Epilepsy, antiepileptic drugs and aggression: An evidence-based review

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ABBREVIATIONS:

AE, Adverse event; AED, Antiepileptic drug; AKT, protein kinase BAMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; AMPA-R, AMPA receptor; BAQ, Buss-Perry

aggression questionnaire; CBCL, Achenbach child behaviour checklist; CHQ-PF50, child health questionnaire–parent form 50; CI, confidence interval; DA, dopamine; EEG, electroencephalogram; ERK, extracellular-signal-regulated protein kinase; FBC, focal brain cooling; GABA-R, GABA receptor; GAT, GABA transporter; 5-HT, serotonin; LGS, Lennox–Gastaut syndrome; MAO, monoamine oxidase; MedDRA, medical dictionary for regulatory activities; mTOR, mammalian target of rapamycin; NA, noradrenaline; NMDA, N-methyl-D-aspartate; NMDA-R, NMDA receptor; PCP, phencyclidine; PK/PD, pharmacokinetic–pharmacodynamic; POMS, Profile of mood states; RCT, randomised controlled trial; SMQ, standardised MedDRA query; TLE, temporal lobe epilepsy; VGLUT, vesicular glutamate transporter.

Abstract

Antiepileptic drugs (AEDs) bring with them many benefits, but also many side effects, including aggression, agitation and irritability, in some patients with epilepsy. This review offers a comprehensive summary of current understanding of aggressive behaviours in patients with epilepsy, including an evidence-based review of aggression during AED treatment. Aggression is seen in a minority of people with epilepsy. It is rarely seizure-related, but inter-ictal, sometimes occurring as a part of complex psychiatric and behavioural comorbidities, and sometimes associated with AED treatment. We review the common neurotransmitter systems and brain regions implicated in both epilepsy and aggression, including the GABA, glutamate, serotonin, dopamine and noradrenaline systems, and the hippocampus, amygdala, prefrontal cortex, anterior cingulate cortex, and temporal lobes. Few controlled clinical studies have used behavioural measures to specifically examine aggression with AEDs, and most evidence comes from adverse event reporting from clinical and observational studies. A systematic approach was used to identify relevant publications, and a comprehensive, evidence-based summary is presented of available data surrounding aggression-related behaviours with each of the currently available AEDs in both adults and in children/adolescents with epilepsy. A psychiatric history and history of a propensity towards aggression/anger should routinely be sought from patients, family and carers; its presence does not preclude the use of any specific AEDs, but those most likely to be implicated in these behaviours should be used with caution in such cases.

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I. Introduction

The past twenty years have seen the introduction of over 15 antiepileptic drugs (AEDs), many with unique mechanisms of action (Löscher *et al.*, 2013). Nevertheless, more than 30% of adolescent and adult patients with the common epilepsies continue to have seizures, despite receiving treatment with many of these drugs used either singly or in combination (Brodie *et al.*, 2012). Outcomes in childhood epilepsies, excluding the genetic encephalopathies of infancy, are equally disappointing (Geerts *et al.*, 2010). In parallel with these pharmacological developments has come an increasing awareness that people with epilepsy, possibly as many as 30% of the newly diagnosed population and up to 50% of patients with pharmacoresistant epilepsy, have complex psychiatric, behavioural, cognitive and social problems (Lin *et al.*, 2012). Indeed, these problems often precede the onset of the epilepsy (Hesdorffer *et al.*, 2012). The presence of psychiatric comorbidities contributes to the likelihood that seizures will prove resistant to both AEDs and to epilepsy surgery (Hitiris *et al.*, 2007; Kanner *et al.*, 2009; Petrovski *et al.*, 2010). The situation is further complicated by the beneficial psychotropic effects of some AEDs and the adverse properties of others (Piedad *et al.*, 2012). Behavioural side effects that have been associated with AEDs include depression, aberrant behaviours, and the development or worsening of irritability, impulsivity, anger, hostility and aggression. While prior reviews have focused on the associations between AEDs and depression or aberrant behaviours, the specific topic of aggression in response to AEDs has been largely neglected. We have endeavoured in this evidence-based review to explore the neurobiology, epidemiology, presentation, clinical

relevance and management of issues relating to aggression in children, adolescents and adults with newly-diagnosed and chronic epilepsy exposed to a range of established and modern AEDs.

II. Aggressive behaviour in epilepsy: definitions

Aggressive behaviour in epilepsy has been the subject of many misconceptions and controversies (Schachter, 2007). In the context of seizures, aggressive behaviours have been observed in the pre-ictal, ictal, and post-ictal states (before, during, and after the seizure, respectively), although directed and purposeful ictal aggression has only rarely been observed (Delgado-Escueta *et al.*, 1981). Inter-ictal aggressive behaviours (during periods between seizures) have sometimes been attributed to the irritability described in what some have termed an "inter-ictal dysphoric disorder" of epilepsy (Blumer, 1997).

Medications, including some antiepileptic drugs (AEDs), have been associated with the induction or exacerbation of adverse psychotropic effects including aggression (Ettinger, 2006). Our knowledge of aggression and related effects such as irritability is based on reviews of predominantly spontaneous reporting of psychiatric symptoms in clinical case experience or in premarketing drug trials. One challenge in determining the rate and nature of AED-induced aggression is the fact that most studies are focused on the anti-seizure efficacy of AEDs, and on the capture of more traditional potential adverse events (AEs) such as fatigue or rash, and do not rigorously assess psychiatric symptoms. Furthermore, the terminology for aggression and related terms is not well-defined and not universally accepted even among experts in the field of psychiatry.

Some measures have been developed to detect or rate aggression-related behaviours, but these are rarely used in the context of premarketing trials of AEDs. Instead, psychiatric symptoms are typically reported by patients using informal terms that do not adhere to strict diagnostic criteria. These informal terms are usually standardised and categorised using the Medical Dictionary for

Regulatory Activities (MedDRA), an internationally-endorsed dictionary and thesaurus for medical terminology. For example, when a patient reports "feeling queasy" and this is entered into the study database, this is categorised into a more specific Preferred Term (nausea), to which other related symptom descriptors are also linked. Related Preferred Terms are grouped into High Level Terms (nausea and vomiting), which are in turn grouped into High Level Group Terms and ultimately System Organ Classes (gastrointestinal disorders). Standardised MedDRA queries (SMQs) have been developed (and extensively reviewed and tested) that can look across these groupings for terms that are related to the condition of interest. SMQs can be narrow (terms that are highly likely to represent the condition of interest), and thus have high specificity but low sensitivity; or broad, with higher sensitivity at the expense of more false positives (i.e. will select some AEs that will, on inspection, not be related to the event in question). Thus the narrow SMQ for hostility/aggression identifies AE terms that are very likely to be related (e.g. 'anger' and 'physical assault'). The broad SMQ also includes broadly related terms like "skin laceration" that will often not be related to hostility or aggression, but will be a direct result in some cases.

