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CNS Adverse Events Associated with Antiepileptic Drugs

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Abstract

A variety of newer antiepileptic drugs (AEDs) are now available for treating patients with epilepsy in addition to the 'conventional' drugs that have been available throughout a large part of the last century. Since these drugs act to suppress the pathological neuronal hyperexcitability that constitutes the final substrate in many seizure disorders, it is not surprising that they are prone to causing adverse reactions that affect the CNS.

Information on adverse effects of the older AEDs has been mainly observational. Equally, whilst the newer drugs have been more systematically studied, their long-term adverse effects are not clearly known. This is illustrated by the relatively late emergence of the knowledge of visual field constriction in the case of vigabatrin, which only became known after several hundred thousand patient-years of use. However, older drugs continue to be studied and there has been more

recent comment on the possible effect of valproate (valproic acid) on cognition following exposure to this drug *in utero*.

With most AEDs, there are mainly dose-related adverse effects that could be considered generic, such as sedation, drowsiness, incoordination, nausea and fatigue. Careful dose titration with small initial doses can reduce the likelihood of these adverse effects occurring. Adverse effects such as paraesthesiae are more commonly reported with drugs such as topiramate and zonisamide that have carbonic anhydrase activity. Weight loss and anorexia can also be peculiar to these drugs. Neuropsychiatric adverse effects are reported with a variety of AEDs and may not be dose related. Some drugs, such as carbamazepine when used to treat primary generalized epilepsy, can exacerbate certain seizure types. Rare adverse effects such as hyperammonaemia with valproate are drug specific. There are relatively very few head-to-head comparisons of AEDs and limited information is available in this regard.

In this review, we discuss the available literature and provide a comprehensive summary of adverse drug reactions of AEDs affecting the CNS.

The last two decades have seen an exponential increase in antiepileptic drug (AED) development. The pharmaceutical ideal of an efficacious drug with a minimum of adverse effects remains a relative concept and epilepsy treatment strategies usually balance pursuit of seizure freedom with an acceptable threshold for tolerating adverse effects. Despite this, there is a surprising paucity of recorded adverse drug reactions (ADRs) in a standardized format.[1] ADRs can occur in a variety of organ systems and often involve multiple systems. This review concentrates on the effects of AEDs on the CNS and provides a review of the available literature on this subject. Drug efficacy is not discussed. The literature was reviewed using an internet-based PubMed search, using search terms that included the names of individual drugs and the terms 'side effects', 'adverse reactions' and 'central nervous system'. Individual study articles and review articles were further cross-referenced to widen the search.

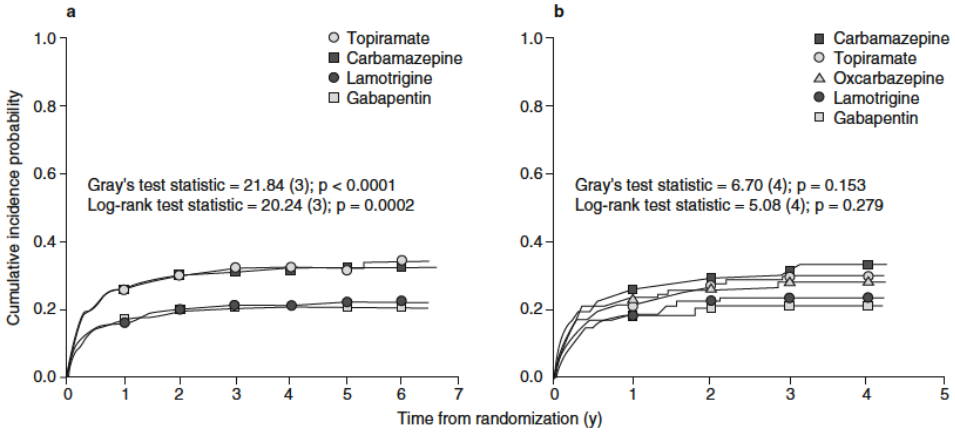
1. Comparisons between Conventional and Newer Antiepileptic Drugs (AEDs)

To help gain an understanding of the comparative effectiveness and tolerability of both conventional and newer AEDs, an overview of the most current study, the SANAD (UK Standard And New Antiepileptic Drugs) study,[2-4] is provided in this section before each drug is further analysed individually in sections 2 and 3.

