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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.

Table 2
Psychiatric comorbidities in patients prior to adjunctive antiepileptic drug treatment[a].

	Topiramate n = 46 of 170, (27.1%)	Levetiracetam n = 43 of 220, (19.1%)	Pregabalin n = 20 of 135, (15.0%)	Zonisamide n = 30 of 203, (14.8%)	Lacosamide n = 35 of 160, (21.9%)	Eslicarbazepine acetate n = 14 of 52, (26.9%)	Retigabine n = 13 of 64, (20.3%)	Perampanel n = 8 of 54, (14.8%)
Depression	32 (18.8%)	29 (13.2%)	16 (11.9%)	22 (10.8%)	30 (18.8%)	10 (19.2%)	12 (18.8%)	7 (13.0%)
Anxiety	9 (5.3%)	11 (5.0%)	6 (4.4%)	10 (4.9%)	10 (6.3%)	3 (5.8%)	5 (7.8%)	5 (9.3%)
Aggression	2 (1.2%)	5 (2.3%)	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)	0 (0%)	0 (0%)
Delusions	2 (1.2%)	1 (0.45%)	0 (0%)	1 (0.49%)	1 (0.63%)	0 (0%)	0 (0%)	0 (0%)
Irritable mood	2 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mood instability	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	1 (0.63%)	0 (0%)	0 (0%)	0 (0%)
Paranoid ideation	0 (0%)	1 (0.45%)	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)	0 (0%)	0 (0%)

[a] Some patients had more than one comorbidity.

RTG, PER; 68 of 846, 8.0%; p = 0.012; Fig. 1). Patients with a pre-treatment psychiatric history (22 of 209, 10.5%) were statistically more likely to discontinue their new AED due to psychiatric problems compared to patients with no previous psychiatric diagnosis (50 of 849; 5.9%; p = 0.017, Table 1). A further 14 (1.3%) patients (8 TPM [6 depression, 1 aggression, 1 depression/irritability], 3 LEV [1 depression, 1 anxiety, 1 anger], 2 PGB [2 depression] and 1 ZNS [1 depression]). who reported similar symptoms elected to continue their AED.

Depression was the commonest issue, leading to discontinuation of AEDs in 16 (3.0%) women and 14 (2.7%) men (Table 4). Intolerable psychiatric side effects were as likely to occur in men (40 of 527, 7.6%) as women (32 of 531, 6.0%; p = 0.313), although men were statistically more likely to report intolerable aggression (p = 0.004), depression, irritability, anxiety and mood instability compared to women. Patients with focal-onset seizures (60 of 942, 6.4%) were statistically as likely to have AEDs withdrawn due psychiatric side effects as those with GGEs (12 of 116, 10.3%; p = 0.11). Of the 72 patients in whom AED therapy was withdrawn due to psychiatric side effects, 84.7% (n = 61) were ≤50 years (median age 38 years; range 16–64 years), compared with those who continued their AED treatment of whom 77.3% (n = 762) were ≤50 years (median age 41 years, range 16-80 years).

In total, 122 patients participating in the audits had learning disability (64 LEV, 28 TPM, 15 ZNS, 6 PGB, 6 LCM, 2 ESL, 1 PER). Each had been diagnosed by a consultant psychiatrist with an interest in that discipline and the learning disability graded as mild (IQ 50–70), moderate (IQ 35–49), severe (IQ 20–34) or profound (IQ < 20) [18]. A separate audit of outcomes with adjunctive LEV was undertaken in this patient population which accounts for the higher number of patients recruited [20]. Compared to patients without learning disability (208 of 936, 22.2%), a statistically smaller percentage had psychiatric issues prior to adjunctive AED treatment (12 of 122, 9.8%; p = 0.0015). Once started on a new AED, these patients were statistically as likely to develop intolerable psychiatric problems (8 of 122, 6.6%) compared to those without learning disability (64 of 936, 6.8%, p = 0.91).