We considered agitation, anger, hostility, impulsivity and irritability as the most important terms that are related to and encompass aggression and related behaviours. We therefore used these terms to direct our searches for evidence of aggression associated with AEDs, and we review the terms here, in the way they are traditionally used in the psychiatric literature. None of these terms themselves are individual diagnoses in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), but some (particularly irritability, impulsivity, and aggression) are used to describe important components and symptoms of psychiatric diagnoses (American Psychiatric Association, 2013).

A. Aggression

Even in the fields of psychology or psychiatry, terms like aggression, anger, hostility or irritability have been used loosely and interchangeably. Proposed definitions have gone through numerous iterations. Dollard and colleagues defined aggression as "*the affectively driven attack on another with the intent to do harm*" (Dollard *et al.*, 1939). Feshbach proposed a distinction between anger-motivated hostile aggression and instrumental aggression (in which anger and intent to harm could be absent but harm does result) (Feshbach, 1964). DiGiuseppe and Tafrate returned to the concept of intent to harm, defining aggression as "*overt motor behaviour enacted with the intent to do harm or injury to a person or object, with the expectation that harm will occur*" (DiGiuseppe and Tafrate, 2007). Associated affective states may include irritation, frustration, fear and even pleasure (Campbell, 2009).

Aggression may appear as *"hostile, threatening, and violent behaviors*" (Onyike and Lyketsos, 2011). And it has been noted that "*behaviors range from assertiveness to coercion (including the use of force) and from hostile attitudes and verbal abuse to threats, belligerence, and violence*" (Campbell, 2009). There may be no, trivial or minimal provocation (Onyike and Lyketsos, 2011).

Aggression may be a symptom of diverse psychiatric conditions including "*delusional psychoses, dementia, agitated delirium, intoxication, conduct disorder in children or personality disorders (particularly antisocial, borderline, paranoid, and narcissistic types) in adults, and even adjustment disorder*" (Onyike and Lyketsos, 2011). Aggression also may complicate non-psychiatric illnesses because it can develop when patients feel disregarded or "*angered by perceived unfairness or mistreatment, or as a 'primary' symptom of the illness*" (Onyike and Lyketsos, 2011). Aggressive behaviours have also been described as an adverse psychotropic

effect of medications such as AEDs (Dinkelacker *et al.*, 2003). Indeed, Gollan and colleagues distinguished medically-related aggression from premeditated or impulsive types (Gollan *et al.*, 2005).

From an evolutionary perspective, aggression may have developed in humans for self-preservation (e.g. protecting offspring), but also for "*retaliation, material advantage, and power*" (Onyike and Lyketsos, 2011). It can serve as a behaviour designed to attain a goal or defend against threats (Miczek *et al.*, 2002; Takahashi *et al.*, 2011). Aggression in some situations is a manifestation of "*appetitive drives*" while in others, it is a defensive behaviour (Onyike and Lyketsos, 2011).

B. Agitation:

Agitation is "*a state of pathologically intense emotional arousal and motor restlessness*" (Onyike and Lyketsos, 2011), typically associated with hyperactive behaviours such as handwringing or aimlessly pacing (Campbell, 2009), "*cursing, screaming, biting, and fighting, and it may evolve through a verbally or physically aggressive behavior*" (Comai, Tau, and Gobbi, 2012; Comai, Tau, Pavlovic, *et al.*, 2012). It is characterised by "*inappropriate verbal, vocal, or motor activity that is not explained by apparent needs or confusion* per se" (Comai, Tau, and Gobbi, 2012; Comai, Tau, Pavlovic, *et al.*, 2012).

C. Anger

Anger was defined by Spielberger as "*an emotional state, varying in intensity from mild annoyance to rage, that is accompanied by arousal of the autonomic nervous system*" (Spielberger, 1996). Spielberger distinguished the anger state (the experience of these emotions) from trait (a tendency toward recurrently experiencing these emotions). DiGiuseppe and Tafrate

proposed a more multi-dimensional construct defining anger as "*a constellation of specific uncomfortable subjective experiences and associated cognitions (e.g. thoughts, beliefs, images) that have variously associated verbal, facial, bodily, and automatic reactions*" (DiGiuseppe and Tafrate, 2007). They further emphasise that anger is experienced in "*people's conscious awareness and is communicated through verbalizations and bodily reactions*" (DiGiuseppe and Tafrate, 2007).

D. Hostility

An older literature describes hostility in the context of personality traits; i.e., "*an attitude of resentment, suspiciousness, and bitterness coupled with the desire to get revenge or to have destructive goals for one's anger*" (Endler and Hunt, 1968). Spielberger defined it as "*the disposition to perceive a wide range of situations as annoying or frustrating, and the tendency to respond to such situations with more frequent elevations in state anger*" (Spielberger, 1988). Both Spielberger and Barefoot divide hostility into cognitive components (e.g. negative beliefs, cynicism, mistrust), an affective or emotional component (i.e. varying degrees of anger) and the behavioural component (verbal or physical assault with intent to cause harm) (Barefoot, 1992), while others contend that the term hostility should be reserved for the cognitive component (Vollrath, 2006).

E. Impulsivity

Impulsivity may be described as "*acting without control or premeditation*" (Comai, Tau, and Gobbi, 2012), or "*behaving recklessly without regard to consequences*" (Hollander *et al.*, 2000). In less formal terms, it may be conceptualised as "a*cting without thinking*" (Barratt, 2000) or without self-restraint, with a tendency toward 'hair-trigger' actions (Onyike and Lyketsos, 2011).

Campbell's Psychiatric Dictionary defines impulsivity as "*a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or others.*" They further note it to be "*a pattern of behavior consisting of rapid, unplanned actions which occur unexpectedly, without reflection or conscious judgment, and without regard for possible consequences*" (Campbell, 2009).

F. Irritability

Irritability is a term that is commonly used in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013) as a component of psychiatric diagnoses such as Major Depressive Disorder or Generalised Anxiety Disorder (DiGiuseppe and Tafrate, 2007), but the term itself is not defined there. Irritability also accompanies many neurologic disorders such as dementia and is a component of the controversial interictal dysphoric disorder of epilepsy (Blumer *et al.*, 2004; Amiri and Hansen, 2015).

Born and Steiner's work (Born and Steiner, 1999) as summarised by DiGiuseppe, described five components of irritability:

> *"(1) a heightened or excessive sensitivity to external stimuli, (2) a negative affective state, (3) a state of physical and psychological tension that may suddenly and rapidly escalate, (4) reduced control over temper, proneness to anger, annoyance, or impatience, and (5) irascible verbal behavior outbursts, or even explosive behavior"* (DiGiuseppe and Tafrate, 2007).

Piazzini emphasised the extreme sensitivity to stimulation of any kind and excessive response to "*environmental, situational and emotional stimuli*" (Caprara *et al.*, 1992; Piazzini *et al.*, 2011).

