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Psychiatric side effects and antiepileptic drugs: Observations from prospective audits

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ABSTRACT

Psychiatric comorbidities are common in people with epilepsy. A retrospective study of characteristics associated with withdrawal due to psychiatric side effects was undertaken in patients with treated epilepsy participating in prospective audits with new antiepileptic drugs (AEDs). A total of 1058 treated patients with uncontrolled seizures (942 focal-onset seizures, 116 generalized genetic epilepsies [GGEs]) participated in eight prospective, observational audits from 1996 to 2014. These patients were prescribed adjunctive topiramate (n = 170), levetiracetam (n = 220), pregabalin (n = 135), zonisamide (n = 203), lacosamide (n = 160), eslicarbazepine acetate (n = 52), retigabine (n = 64), or perampanel (n = 54). Doses were titrated according to efficacy and tolerability to optimize zeizure outcomes and reduce side effects. Psychiatric comorbidities were recorded prior to and after the addition of each AED. At baseline, patients with focal-onset seizures (189 of 942; 20.1%) were statistically more likely to have psychiatric diagnoses compared to patients with GGEs (14 of 116, 12.1%; p = 0.039). Following adjunctive AED treatment, neuropsychiatric adverse effects led to AED withdrawal in 1.9–16.7% of patients. Patients with a pre-treatment psychiatric history (22 of 209; 10.5%) were statistically more likely to discontinue their new AED due to psychiatric issues compared to patients with no previous psychiatric diagnosis (50 of 849; 5.9%; p = 0.017). Patients receiving sodium channel blocking AEDs (4 of 212, 1.9%) were statistically less likely to develop intolerable psychiatric problems, compared to those on AEDs possessing other mechanisms of action (68 of 846, 8.0%; p = 0.012). Depression was the commonest problem, leading to discontinuation of AEDs in 2.8% (n = 30) patients. Aggression was statistically more common in men (11 of 527, 2.1%) compared to women (1 of 531, 0.2%; p = 0.004). Patients with learning disability (12 of 122, 9.8%; p = 0.0015) were statistically less likely to have psychiatric issues prior to adjunctive AED treatment compared to other patients (208 of 936, 22.2%), but there were no statistically significant differences once the new AEDs were added (8 of 122 patients with learning disability, 6.6%; 64 of 936 other patients, 6.8%). Awareness of these issues may assist clinicians in avoiding, identifying and treating psychiatric comorbidities in people with epilepsy.

1. Introduction

The prevalence of psychiatric comorbidities is high in people with epilepsy. As many as 30% of newly diagnosed patients and 50% of those with drug resistant epilepsy are thought to be affected [1]. Depression, anxiety disorders and psychoses are particularly frequent [2–4]. Younger patients with employment and educational issues and a past history of depression, anxiety, perceived stress and stigma are especially at risk [5]. Despite these associations, psychiatric conditions may go undiagnosed and untreated in this population [6]. The resultant adverse consequences can have a negative impact on quality of life, utilization of epilepsy services [7], response to and adherence with antiepileptic drugs (AEDs) [8] and epilepsy surgery outcomes [9–11].

Psychiatric conditions often precede the onset of epilepsy [12]. The situation is further complicated by AED treatment, which can impact adversely on mood, behaviour and cognition [13]. This can make the selection of AEDs challenging, particularly for patients already affected by psychiatric symptoms [14]. Over the past two decades, eight prospective audits of novel AEDs as adjunctive therapy have been undertaken at the Western Infirmary, Glasgow and more recently, the West Glasgow Ambulatory Care Hospital. This paper examines the characteristics of participating patients with psychiatric comorbidities prior to and following the introduction of each AED.

2. Materials and methods

Following approval by the local regulatory body of topiramate (TPM), levetiracetam (LEV), pregabalin (PGB), zonisamide (ZNS), lacosamide (LCM), eslicarbazepine acetate (ESL), retigabine (RTG) and perampanel (PER) for the adjunctive treatment of seizures, audits

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were instituted to assess efficacy and tolerability of these agents in everyday clinical practice [15–17]. Patients aged ≥12 years were recruited if they continued to have seizures despite taking one or more AEDs. As well as those with focal-onset seizures, patients with generalized genetic epilepsies (GGEs) were also recruited into the audits with TPM, LEV and ZNS. Patients who were intermittently non-compliant with their treatment or clinic attendances and those who did not document their seizures appropriately were excluded from the audits.

Each patient recorded baseline seizure frequency for 12 weeks on an unchanged AED regimen. Medical, psychiatric and drug history, and demographic details were recorded on a computerized database. Psychiatric diagnoses were defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [18]. The new AED was then introduced and the dose titrated according to efficacy and tolerability. Seizures, adverse effects, psychiatric symptoms and weight were recorded thereafter at 6–8 weekly visits to the Epilepsy Unit. Patients were given telephone numbers to facilitate direct contact if they had problems with adverse effects or seizure control.

Patients were kept under observation until one of the following endpoints was reached: no seizures for at least 6 months on unchanged dosage; ≥50% reduction on the highest tolerated dose compare with baseline; <50% seizure frequency reduction compared with baseline in patients wishing to continue treatment with the new AED; or withdrawal of treatment due to lack of efficacy, adverse effects or both [15].

