 4. Thereafter, dosing was adjusted as necessary in 2 weekly increments of 50 mg, with initial target dosing of 100–150 mg twice daily. Pregabalin was prescribed initially in a dose of 75 mg daily for 2 weeks, increasing to 75 mg twice daily [9]. The dose was then increased by 75-mg increments every 2 weeks according to seizure frequency and tolerability. Dosing with LCM began with 50 mg daily for 2 weeks, increasing to 50 mg twice daily thereafter, with a target daily dose of 200–400 mg [10].

The optimum maintenance amount of the new AED was identified for each patient according to efficacy and tolerability. Patients becoming seizure-free on any given dose of any AED remained on that dose. The doses of other AEDs could be reduced as necessary in an effort to minimize adverse effects and/or to reduce drug burden. A few patients were established on monotherapy with the newer agents.

3. Results

Outcomes in patients with localization-related epilepsies for all 5 similarly conducted prospective audits are summarized in Table 2. Seizure freedom according to treatment schedules is illustrated in Fig. 1. The best results occurred with LEV (23.5% seizure-free), LCM (21.9% seizure-free), and TPM (20.7% seizure-free). Most patients whose seizures were controlled did so when the new AED was introduced as first or second add-on (TPM 96%; LEV 97%; ZNS 89%; PGB 86%; LCM 97%). Some patients with uncontrolled epilepsy became seizure-free on a later schedule. The majority of seizure-free patients were able to control their seizures on modest dosing of each drug (TPM 68%, ≤200 mg/day; LEV 63%, ≤1000 mg/day; ZNS 61%, ≤100 mg/day; PGB 86%, ≤300 mg/day; and LCM 74%, ≤200 mg/day; Fig. 2). Overall, monotherapy was successfully maintained in 7 TPM patients, 3 LEV patients, 1 ZNS patient, 0 PGB patients, and 5 LCM patients.

Fig. 3 highlights the number of patients remaining on each AED and the reasons for coming off treatment. Adverse effects leading to drug withdrawal are listed in Table 3. The commonest problems were fatigue and weight loss with TPM, sedation with LEV, sedation and nausea and vomiting with ZNS, sedation and weight gain with PGB, and nausea and vomiting and dizziness with LCM. The best-tolerated AED appeared to be LCM with 77% of patients remaining on treatment and just 14% withdrawing due to side effects (Fig. 3). Topiramate (69% remaining on treatment) and levetiracetam (68% remaining on treatment) followed closely behind. Zonisamide (58% remaining on treatment) and pregabalin (50% remaining on treatment) appeared to be the least

Table 2
Outcomes in prospective audits with adjunctive new antiepileptic drugs (AEDs) in localization-related epilepsies.

AED	Number of patients	Seizure-free (%)	Responders[a] (%)	Marginal response[b] (%)	Withdrawn (%)
Topiramate	135	28 (20.7)	65 (48.2)		42 (31.1)
Levetiracetam	136	32 (23.5)	28 (20.6)	32 (23.5)	44 (32.4)
Zonisamide	141	18 (12.8)	21 (14.9)	43 (30.5)	59 (41.8)
Pregabalin	135	14 (10.4)	33 (24.4)	20 (14.8)	68 (50.4)
Lacosamide	160	35 (21.9)	35 (21.9)	54 (33.7)	36 (22.5)

[a] ≥50% reduction in seizure frequency compared with baseline seizure frequency.
[b] <50% reduction in seizure frequency compared with baseline seizure frequency.

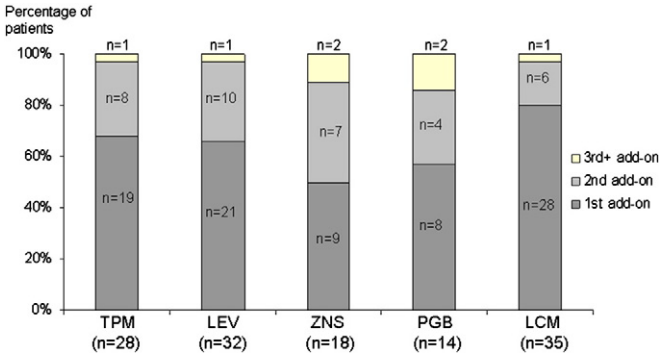

Fig. 1. Seizure freedom according to antiepileptic drug schedule in patients receiving adjunctive topiramate (TPM), levetiracetam (LEV), zonisamide (ZNS), pregabalin (PGB), or lacosamide (LCM).