Coccaro defines irritability succinctly as "*a tendency to respond with negative affect in reaction to aversive stimuli or with hypersensitivity to aversive stimuli*" (Coccaro *et al.*, 1991, 2000).

To summarise, although there is a diversity of terms that relate to the concept of aggressive behaviours, in this review article we use the phrases "aggression" and "aggressive behaviours" to express the broad range of associated concepts including agitation, anger, hostility, impulsivity and irritability.

III. Aggressive behaviour in epilepsy: clinical aspects

There is clear evidence that psychiatric disorders are more frequently encountered in patients with epilepsy than in the general population with prevalence rates in the region of 20%–30% for mood and anxiety disorders and 2%–7% for psychoses (Lin *et al.*, 2012).

In general terms, the wide range of manifestations of aggression described earlier have been reported in people with epilepsy, by many different authors (Bach-y-Rita *et al.*, 1971; Maletzky, 1973; Maletzky and Klotter, 1974; Ratner and Shapiro, 1979; Leicester, 1982; Elliott, 1984, 1990; Stone *et al.*, 1986; van Elst *et al.*, 2000). However, in several cases, it was a general impression of aggression, not supported by scientific evidence, and possibly influenced by old-fashioned prejudices about epilepsy (de Boer *et al.*, 2008; Monaco and Mula, 2011). In fact, studies on the true prevalence of aggressive behaviours in people with epilepsy are scarce.

As stated earlier, psychiatric symptoms in epilepsy have been historically classified according to their temporal relation with seizures as peri-ictal, ictal, and inter-ictal. Ictal symptoms are the clinical expression of an epileptic seizure. Peri-ictal refers to symptoms preceding (pre-ictal) or following (post-ictal) the seizure while inter-ictal symptoms are those that occur in no clear time relationship to the seizures (Table 1).

Peri-ictal aggression is often associated with confusion or psychosis. Although pre-ictal (prodromal) aggressive behaviour has been described (Hughes *et al.*, 1993; Devinsky, 2003) very little detail has been published. Aggressive behaviour has been reported in 22.8% of cases of post-ictal psychoses (Kanemoto *et al.*, 2010). Aggressive behaviour as an ictal phenomenon is extremely rare. A large survey of several thousand seizures documented on video electroencephalogram (EEG) reported an incidence rate of 1 in 1000 for aggressive conduct during seizure (Delgado-Escueta *et al.*, 1981). However, in all these cases, violent motor automatisms during seizures were misinterpreted as threatening or assaultive. In fact, although the aggressive act may appear orchestrated, it is poorly directed and does not involve intricate skills or purposeful and detailed behaviours (Marsh and Krauss, 2000). The aggressive conduct is directed towards nearby objects or persons, involving mainly pushing and shoving. Typical epileptic phenomena such as staring, oral and motor automatisms, may be present. The patient is usually amnestic for these episodes, expressing subsequent profound remorse (Devinsky and Bear, 1984; Herzberg and Fenwick, 1988; Fenwick, 1989). In the few cases reported from a series in monitoring units, aggressive automatisms were shown to be related to epileptic activity rising from the amygdala and spreading through the diencephalic regions (Lee *et al.*, 1998). No clear lateralising features were described, although associated symptoms point to the non-dominant hemisphere (Marsh and Krauss, 2000). The attribution of violent behaviours to an ictal

event is not always simple and video-EEG monitoring always elucidates. Treiman recommended five criteria to determine whether a specific violent act was the result of an epileptic seizure: (a) an established diagnosis of epilepsy; (b) the video-EEG documentation of epileptic automatisms; (c) the video-EEG documentation of the aggressive behaviour; (d) the aggressive act should be characteristic of the patient's habitual seizures; (e) a clinical judgment should be made by the neurologist as to the possibility that the violent act was part of a seizure (Treiman, 1986; Marsh and Krauss, 2000). These video EEG studies also revealed that aggressive behaviour tended to occur as "resistive" violence, typically when an attendant went to assist the patient during ictal or postictal confusional states; the implication is that the patient may have misinterpreted the attendant's actions in their confusional state and may consequently have resisted aggressively (Treiman, 1986).

The available data, therefore, clearly indicate that aggressive behaviour in epilepsy is most commonly unrelated to seizures themselves. A recent paper focusing on homicide identified 30 articles and 176 cases (published up to 2013) involving alleged perpetrators with epilepsy (Pandya *et al.*, 2013). In 78% of cases, there was no temporal relationship of the homicide with seizures. In the remaining 22%, the violent episode occurred as a post-ictal event in the majority of cases (82%). Patients were usually young males, with low average intelligence and a history of behavioural problems starting during childhood. Alcohol abuse and stressful situations were precipitating factors. This is of interest when we consider psychiatric disorders associated with aggressive behaviour. DSM-5 states that aggressive behaviour can occur in association with disruptive, impulse-control or conduct disorders or antisocial personality disorder (American Psychiatric Association, 2013). These disorders are all characterised by problems in emotional and behavioural self-control and often start during childhood. Data from the Epidemiology

Catchment Area survey reported a 1-year prevalence of violent behaviours of 2.05% (2.7% for males and 1.1% for females) among respondents without any psychiatric disorder (Swanson *et al.*, 1990). In the large DSM-5 chapter on impulse control disorders, intermittent explosive disorder is the most pertinent in this discussion. It is characterised by aggressive outbursts that should be impulse- and/or anger-based in nature and must cause marked distress, cause impairment in occupational or interpersonal functioning or be associated with negative financial or legal consequences. According to the DSM criteria (American Psychiatric Association, 2013), antisocial personality disorder is defined by a pervasive pattern of disregard for the rights of other people that often manifests as hostility and/or aggression. It also starts during childhood. Conduct disorder is often considered the precursor of the antisocial personality disorder. As for impulse control disorders, patients with antisocial personality disorder frequently act on impulsive urges without considering the consequences. This difficulty with impulse control can result in loss of employment, accidents, legal difficulties, and incarceration. Remorse is quite common after behaviours that are the result of poor impulse control. In contrast, a typical and distinguishing feature for antisocial personality disorder is the lack of genuine remorse for the harm they cause others, although these patients can become adept at feigning remorse when it is in their best interest to do so.