The recently completed SANAD study, a randomized, unblinded, controlled trial, published its findings in two papers, one examining the use of carbamazepine, gabapentin, lamotrigine, oxcarbazepine and topiramate in the treatment of partial epilepsy (Arm A),[2] the other examining the use of valproate (valproic acid), lamotrigine and topiramate in generalized and unclassifiable epilepsy (Arm B).[3] 1721 and 716 patients, respectively, were recruited into the two arms. Although this study was primarily designed to examine drug effectiveness and not to specifically compare ADRs with different drug treatments, one of the primary outcomes was time to treatment failure. Treatment failure resulting in drug withdrawal is usually a consequence of adverse effects when it occurs early in the course of treatment, and a consequence of poor efficacy when it occurs late; therefore, this study provides at least some systematic and comparative information on ADRs with a limited number of AEDs. The clinical setting was generally one of patients being initiated on drug therapy and, therefore, one in which patients were receiving monotherapy. The median number of days (25th–75th centiles) to treatment failure in Arm A was 84 (26–215) for unacceptable adverse events and 313

(152–642) for inadequate seizure control. Carbamazepine (n = 102; 27%) and topiramate (n = 101; 27%) therapy were associated with the greatest numbers of patients reporting unacceptable adverse events compared with gabapentin (n = 57; 15.2%), lamotrigine (n = 60; 15.9%) and oxcarbazepine (n = 49; 23.3%). However, treatment with carbamazepine (n = 43; 11.4%) and topiramate (n = 55; 14.7%) was also associated with the lowest number of patients discontinuing treatment due to inadequate seizure control, i.e. these AEDs can be interpreted as being more effective than lamotrigine (n = 60; 15.9%) and gabapentin (n = 99; 26.3%). When unacceptable adverse events and inadequate seizure control were considered as a combined reason for treatment termination, there were a greater number of patients discontinuing treatment with topiramate (n = 28; 7.4%), gabapentin (n = 32; 8.5%) or lamotrigine (n = 11; 7.9%) than carbamazepine (n = 20; 5.3%) or oxcarbazepine (n = 11; 5.2%). This highlights the subjective greater importance of efficacy compared with adverse effect profiles of AEDs for the majority of patients.

Cumulative incidence analysis showed that carbamazepine (lamotrigine : carbamazepine hazard ratio [HR; 95% CI] 0.62 [0.46, 0.83]) was most frequently associated with treatment failure for unacceptable adverse events, whereas gabapentin was least likely to result in this kind of treatment failure (gabapentin : carbamazepine HR [95% CI] 0.60 [0.44, 0.81]) [figure 1]. As far as the estimates for the proportion of patients with treatment failure events were concerned, lamotrigine was 10–11% better with respect to treatment withdrawal because of adverse events, and statistically different at all timepoints between 1 and 6 years. This estimate has been criticized as being biased against carbamazepine because of faster dose titration and higher dos-



	Baseline drug			
	Carbamazepine	Gabapentin	Lamotrigine	Topiramate
Gabapentin	0.60 (0.44, 0.81)			
Lamotrigine	0.62 (0.46, 0.83)	1.04 (0.75, 1.44)		
Topiramate	0.99 (0.77, 1.30)	1.66 (1.24, 2.24)	1.60 (1.20, 2.15)	
Oxcarbazepine	0.85 (0.59, 1.24)	1.36 (0.90, 2.05)	1.21 (0.81, 1.81)	0.98 (0.67, 1.44)

Fig. 1. Cumulative incidence of unacceptable adverse events of antiepileptic drugs for the entire treatment period (**a**) and after June 2001 (**b**). Data in the table below the figures are hazard ratios (HRs, 95% CIs), where HR >1 indicates that treatment failure occurs more rapidly on drug compared with baseline (reproduced from Marson et al.,[2] with permission from Elsevier).