4. Discussion

At recruitment, 14.8–27.1% of patients with uncontrolled epilepsy had a documented psychiatric history, regardless of gender. Psychiatric comorbidities are more common in people with epilepsy than in the general population [25,26] and people with other chronic conditions [27]. Prevalence tends to be higher in hospital compared to community settings [28] and in those with drug-resistant seizures [29]. The percentages in these audits tended to be lower than in some other studies. This may reflect the fact that the uncovering of psychiatric symptoms was not the primary aim, or could be the result of clinicians at the epilepsy clinic being less skilled at uncovering these diagnoses as those with an expertise in psychiatry. A sensitive and specific screening tool for use in this setting may help to improve this situation [28]. In addition, although all the prospective audits were undertaken using the same methodology, some were initiated as much as 20 years ago [19–21] — at that time it is possible that psychiatric comorbidities in people with epilepsy were less recognized or identified compared to the present day. It is difficult to be certain as to how much the psychiatric diagnoses were associated with baseline AED treatment, comedication or whether they existed prior to the diagnosis of epilepsy and the institution of AED treatment.

As found by others [30–32], depression and anxiety were the commonest psychiatric diagnoses. At baseline, psychiatric comorbidities were statistically more likely in patients with focal-onset seizures compared to those with GGEs, but after the addition of each new AED there was no difference in incidence. Temporal lobe epilepsy has been cited as being a particular association with psychiatric problems [33,34]. Anxiety and depression are particularly common and can go undiagnosed and under-treated. It is increasingly recognized that epilepsy syndromes, including juvenile myoclonic epilepsy [35,36], benign epilepsy with centrotemporal spikes [37] and childhood absence epilepsy [38], can also be complicated by psychiatric comorbidities. Juvenile myoclonic epilepsy is associated with cognitive frontal lobe dysfunction [39] and many people with the syndrome are prone to depression and impulsiveness [40].

Table 3
Psychiatric symptoms leading to antiepileptic drug discontinuation[a].

	Topiramate n = 13 of 170 (7.6%)	Levetiracetam n = 15 of 220 (6.8%)	Pregabalin n = 7 of 135, (5.2%)	Zonisamide n = 15 of 203 (7.4%)	Lacosamide n = 3 of 160, (1.9%)	Eslicarbazepine acetate n = 1 of 52 (1.9%)	Retigabine n = 9 of 64 (14.0%)	Perampanel n = 9 of 54, (16.7%)
Depression	9	1	4	8	2	1	2	3
Aggression	2	2	1	4	0	0	0	1
Irritable mood	3	3	1	2	0	0	2	3
Anxiety	2	0	0	2	0	0	1	1
Mood instability	0	6	2	2	0	0	0	0
Paranoid ideation	1	0	0	0	1	0	2	1
Delusions	0	2	0	1	0	0	0	0
Hallucinations	0	1	0	1	0	0	2	0
Thought disorder	0	0	0	1	0	0	1	0

[a] Some patients had more than one side effect.