The lack of data about prevalence of these disorders in patients with epilepsy is quite striking. Despite the huge volume of publications on the controversial issue of personality changes in epilepsy, we could find no studies that have investigated antisocial personality disorder or impulse control disorders in adults with epilepsy, although it is of interest to note that in childhood epilepsy the prevalence of ADHD (in which impulsivity is a core feature) is common, around 20-30% (Hermann *et al.*, 2007). Studies investigating inter-ictal aggressive symptoms are

also limited. In the 1970s, Rodin reported the prevalence of aggressive behaviour as 4.3% in unselected samples of patients with epilepsy (Rodin, 1973), while Currie et al. reported up to 7% (Currie *et al.*, 1971). More recently, a multicentre study using a newly developed questionnaire suggested that people with epilepsy have slightly less aggressive behaviours than the general population, and that cognitive impairment and polytherapy are the major associated variables (Piazzini *et al.*, 2011). However, significantly more aggressive behaviour was presented in patients without comorbid psychiatric disorders than patients with psychiatric comorbidities. Prevalence rates for aggression were not reported, as aggressive symptoms were reported as a dimension. One research group has investigated the neuroanatomical correlates of aggressive behaviour in temporal lobe epilepsy, showing a reduction in neocortical grey matter in the frontal areas and amygdala atrophy, but no association with hippocampal pathology (van Elst *et al.*, 2000; Woermann *et al.*, 2000).

IV. Neurobiology and psychopharmacology of epilepsy and aggression

A. Epilepsy and aggression: neurobiological and neuropharmacological correlates

Aggressive behaviour is one of the psychiatric disorders that has long been described in people with epilepsy (Kligman and Goldberg, 1975; van Elst *et al.*, 2000; Sumer *et al.*, 2007). Both the epilepsy itself (Marsh and Krauss, 2000), and AED use, have been suggested as factors that can increase the risk of aggressive behaviour in epilepsy patients. In this section, we will examine this topic from a neurobiological and psychopharmacological perspective.

The underpinnings of aggression (Siever, 2008; Comai, Tau, and Gobbi, 2012) and epilepsy (Engel *et al.*, 2007; Scharfman, 2007; Moshé *et al.*, 2015) are clearly multifaceted, and some forms of pathological aggression associated with epilepsy have an underlying neurobiology that we are only beginning to understand. While well-characterised and approved pharmacological strategies are currently available for the treatment of the different forms of epilepsy (Kwan *et al.*, 2001; Moshé *et al.*, 2015), national and international guidelines for the pharmacotherapy of aggression are still controversial and regulatory drug agencies do not presently consider aggressive behaviour as a distinct disease (Comai, Tau, Pavlovic, *et al.*, 2012). Consequently, no medication is specifically approved for the treatment of aggression. One of the main reasons behind this lack of guidelines is that the complex neurobiological basis of aggressive behaviour has not yet been elucidated by fundamental and clinical research.

B. Neuropharmacology of epilepsy

Seizures, at a basic level, originate from an imbalance between excitatory and inhibitory inputs to cells, i.e. increased excitation or decreased inhibition. The result is an abnormal synchronisation of electrical activity in a group of active neurones and, depending on the site of origin and the subsequent brain structures and networks affected, seizures may produce a variety of clinical features and symptoms, and may remain localised or generalise across the entire brain. Epilepsy is a network disorder in which the normal physiological connections between cortical and subcortical pathways/regions are interrupted or disturbed.

The terminology and classification of seizures in epilepsy is currently under revision. Seizures are broadly defined as either focal – which originate within networks in one hemisphere – or

generalised – which originate and rapidly engage bilaterally distributed networks (Berg *et al.*, 2010). The older term 'partial onset' is no longer preferred, and the distinctions between primary and secondarily generalised (i.e. affecting both hemispheres from the outset, or progressing to both hemispheres after a focal onset) are not preserved in the new classification, but are still in widespread use. Seizures can then be described in terms of their type (for example, generalised tonic–clonic, absence, myoclonic, clonic, tonic, or atonic) and by their underlying cause (genetic *vs* structural/metabolic *vs* unknown). Many syndromes are also defined – such as juvenile myoclonic epilepsy (JME) and Lennox–Gastaut syndrome (LGS) – which are characterised by complex and specific clinical features, signs, and symptoms that frequently cluster together (Berg *et al.*, 2010).

At a cellular level, the electrical activity of neurons is under the control of ion transporters, pumps and ion channels which allow amounts of positively or negatively charged ions to flow in and out of cells. In turn, these pumps and ions channels are regulated by factors such as voltage or the binding of ligands either directly or via G-protein-coupled receptors (GPCRs) (Kandel *et al.*, 2000; Dascal, 2001; Bean, 2007). The pivotal channels in these processes are Na^+, K^+, Ca^{2+} and Cl^- channels, which are also the target of many of the current available antiepileptic drugs (Table 1).

The major excitatory and inhibitory neurotransmitters are, respectively, glutamate and γ-aminobutyric acid (GABA) (Kandel *et al.*, 2000), and these neurotransmitter systems are also targeted by many other AEDs (Table 1). Monoamines including serotonin (5-HT), dopamine (DA) and noradrenaline (NA) represent another group of neuroactive compounds that regulate neural activity and thus could influence the initiation and spread of seizure activity (Starr, 1996;

Giorgi *et al.*, 2004; Stefulj *et al.*, 2010); however these are not primarily targeted by any current AEDs.

C. Neurobiology and neuropharmacology of aggression

Aggression is a complex behaviour governed by several cortical and subcortical brain networks which are modulated by neurotransmitter systems including monoamines, glutamate, GABA, and by ion channels (Gedye, 1989; Sumer *et al.*, 2007). The neurobiological impairments observed in aggression occur at genomic and transcriptional levels as well as at the level of the synthesis and the metabolism of various neurotransmitters and their receptors. The main receptors and enzymes involved in the neurobiology of aggression, and which are also targeted by anti-aggressive medications, include those involved in monoamine neurotransmission – serotonin 5-HT_{1A} and 5-HT_{2A} receptors, serotonin transporters, dopamine D_1 and D_2 receptors, dopamine transporters, α_1- and α_2-adrenoceptors, and the enzyme monoamine oxidase A (MAO-A) – the GABA system ($GABA_A$, and $GABA_B$, receptors, and GABA transaminase), the glutamate NMDA and AMPA receptors, and voltage-gated Na^+ and Ca^{2+} channels (Siever, 2008; Comai, Tau, and Gobbi, 2012) (Figure 1). Genetic and epigenetic regulation of these neurotransmitters, channels and enzymes as well as the intracellular events following their cell activation/deactivation are also involved in aggressive behaviour (Comai, Tau, and Gobbi, 2012). For example, polymorphic variation in the gene for MAO-A (Manuck *et al.*, 2000), and MAO-A gene promoter hypermethylation, which causes a downregulation of MAO-A activity (Checknita *et al.*, 2015), have been associated with aggressive behaviour.