Table I. Frequency of clinically important adverse events of antiepileptic drugs in patients with partial epilepsy (reproduced from Marson et al.,[2] with permission from Elsevier)

No. of patients/adverse effects	Carbamazepine	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate	Total
No. of patients randomized	378	377	378	210	378	1721
Total number (%) of patients with at least one adverse event	183 (48)	178 (47)	169 (45)	100 (48)	200 (53)	830 (48)
Tiredness/drowsiness/fatigue/lethargy[a]	48 (36)	46 (34)	31 (17)	22 (16)	43 (33)	190 (136)
Depression[a]	14 (8)	18 (10)	20 (13)	7 (5)	29 (24)	88 (60)
Headache[a]	21 (9)	20 (15)	21 (13)	9 (6)	17 (11)	88 (54)
Allergic rash[a]	38 (32)	13 (4)	17 (15)	20 (16)	17 (8)	105 (75)
Memory problems[a]	20 (12)	22 (19)	13 (10)	13 (8)	26 (19)	94 (68)
Dizziness/vertigo[a]	14 (10)	23 (15)	15 (9)	13 (12)	15 (8)	80 (54)
Other psychiatric[a]	16 (7)	17 (9)	11 (7)	7 (5)	37 (31)	88 (59)
Worsening of seizures[a]	17 (5)	22 (13)	17 (12)	3 (1)	17 (8)	76 (39)
Other neurological[a]	9 (6)	21 (14)	15 (9)	8 (5)	18 (12)	71 (46)
Other general[a]	13 (6)	19 (11)	19 (13)	9 (6)	16 (12)	76 (48)
Behaviour/personality change/aggression[a]	12 (4)	9 (6)	12 (7)	2 (1)	24 (19)	59 (37)
Ataxia[a]	9 (6)	24 (12)	14 (9)	8 (6)	9 (3)	64 (36)
Confusion/difficulty thinking/disorientation[a]	9 (9)	16 (15)	8 (4)	8 (6)	22 (19)	63 (53)
Anxiety/agitation/nervousness[a]	7 (7)	15 (11)	8 (5)	7 (6)	15 (12)	52 (41)
Weight loss[a]	2 (1)	4 (2)	4 (2)	3 (1)	29 (27)	42 (33)
Diplopia[a]	5 (2)	11 (4)	4 (2)	8 (6)	6 (3)	34 (17)
Nausea[a]	9 (6)	7 (3)	9 (6)	15 (13)	4 (4)	44 (32)
Weight gain[a]	9 (7)	15 (12)	4 (1)	1 (0)	5 (4)	34 (24)
Accidental injury[a]	7 (2)	11 (6)	12 (8)	3 (1)	8 (3)	41 (20)
Pins and needles/dysaesthesiae[a]	4 (1)	5 (1)	3 (1)	0 (0)	26 (24)	38 (27)
Sleep disturbance[a]	5 (2)	4 (4)	9 (8)	4 (2)	9 (8)	31 (24)
Other events[a,b]	108 (71)	113 (73)	110 (70)	46 (38)	103 (64)	480 (316)

a Data presented are number of patients with the adverse event by intention-to-treat analysis (per-protocol analysis inside brackets).

b Other cardiac or vascular; other skin and appendages; abdominal pain, dyspepsia; other gastrointestinal; other visual disturbance; other renal tract or genital; diarrhoea; tremor; aches and pains; constipation; infection; mouth or gum problem; other respiratory or pulmonary; ischaemic heart disease or myocardial infarct; other haematological; other musculoskeletal; vomiting; impotence or libido problems; alopecia; word-finding difficulty; status epilepticus; stroke-infarction; diabetes mellitus; hearing problem or tinnitus; hypertension; anorexia; bruising; flu-like symptoms; haemorrhage; malignancy; shortness of breath; vaginal bleeding; arthritis; eczema; peptic ulceration; asthma; other hepatobiliary; urinary retention; abnormal liver function tests; anaemia; childbirth; myalgia; other endocrine; psoriasis; upper respiratory tract infection; catarrh; sinusitis; rhinorrhoea; urinary tract infection; faints; hallucinations; hepatitis; pancreatitis; psychosis; transient ischaemic attack; tachycardia; thyroid disease; venous thrombosis (sorted by descending total frequency).

age levels in the study population than are seen in routine clinical practice.[4] In addition, the study design did not emphasize the use of slow-release carbamazepine, thought to be a factor in avoidance of adverse events when compared with usage of standard carbamazepine. Around 50% of study patients reported adverse events at some point, with only small differences seen between drugs. For the intention-to-treat population, the lamotrigine group reported the lowest number of adverse events, while the topiramate group reported the greatest number of adverse events (table I).

In Arm B of the SANAD study, which studied mainly patients with generalized and unclassifiable epilepsy, the median number of days (25th–75th centiles) to treatment failure because of unacceptable adverse events was 90 (28–245) and because of inadequate seizure control was 234 (136–481).