Characteristics of patients 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; week 4–5, 50 mg twice daily [19]. Thereafter, upward and downward adjustments were made by 25–50 mg daily increments according to clinical response or development of side-effects. With LEV, the initial starting dose varied between 250 mg once daily, 500 mg once daily, or 500 mg twice daily depending on patient preference and seizure density [20,21]. 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 [22]. 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 inducers 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. PGB was prescribed initially in a dose of 75 mg daily for 2 weeks, increasing to 75 mg twice daily [23]. The dose was then increased further in 75 mg increments every 2 weeks according to clinical need 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 [24]. ESL was instituted at a dose of 400 mg daily for 1 week, increasing to 800 mg daily and then to 1200 mg daily if clinically indicated [16]. Patients receiving RTG were started on a dose of 100 mg three times daily, increasing to 200 mg three times daily. If required, the dose was increased to 300 mg three times, then 400 mg three times daily [16]. Enzyme induced patients prescribed PER received 2 mg at bedtime during week 1 and 4 mg at bedtime during week 2 [17]. Thereafter, dosing was adjusted as clinically indicated in weekly increments of 2 mg with target dosing of 8–12 mg/day. Patients not taking hepatic enzyme inducing AEDs received 2 mg at bedtime during weeks 1 and 2, and 4 mg at bedtime during weeks 3 and 4. Dosing was then adjusted as clinically indicated in two weekly increments of 2 mg with target dosing of 8–12 mg/day.

Patients becoming seizure-free on any given AED dose remained on that dose. The optimum maintenance amount was identified for each patient according to efficacy and tolerability. Doses of other AEDs were reduced as necessary in an effort to minimize side-effects and/or balance drug burden. Concomitant AEDs were occasionally withdrawn in some patients. Among other analyses, data were examined for characteristics of patients developing psychiatric symptoms. The Chi-square test was used to compare categorical data; $p < 0.05$ was considered as statistically significant.

3. Results

A total of 1058 patients (527 men, 531 women, aged 16–80 [median 45]) years with uncontrolled seizures (942 focal-onset seizures, 116 GGEs) were recruited into the audits (Table 1). Patients were taking stable doses of 1–4 (median 2) AEDs. At recruitment, 14.8–27.1% patients had a psychiatric history (Table 2). Compared to patients with GGEs (14 of 116, 12.1%), those with focal-onset seizures (189 of 942; 20.1%) were statistically more likely to have psychiatric diagnoses prior to the institution of their new AED ($p = 0.039$). Gender (92 of 527 men, 17.5%; 111 of 531 women, 20.9%) did not significantly influence the likelihood of psychiatric comorbidities at baseline ($p = 0.15$). Depression and anxiety were the commonest problems noted, affecting 10.8–18.9% and 4.4–9.3% of patients, respectively.

Following the addition and optimal titration of TPM (n = 170), LEV (n = 220), PGB (n = 135), ZNS (n = 203), LCM (n = 160), ESL (n = 52), RTG (n = 64) or PER (n = 54), one or more neuropsychiatric adverse effects led to AED withdrawal in 1.9–16.7% of patients (Table 3). Of patients who discontinued treatment due to psychiatric problems, there was a statistically significant difference between those receiving sodium channel blocking AEDs (ESL, LCM; 4 of 212, 1.9%) compared to those on AEDs with other mechanisms of action (TPM, LEV, PGB, ZNS,

Table 1
Characteristics of patients receiving adjunctive antiepileptic drugs in prospective audits.

	Topiramate	Levetiracetam	Pregabalin	Zonisamide	Lacosamide	Eslicarbazepine acetate	Retigabine	Perampanel	TOTAL
n	170	220	135	203	160	52	64	54	1058
Median (range) age (years)	46 (18–75)	38 (16–78)	44 (18–76)	39 (15–80)	42 (14–74)	46 (16–72)	45 (20–67)	48 (21–65)	45 (16–80)
Male:Female	82:88	109:111	73:62	82:121	74:86	34:18	35:29	38:16	527:531
FOS[d]:GGE[a]	134:36	200:20	135:0	143:60	160:0	52:0	64:0	54:0	919:139
n (%) with previous psychiatric history	46 (27.1)	43 (19.5)	20 (14.8)	30 (14.8)	35 (21.9)	14 (26.9)	13 (20.3)	8 (14.8)	209 (19.8)
Male:Female	21:25	24:19	7:13	12:18	13:22	10:4	6:7	2:6	95:114
n (%) discontinuing AED[b] due to psychiatric side effects	13 (7.6)	15 (6.8)	7 (5.2)	15 (7.4)	3 (1.9)	1 (1.9)	9 (14.0)	9 (16.7)	72 (6.8)
Male:Female	8:5	9:6	6:1	6:9	2:1	0:1	3:6	6:3	40:32
n with previous psychiatric history discontinuing AED[b] due to psychiatric side effects	5	6	2	2	2	0	1	4	22 ($p = 0.017$)[c]
Male:Female	2:3	4:2	1:1	2:0	1:1	0:0	0:1	1:3	11:11

[a] Genetic generalized epilepsies.
[b] Antiepileptic drug.
[c] Patients with a psychiatric history at baseline were statistically more likely to discontinue their adjunctive AED due to psychiatric side effects compared to other patients.
[d] Focal-onset seizures.