At a structural level, the study of brain lesions, brain injury, and imaging techniques have identified several regions as important in the pathophysiology aggression, particularly the amygdala, hippocampus, and frontal lobes (Bannon *et al.*, 2015). Functional imaging techniques such as PET and SPECT provided further evidence for the contribution of the ventromedial cortex, limbic system, amygdala, and thalamus in impulsivity and aggression; in particular, a general reduction of activity in the medial temporal subcortical lobe was demonstrated (reviewed by Soyka, 2014,Perez-Rodriguez *et al.*, 2012) in aggressive behaviour. In the search for possible imaging biomarkers of aggression, a reduced grey matter volume at the level of the orbitoprefrontal cortex and low amygdala volume have both been linked with predisposition to violence (Matthies *et al.*, 2012; Pardini *et al.*, 2014; Bannon *et al.*, 2015). Collectively, although brain imaging studies have detailed important neuroanatomical information underlying aggressive and impulsive behavior, this knowledge cannot yet be used to predict aggression in humans. However, future imaging studies specifically designed to examine epileptic patients who display enhanced aggression or develop aggression following AEDs treatment, may help disentangling brain imaging abnormalities due to epilepsy or to aggression, and possibly to find a prognostic/clinical imaging marker of aggression in epilepsy. (Razafsha *et al.*, 2015).

D. Networks and neurotransmitters common to epilepsy and aggression

EEG changes during seizures and their clinical manifestation reflect the localisation of the seizure activity (Engel *et al.*, 2007); subcortical structures (including thalamus and brain stem), may play a crucial role in the propagation and behavioural manifestations of epileptic seizures rather than just being a site of seizure origin (Norden and Blumenfeld, 2002).

1. Temporal lobes and hippocampus

One of the most common and studied forms of focal epilepsy is temporal lobe epilepsy (TLE). Seizures originate in the temporal lobes (either the inner surface/structures or more rarely the neocortex), and can be associated with psychiatric symptoms, including mood changes and aggressivity (Zhao *et al.*, 2014). The temporal lobe is also important in aggression: in milestone research by Klüver and Bucy, bilateral temporal lobectomy in rhesus monkeys reduced aggression (Klüver and Bucy, 1937). The temporal lobe is part of the limbic system that controls emotions and memory, and subjects with histories of extremely violent behaviour have shown metabolic abnormalities in the temporal lobes (Seidenwurm *et al.*, 1997); functional and/or structural abnormalities in neural networks regulating emotions have been related to an increased susceptibility for impulsive aggression and violence (Davidson *et al.*, 2000). TLE is often associated with an extensive loss of dentate hilar neurons and hippocampal pyramidal cells – the so called "hippocampal sclerosis" (Sloviter, 1994) – and interestingly, hippocampal pathology has been identified in pathological aggression (see later).

2. Amygdala

The amygdala has been implicated in epilepsy, particularly in TLE and in epileptogenesis, since the landmark studies by Penfield in the early 1950s (Feindel and Penfield, 1954) and later by Goddard (Goddard *et al.*, 1969). Since this early work, many studies have shown that different forms of epilepsy are associated with damage to the amygdaloid complex (23 distinct subnuclei in humans) and to its connectivity to the surrounding brain regions and to the cortex (Pitkänen *et al.*, 1998; Elst *et al.*, 2002; Takaya *et al.*, 2014). The amygdala is also implicated in aggressive behaviour: amygdalectomy in both animals and humans can stop aggressive behaviour (Terzian and Ore, 1955), and stereotactic amygdalotomy of specific amygdaloid nuclei (e.g. the lateral or

the anteromedial group) has been shown to control behaviour in highly aggressive, treatment-refractory individuals (Mpakopoulou *et al.*, 2008).

3. Frontal lobes

Frontal lobe epilepsy, the second most common type of focal epilepsy, is also associated with aggressive behaviour during and after seizures (Gedye, 1989; Sumer *et al.*, 2007). Damage to the frontal lobes is implicated in violent and aggressive behaviour – patients with frontal ventromedial lesions consistently demonstrated higher rates of aggression/violence (especially verbal confrontations) than patients with lesions in other brain areas (Grafman *et al.*, 1996). Motor agitation and aggressive behaviour have also been shown in patients with orbitofrontal seizures (Tharp, 1972), further supporting the role of dysfunction in this brain region in aggression (Giancola, 1995).

4. Hypothalamus

Other brain areas implicated in the pathophysiology of aggressive behaviour and which are components of emotional regulation circuits include the anterior cingulate cortex, the amygdala, hypothalamus, septal nuclei, and periaqueductal grey matter of the midbrain (Figure 2). The hypothalamus is an important part of the diencephalon that is implicated in both epilepsy and aggression. Studies in cats have shown that the hypothalamus, in particular the anterior medial hypothalamus, is involved in the modulation of defensive rage behaviour (Gregg and Siegel, 2001). A positron emission tomography study in humans found low hypothalamic activity in male perpetrators of domestic violence and decreased correlations between cortical and subcortical brain structures (George *et al.*, 2004). Anterior hippocampal asymmetries have been demonstrated in antisocial and violent subjects (Raine *et al.*, 2004), and an inverse correlation

between hippocampal grey matter volume and lifetime aggression in borderline personality disorder (Zetzsche *et al.*, 2007).

Considered together, it is clear that neurobiological networks that are important in epilepsy are also common neural substrates implicated in aggressive behaviour. A summary of the networks and brain regions that are important in both epilepsy and aggression is shown in Figure 2.

Within these brain regions and networks, the receptors and ion channels that are implicated in both epilepsy and aggression are also the targets of AEDs and mood stabilisers. In addition, alterations at the level of intracellular signalling cascades, gene sequence or gene expression have been shown in both epilepsy and aggression in these areas.

5. GABA

Clinical and preclinical studies have shown that seizures are liable to occur with an increase in glutamate and/or decrease in GABA neurotransmission in the brain. However, the changes in glutamate and/or GABA levels are different in different types of epilepsy, animal models and brain regions (Engel *et al.*, 2007). $GABA_A$ receptors are ligand-gated chloride ion channels and are the major inhibitory receptors in the central nervous system (Olsen and Tobin, 1990). $GABA_A$ receptor expression, subunit composition, and function in epilepsy has been extensively reviewed recently (Houser *et al.*, 2012). Changes in $GABA_A$ receptor expression and function have been reported in animal models of TLE (Peng *et al.*, 2004), and the composition and function of $GABA_A$ receptors changes not only in epilepsy, but also after prolonged exposure to $GABA_A$ allosteric modulators such as the AEDs diazepam and phenobarbital (Raol *et al.*, 2005).

GABA neurotransmission has been also been investigated in the pharmacology and pathophysiology of aggression (Comai, Tau, and Gobbi, 2012). The situation is complex, and

there is no clear agreement on whether GABA levels are decreased or increased in aggression, or whether enhancing GABA is anti- or pro-aggressive. For example, while Bjork *et al.* found a negative correlation between plasma GABA levels and aggressiveness in psychiatrically healthy people with a family history of depression (Bjork *et al.*, 2001), Lee *et al.* reported a positive correlation between GABA levels in the cerebrospinal fluid and impulsivity (but not aggression) in both non-medicated normal controls and personality disordered subjects (Lee *et al.*, 2009). Allosteric modulators of $GABA_A$ receptors, including barbiturates and benzodiazepines, have been shown to influence aggression levels in rodents with an inverted U-shaped dose–response curve: moderate doses induce aggression whereas low or high doses reduce aggressive behaviour (Miczek *et al.*, 2002).