Cumulative incidence analysis of treatment failure for unacceptable adverse events showed that lamotrigine was least likely and topiramate most likely to cause treatment-limiting adverse events. Topiramate was significantly inferior to both valproate (topiramate **:** valproate [HR; 95% CI] 1.55 [1.07, 2.26]) and lamotrigine (topiramate **:** lamotrigine [HR; 95% CI] 2.15 [1.41, 3.30]). The reported adverse events are listed in table II. Thirty-six percent of patients receiving valproate reported adverse events compared with 45% of patients receiving topiramate. CNS adverse events were the most common reason for treatment failure, except in the case of lamotrigine, for which drug rash was the most common reason.

2. Conventional AEDs

The 'conventional' AEDs refer, in a somewhat arbitrary fashion, to those AEDs in use prior to the advent of the 'newer' AEDs, typified by drugs such as lamotrigine. Conventional AEDs still in use are

Table II. Frequency of clinically important adverse events of antiepileptic drugs in patients with generalized and unclassifiable epilepsy (reproduced from Marson et al.,[3] with permission from Elsevier)

No. of patients/adverse effects	Lamotrigine	Topiramate	Valproate (valproic acid)	Total
No. of patients randomized	239	239	238	716
Total number (%) of patients with at least one adverse event	88 (37)	107 (45)	85 (36)	280 (39)
Tiredness/drowsiness/fatigue/lethargy[a]	15 (9)	25 (20)	18 (12)	58 (41)
Other psychiatric[a]	7 (4)	19 (15)	8 (7)	34 (26)
Weight gain[a]	8 (5)	7 (2)	17 (16)	32 (23)
Behaviour/personality change/aggression[a]	6 (4)	20 (18)	4 (4)	30 (26)
Worsening of seizures[a]	10 (6)	13 (9)	7 (3)	30 (18)
Accidental injury[a]	11 (7)	5 (3)	4 (2)	20 (12)
Other neurological[a]	4 (3)	7 (4)	10 (5)	21 (12)
Headache[a]	6 (4)	7 (4)	5 (4)	18 (12)
Memory problems[a]	2 (2)	12 (10)	3 (0)	17 (12)
Weight loss[a]	3 (0)	14 (12)	0 (0)	17 (12)
Allergic rash[a]	13 (12)	1 (1)	2 (0)	16 (13)
Tremor[a]	4 (2)	1 (0)	8 (6)	13 (8)
Depression[a]	1 (1)	9 (6)	3 (3)	13 (10)
Confusion/difficulty thinking/disorientation[a]	3 (2)	7 (7)	3 (2)	13 (11)
Dizziness/vertigo[a]	3 (2)	6 (3)	1 (1)	10 (6)
Anxiety/agitation/nervousness[a]	7 (6)	2 (2)	1 (1)	10 (9)
Nausea[a]	4 (4)	2 (1)	4 (3)	10 (8)
Other renal tract/genital[a]	4 (3)	4 (2)	3 (2)	11 (7)
Pins and needles/dysaesthesiae[a]	0 (0)	8 (6)	2 (0)	10 (6)
Ataxia[a]	4 (3)	3 (2)	2 (2)	9 (7)
Other skin and appendages[a]	1 (1)	5 (4)	5 (3)	11 (8)
Mouth/gum problems[a]	1 (1)	2 (1)	3 (3)	6 (5)
Sleep disturbances[a]	3 (3)	4 (3)	1 (1)	8 (7)
Other[b]	30 (21)	40 (25)	36 (25)	106 (71)

a Data presented are number of patients with the adverse event by intention-to-treat analysis (per-protocol analysis inside brackets).

b Sorted by descending total frequency: abdominal pain, dyspepsia; alopecia; other general; other visual disturbance; word-finding difficulty; vomiting; aches and pains; other gastrointestinal; other musculoskeletal; other respiratory or pulmonary; diarrhoea; psychosis; anorexia; bruising; constipation; diplopia; renal or bladder stones; influenza-like symptoms; hallucinations; infection; vaginal bleeding; arthritis; asthma; chest infection; childbirth; faints; hypertension; ischaemic heart disease or myocardial infarct; other cardiac or vascular; other haematological; psoriasis; shortness of breath; status epilepticus; urinary tract infection; urinary retention.

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