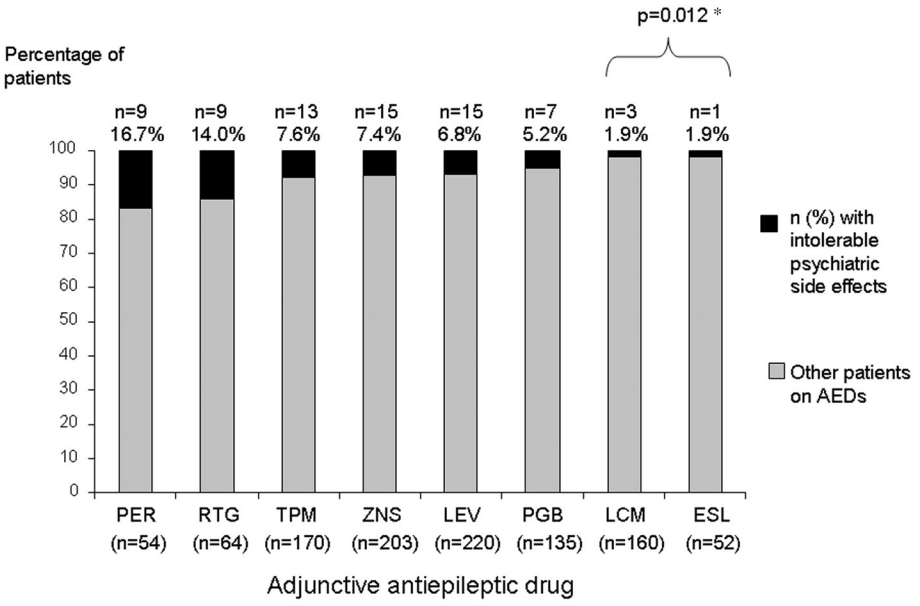

Fig. 1. Patients who discontinued adjunctive antiepileptic drug treatment due to intolerable psychiatric side effects *Patients receiving sodium channel blocking antiepileptic drugs were significantly less likely to have psychiatric side effects compared to those taking antiepileptic drugs with other mechanisms of action.

One or more neuropsychiatric adverse effects led to AED discontinuation in 1.9–16.7% of patients. Patients receiving sodium channel blocking AEDs were statistically less likely to discontinue treatment due to psychiatric problems, compared to those on AEDs with other mechanisms of action. There are few data with which to compare these results. Regulatory trial results do not necessarily reflect everyday clinical practice with factors such as fixed dosing and short term AED administration often failing to unmask potential neuropsychiatric side effects associated with novel agents. Product information labels for commonly used AEDs list neuropsychiatric side effects as potential problems for all the agents [14]. Of 1394 patients receiving new AEDs at an American epilepsy centre, 8.4% had AED-related psychiatric/behavioural side effects [41]. LEV was associated with the highest incident rate (16%), followed by TPM, ZNS and lamotrigine, with gabapentin having the lowest rate (0.6%). Conversely, carbamazepine, sodium valproate and lamotrigine can have positive psychotropic properties [14]. The relationship between AED mechanisms of action and psychiatric symptoms is little understood and is likely to involve numerous cortical and subcortical brain networks, regions such as the amygdala and hippocampus, as well as sharing ion channels and neurotransmitter systems including monoamines, glutamate and gamma aminobutyric acid [4,14].

Patients with a pre-treatment psychiatric history were statistically more likely to discontinue their new AED due to intolerable psychiatric problems compared to patients who had no previous psychiatric diagnosis. Other studies support this observation [31,32]. However, whether these diagnoses preceded the onset of seizures or institution of AED treatment is not clear. Patients participating in these audits had a long history of epilepsy and were taking at least one other AED prior to having their new AED added. Many were also taking other medication. It is possible that baseline drugs influenced the presence of psychiatric diagnoses. The relationship between epilepsy and psychiatric complications is complex, may be bidirectional [10] and subject to influences such as core characteristics of the condition, genotypic, pharmacological, psychological and sociocultural influences, neurobehavioural comorbidities, brain development and ageing and co-existing brain pathology [1,2]. It may be that there is a common pathophysiology in some patients [4]. Rates of behavioural side effects were lower in LEV and PER studies for non-epilepsy indications, suggesting that patients with epilepsy are biologically more vulnerable to neuropsychiatric side effects [14,42,43]. The majority of patients affected in these audits improved following AED withdrawal, but others required interventions, mainly in the form of antidepressant medication or cognitive behavioural therapy.