6. Glutamate

Glutamate is the principal excitatory neurotransmitter in the brain. It acts through ionotropic (NMDA, AMPA and kainite) and metabotropic receptors and plays a significant role in the initiation, spread, and maintenance of epileptic activity. Research has demonstrated that epilepsy is linked to dysfunction of the glutamate system at different levels: genetic, neurotransmitter release, and receptor expression (Bradford, 1995; Barker-Haliski and White, 2015). Studies have reported increased plasma levels of glutamate in epilepsy (van Gelder *et al.*, 1980; Janjua *et al.*, 1992), and sustained increases in extracellular glutamate levels during seizures in the epileptogenic hippocampus (During and Spencer, 1993). Focal brain cooling (FBC), which can suppress epileptic seizures in refractory epilepsy, has been shown to significantly decrease glutamate levels in patients who have elevated glutamate in the cortex and/or hippocampus during seizures (Nomura *et al.*, 2014). Glutamate is cleared from synapses by the membrane glutamate transporters (GLUT), and loaded into synaptic vesicles by the vesicular glutamate

transporters VGLUT1, VGLUT2, and VGLUT3 (El Mestikawy *et al.*, 2011). A recent post-mortem study comparing VGLUT expression in the hippocampus, found significantly decreased VGLUT2 expression and significantly increased VGLUT3 expression in patients with TLE with hippocampal sclerosis, compared with autopsy controls (Van Liefferinge *et al.*, 2015). Glutamate receptors, both ionotropic and metabotropic have been extensively studied for their role in epilepsy in both human and animal studies (Moldrich *et al.*, 2003; Ghasemi and Schachter, 2011; Szczurowska and Mareš, 2013). Glutamate receptors are targeted selectively and non-selectively by several AEDs (Table 1), and novel glutamate receptor ligands are also under development as potential AEDs (Löscher *et al.*, 2013; Nicoletti *et al.*, 2015).

Attention was initially directed towards antagonists of NMDA receptors, but they failed in several clinical trials (Rogawski, 2011). Interestingly , the NMDA antagonists phencyclidine (PCP) and ketamine have pro-convulsant action at very high doses while at low doses they have anticonvulsant properties (Leccese *et al.*, 1986). Research then moved to AMPA receptors (Rogawski, 2011), and 2012 saw the approval of the first selective AMPA receptor antagonist, perampanel, for the treatment of focal seizures. The role of kainate receptors in the pathophysiology of epilepsy is becoming better understood, particularly in temporal lobe epilepsy, and this has been recently reviewed (Crépel and Mulle, 2015). Kainate receptors are located either presynaptically at both GABAergic and glutamatergic synapses where they control neurotransmitter release and are involved in presynaptic plasticity (Schmitz *et al.*, 2001), or postsynaptically in several regions deeply involved in epilepsy including the cortex, the hippocampus and the amygdala (Crépel and Mulle, 2015).

Few studies have so far investigated the role of glutamate in aggression (Comai, Tau, and Gobbi, 2012); however, there is strong evidence of the involvement of glutamate in the pathophysiology

and treatment of mood disorders such as depression (Kugaya and Sanacora, 2005; Niciu *et al.*, 2014) that often co-exist with aggressive behaviour. Support for the glutamate hypothesis of aggression includes the demonstration of a positive relationship between CSF glutamate levels and measures of impulsive aggression in both healthy human subjects and subjects with personality disorders (Coccaro *et al.*, 2013). Studies in mice with genetic modifications at the levels of the genes encoding for the NMDA and AMPA receptors have shown altered levels of aggression in the resident intruder test (Brodkin *et al.*, 2002; Duncan *et al.*, 2004; Vekovischeva *et al.*, 2004), an animal paradigm of aggressive behaviour, suggesting a role for glutamate ionotropic receptors in aggression in rodents. In mice, the NMDA receptor channel blocker phencyclidine (PCP) produces a non-significant trend toward increased aggressiveness at low doses, while at high (near ataxic) doses, it seems to reduce aggression (Belozertseva and Bespalov, 1999). The fact that medications that can decrease aggression, such as valproic acid and topiramate, have inhibitory effects at NMDA and AMPA receptors (Comai, Tau, Pavlovic, *et al.*, 2012) provides further supportive evidence for the involvement of glutamate in aggression; however, the association of these same AEDs with aggression in some patients with epilepsy shows that the mechanisms are complex.

7. Serotonin

Bonnycastle *et al.* were the first to demonstrate a link between anticonvulsant activity and serotonin (5-HT), showing that several AEDs, including phenytoin, significantly increased 5-HT levels (Bonnycastle *et al.*, 1957). Pharmacological agents that elevate 5-HT levels such as the selective serotonin reuptake inhibitor (SSRI) fluoxetine and 5-hydroxytryptophan have anticonvulsant effects in several animal models of epilepsy (Pasini *et al.*, 1992), whereas agents

that reduce and/or deplete 5-HT such as parachlorophenylalanine, a selective and irreversible inhibitor of tryptophan 5-hydroxylase, increase susceptibility to sound-induced seizures (Schlesinger *et al.*, 1968). 5-HT receptors are expressed in almost all networks involved in epilepsy. With the exception of 5-HT_5 receptors, for which there is no evidence yet of involvement in epilepsy, Gharedaghi *et al.* have recently reviewed and commented on the role of each 5-HT receptor subtype in epilepsy and seizure susceptibility (Gharedaghi *et al.*, 2014).

Activation of 5-HT_{1A} receptors is anticonvulsant in various experimental seizure models. A study administering a 5-HT_{1A} agonist in lithium-pilocarpine-induced status epilepticus in mice, showed that hippocampal 5-HT_{1A} receptors are involved in reducing seizure severity while those located in extra-hippocampal areas contribute to delayed seizure propagation (Yang *et al.*, 2014). In patients with TLE, decreased 5-HT_{1A} receptor binding has been observed in the midbrain raphe, ipsilateral thalamus and the inferior region of the epileptogenic temporal lobe (Toczek *et al.*, 2003). Genetic inactivation of 5-HT_{2C} receptors in mice produces rare spontaneous seizures that are occasionally fatal (Heisler *et al.*, 1998).

In aggression, 5-HT has a central role, and hundreds of papers have examined this topic since the early 1960s. It was believed that 5-HT generally inhibits aggression, but recent findings challenge this hypothesis, showing that this may be limited to certain types of aggression, such as impulsive aggression, or perhaps instead to factors such as impulse control and emotion regulation (Krakowski, 2003). For example, the main metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), is reduced in the cerebrospinal fluid of people with demonstrated auto- or hetero-aggressive behaviour, compared with people who have never shown such behaviour. These observations were made in suicidal individuals (Asberg *et al.*, 1976), in non-depressed men with a history with aggressive behaviour (Brown *et al.*, 1979), violent men in prison (Linnoila *et al.*,

1983), in impulsive arsonists (Virkkunen *et al.*, 1987), and in patients with a personality disorder (Coccaro EF *et al.*, 1989). The 5-$HT_{1A/1B}$ agonist eltoprazine is considered a potent anti-aggressive agent (Comai, Tau, and Gobbi, 2012).

8. Dopamine

The role of dopamine (DA) in epilepsy is still debated, although there is evidence of dopaminergic system involvement in certain animal models of epilepsy and in various forms of epilepsy in humans (Starr, 1996). In particular, alterations of subcortical dopaminergic pathways may be specifically related to the motor manifestations of certain types of seizures (Norden and Blumenfeld, 2002).

In general, DA seems to exert an antiepileptic action, as demonstrated by the fact that the non-selective D_1/D_2 agonist apomorphine, with certain limitations, has anticonvulsant properties, while neuroleptic drugs which act as D_1 and/or D_2 antagonists have predominantly proconvulsant actions. This is important, as some medications used to control aggression are D_1 and/or D_2 antagonists (Comai, Tau, Pavlovic, *et al.*, 2012). Looking at the role of specific DA receptors in epilepsy, evidence from both animal (Turski *et al.*, 1988; al-Tajir *et al.*, 1990) and human (Ring *et al.*, 1994) studies has implicated D_2 receptors.

The dopaminergic system is mainly implicated in behavioural activation, motivated behaviour, and reward processing (Ikemoto and Panksepp, 1999), but evidence suggests it also modulates aggressive behaviour. CSF levels of homovanillic acid, the final metabolite of DA, are lower in impulsively aggressive violent offenders with antisocial personality disorder than in non-impulsively aggressive offenders with paranoid or passive-aggressive personality disorder (Linnoila *et al.*, 1983). DA receptor antagonists, particularly conventional antipsychotics such as

haloperidol which target D_2 receptors, have been used effectively for decades to treat aggression in psychotic patients. Even though DA has been hypothesised to be necessary for aggressive behaviour to occur, reflecting the motivational aspect of violence (Nelson and Chiavegatto, 2001; de Almeida *et al.*, 2005), the exact role of DA in aggression is still unclear (Comai, Tau, and Gobbi, 2012).

9. Noradrenaline

Endogenous noradrenaline (NA) seems to be generally antiepileptic: NA levels are decreased after seizures, depending on seizure type and brain region (Giorgi *et al.*, 2004), and AEDs such as valproic acid increase NA levels in the rat (Baf *et al.*, 1994). The antiepileptic actions of NA are very likely mediated by both α_1- and α_2-adrenoceptors; indeed, α_2-adrenoreceptor agonists have been shown to suppress, and α_2-adrenoreceptor antagonists to promote seizures in kittens (Shouse *et al.*, 2007).

In aggression, NA seems to play a permissive role, helping to determine whether an individual elects to fight or flee in response to a challenge (Miczek and Fish, 2005). Studies have explored the impact on aggression of experimental depletion or increase of NA levels, and of activation or inhibition of NA receptors. However, research is still limited and no clear positive or negative correlation has yet been demonstrated. Some studies report *reduced* fighting tendency after depletion of brain NA – in male mice with isolation-induced fighting, and intraventricular injection of 6-hydroxydopamine (Crawley and Contrera, 1976). Some studies, in contrast, report increased aggression (shock-induced fighting) after NA depletion in rats (Thoa *et al.*, 1972). The role of α_2-adrenoceptors is important in mediating the effects of NA manipulations on aggression. For example, increasing NA levels with desipramine (a NA reuptake blocker), increases isolation-induced aggression in mice in a dose-dependent manner, and the α_2-

adrenoceptor blocker yohimbine dose-dependently counters this increase (Matsumoto *et al.*, 1991). In addition, the α_2-adrenoceptor agonist clonidine, which decreases NA neuronal activity by activating NA autoreceptors, has been shown to decrease pathological aggression in humans and is used largely in clinical settings in irritable autistic children, children with conduct disorder (Fava, 1997), and also in adults with aggression (Comai, Tau, Pavlovic, *et al.*, 2012). Clonidine is also of value in treating ADHD in children, particularly those with conduct or oppositional defiant disorder (Connor *et al.*, 1999, 2000).

10. Intracellular signalling cascades, genes and epigenetic gene regulation in epilepsy and aggression

Another important framework in which to consider in the neurobiology of epilepsy and AED development is the role of intracellular events – for example, intracellular proteins and signalling cascades, genes and epigenetic modifications (Löscher *et al.*, 2013).

The study of intracellular cascade events following receptor activation has been actively researched in epilepsy. In the pilocarpine-induced status epilepticus model, for example, increased phosphorylation of the mitogen-activated protein kinases (MAPKs) extracellular signal-regulated kinase (ERK)-1, ERK2, and $p38^{MAPK}$ has been demonstrated in the acute period (up to 12 hours after status epilepticus) and protein kinase B (AKT) in the latent period (5 days after pilocarpine induced status epilepticus) (Lopes *et al.*, 2012). These biochemical changes in the serine-threonine kinases which are implicated in neuronal survival and differentiation as well as neuroplasticity may, in turn, alter gene expression and produce long-lasting neuronal changes. However, ERK signalling has multiple roles during epilepsy-related processes; its activation can

contribute to acute seizure activity and might be necessary for epileptiform synchronization (Houser *et al.*, 2008). The mammalian target of rapamycin (mTOR) is a regulator of mRNA translation that is itself regulated by ERK and AKT (Li *et al.*, 2010). As reviewed by Cho, there is evidence to implicate abnormal activity of signalling molecules in the mTOR pathway in epilepsy (Cho, 2011).

There has been less research on the intracellular signalling cascades underlying aggressive behaviour, but as these cascades (and the GPCRs that activate them) are targeted by medications used to treat aggression (Beaulieu, 2012), it is reasonable to hypothesise their active involvement in the pathophysiology of aggression (Comai, Tau, and Gobbi, 2012). Aggressive behaviours are common among abusers of methamphetamine, and repeated injections of methamphetamine in mice have also been shown to increase aggressive behaviour (Sokolov and Cadet, 2006). In these animals, there were significant alterations in the expression of proteins involved in MAP kinase-related pathways in the striatum and frontal cortex (Sokolov and Cadet, 2006).