Intolerable psychiatric side effects were as likely to occur in men as women, although men reported more side effects per person compared to women. Depression was the commonest problem in both. Others have found that in people with epilepsy, depression occurs more often in women than men, but anxiety is equally likely to occur in both [44]. The reasons for high depression rates remain unclear, but a recent systematic review concluded that sociodemographic factors play a significant role [32]. Significantly more men than women reported aggression. In a series of 33 patients with epilepsy who had aggression following the addition of LEV, eight men and one woman had severe manifestations [45]. Patients who discontinued AEDs due to psychiatric side effects tended to be younger than other patients participating in the audits. The lifetime prevalence of major depressive disorders has been shown to decline with age in women and remains stable in men, but is higher, overall, in people with epilepsy [28].

Compared to patients without learning disability statistically fewer patients with learning disability in this analysis had psychiatric diagnoses prior to addition of the new AED treatment. However, there was no statistical difference in the incidence of intolerable psychiatric problems between the two groups following the addition of the adjunctive AED. Around one third of people with epilepsy and learning disability have been shown to meet criteria for possible psychiatric disorder [46]; the

Table 4
Psychiatric side effects leading to antiepileptic drug discontinuation in men and women[a].*

Side effect	Men (n = 40)	Women (n = 32)
Depression	14	16
Aggression	11 ($p < 0.05$)*	1
Irritable mood	9	4
Anxiety	5	2
Mood instability	6	2
Paranoid ideation	4	1
Delusions	2	1
Hallucinations	1	3
Thought disorder	0	2

[a] Some patients had more than one side effect.
* Compared to women, men were significantly more likely to develop aggression leading to antiepileptic drug withdrawal.

prevalence of psychosis has been quoted at 7.4% [47–49]. Untangling psychiatric comorbidities from behavioural and other issues in this population can be particularly challenging, especially in patients with severe and profound learning disability [46]. These patients often have difficulties vocalizing directly emotional manifestations associated with depression, anxiety and other psychiatric diagnoses and may be unable to express their symptoms or communicate these in unusual ways [50]. Clinicians are often reliant on families and carers to identify potential signs. It has therefore been suggested that diagnostic criteria and screening tools for depression in people with learning disability should be different to those used in the general population [51]. Diagnostic issues and uncertainties have led to variability in the reporting of psychiatric comorbidities in this population in different studies [50]. This may make under- and mis-diagnosis more likely than in the general population.

It is recognized that there are several limitations to this project including lack of control groups, differences in AED group sizes, methods of inquiry about psychiatric symptoms and difficulties assessing the influence of baseline AEDs and co-medication on mental health. However, results reflect observations made over the years by clinicians managing patients with difficult-to-control epilepsy attending Glasgow clinics. Outcomes constitute important factors in improving the understanding of these relevant diagnoses in people with epilepsy.

5. Conclusions

Psychiatric comorbidities were common in patients with difficult-to-control epilepsy participating in these prospective AED audits. Depression and anxiety were the commonest diagnoses overall, with intolerable aggression being statistically more likely in men than women. At baseline, psychiatric comorbidities were statistically more likely with focal-onset seizures compared to GGEs, and were more common in patients who discontinued their new AEDs due to psychiatric issues. Patients receiving sodium channel blocking agents were statistically less likely to discontinue treatment due to psychiatric problems, compared to those on AEDs with other mechanisms of action. Psychiatric diagnoses were fewer in patients with learning disability at baseline with an incidence similar to other patients following adjunctive AED institution. Awareness of these issues may assist clinicians in managing the challenge of identifying or treating psychiatric comorbidities in people with epilepsy.

Declaration of interest

Martin Brodie serves on the scientific advisory boards of Eisai Ltd., UCB Pharma, GlaxoSmithKline, Lundbeck, Bial, GW Pharmaceuticals and Takeda. He is on the speakers' bureau for Eisai Ltd., UCB Pharma, GlaxoSmithKline and Lundbeck and has accepted travel grants for scientific meetings from Eisai Ltd., UCB Pharma and Lundbeck.

Linda Stephen has received lecture fees and support for travel to congresses from UCB Pharma and Eisai Ltd.

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