Regarding the specific involvement of genes in both epilepsy/seizure susceptibility and aggressive behaviour, studies have been very limited in number. Two genes that have been implicated in both seizures and aggression are the gene encoding the monoamine oxidase A (MAO-A) enzyme and that encoding the $5HT_{1B}$ receptor. In MAO-A knockout mice, which have high levels of 5-HT and NA, complex changes in seizure susceptibility are seen. After pentylenetetrazol kindling, the latency to seizure development is shorter in knock-out mice than wild type; however, the knock-out mice then have fewer seizures per day and shorter duration seizures compared with wild type, suggesting some protective effect despite the increased susceptibility to the kindling (Teskey *et al.*, 2004). Regarding aggressive behaviours, MAO-A knockout mice are more aggressive than wild-type mice, displaying decreased latency to attack

in the resident intruder test (Cases *et al.*, 1995). The only study in humans that explored links between epilepsy and polymorphisms in the gene encoding MAO-A was negative, but underpowered to detect minor differences (Stefulj *et al.*, 2010). The same study instead found a modest association between the G861C polymorphism in the 5-HT_{1B} receptor gene and temporal lobe epilepsy. Notably, a 5-HT_{1B} polymorphism has been associated with suicide history and personality disorder in humans (New *et al.*, 2001) and 5-HT_{1B} knock-out mice display increased levels of aggression in the resident intruder test (Bouwknecht *et al.*, 2001).

Epigenetic factors, including seizures themselves and AEDs, can alter neural network dynamics by interfering with signalling pathways, enzyme and receptor expression. Epilepsy can be influenced not only by alterations in genetic and environmental factors but also by a spectrum of dysfunctional epigenetic factors and processes (Qureshi and Mehler, 2010; Kobow and Blümcke, 2014). Indeed, hundreds of misregulated genes have been identified in human and experimental models of epilepsy following epigenetic chromatin modifications and DNA methylation. Modifications, such as DNA methylation, may accumulate over time following an initial injury, and a methylation hypothesis of epilepsy has been proposed (Kobow and Blümcke, 2012); such epigenetic changes may explain inter-individual differences in the emergence of epilepsy, for example following brain trauma (Machnes *et al.*, 2013). Interestingly, the AED valproic acid has been shown to inhibit histone deacetylases (HDACs) and thereby normalise expression of HDAC-dependent genes within the epileptic dentate area in rats with kainic-acid-induced seizures (Jessberger *et al.*, 2007).

The epigenetic modifications involved in aggressive behaviour have not been well studied. Evidence so far demonstrates a relationship between epigenetic modifications in the 5-HT system and aggression. In a recent study we found decreased MAO-A activity in antisocial

offenders, resulting from epigenetic modifications in MAO-A gene methylation levels (Checknita *et al.*, 2015). Methylation levels of the serotonin transporter gene promoter (SLC6A4) have also been shown to be altered in individuals displaying physical aggression during childhood (Wang *et al.*, 2012).

E. Pharmacological targets of AEDs for epilepsy and for aggression.

The pathophysiology of epilepsy is multifaceted, involving several neurotransmitter systems and many receptors, ion channels, intracellular signalling cascades, genes and epigenetic modifications (Engel *et al.*, 2007; Scharfman, 2007; Moshé *et al.*, 2015). Several of these possible mechanisms are targeted by current AEDs and are being targeted by new drug development. As shown in Table 1, the majority of current AEDs target primarily either the classical voltage-gated ion channels (Na^+, K^+ and Ca^{2+}), or the GABA system, while many AEDs have mixed mechanisms, and others selectively inhibit other targets (e.g. neurotransmitter release by levetiracetam, AMPA receptors by perampanel) (Rogawski and Löscher, 2004; Brodie, 2010; Comai, Tau, Pavlovic, *et al.*, 2012).

Modulation of genes and epigenetic mechanisms by AEDs has also been reported in recent years (Comai, Tau, and Gobbi, 2012; Comai, Tau, Pavlovic, *et al.*, 2012). Levetiracetam has a clear and distinct mechanism of action; it acts on the SV2A integral membrane glycoprotein present on all synaptic vesicles (Lynch *et al.*, 2004). Very recent work by Vogl *et al.* in superior cervical ganglion neurons demonstrated that SV2A maintained normal neurotransmission by regulating readily releasable pool size, had a facilitatory role in recovery from synaptic depression, and impaired presynaptic voltage-dependent Ca^{2+} channel current density (Vogl *et al.*, 2015).

Specific details on the mechanisms of action of AEDs at the level of receptors and ion channels have been extensively reviewed (Kwan *et al.*, 2001; Löscher *et al.*, 2013; Moshé *et al.*, 2015).

Many AEDs are also used to treat aggression in psychiatric populations; for example, in patients with schizophrenia, schizoaffective disorders, bipolar disorders, and autism spectrum disorders (Comai, Tau, Pavlovic, *et al.*, 2012). AEDs such as valproic acid, topiramate, gabapentin and lamotrigine are frequently used, as are those targeting ion channels, including carbamazepine, oxcarbazepine, lamotrigine and phenytoin (Comai, Tau, Pavlovic, *et al.*, 2012) (Table 1).

The atypical antipsychotics clozapine, olanzapine, quetiapine and risperidone, and also the conventional antipsychotic haloperidol, which are high-affinity antagonists at 5-HT_{2A} and/or 5-HT_{1A} receptors, and D_2 receptor antagonists, are also widely used "off-label" to attenuate aggressive behaviour (Gobbi *et al.*, 1999; Comai, Tau, Pavlovic, *et al.*, 2012). The rationale derives from the abnormalities of 5-HT and DA systems in the pathophysiology of aggressive behaviour (Comai, Tau, and Gobbi, 2012). Clozapine has been demonstrated to be superior to olanzapine and haloperidol in the control of aggression (Volavka *et al.*, 2004). In more resistant cases, the combination of clozapine and an AED such as valproic acid remains the most effective treatment (Gobbi and Debonnel, 2003).

F. Conclusions: Why might AEDs induce aggressive behaviour in epilepsy?

There is a complex comorbidity between aggression and epilepsy, and in this section we have shown that they also have complex and overlapping pathophysiology. In the following sections, the evidence for a link between aggressive behaviour and AEDs in people with epilepsy is reviewed. A critical question is, therefore, how can an AED apparently precipitate aggression in

some people with epilepsy but improve aggressive behaviours in other people. Here, we propose some speculations and hypotheses and speculation on this topic, based on common neurobiological correlates between epilepsy and aggression.

i) Paradoxical pro-aggressive effects of enhancing GABA neurotransmission. The GABA system has the potential for both inhibitory and excitatory actions. In the neonatal brain, GABA is excitatory and not inhibitory, due to the high intracellular concentration of chloride (Ben-Ari and Holmes, 2006). In the mature brain, rhythmic afterdischarge of pyramidal CA1 cells after cessation of the stimulus relies on a powerful $GABA_A$-mediated excitation mechanism (Fujiwara-Tsukamoto *et al.*, 2003). In adults with TLE, the morphology, the hippocampal expression and subcellular distribution of $GABA_A$ receptor subunits is markedly altered (Loup *et al.*, 2000) and, in mature neurons, recurrent and prolonged seizures may trigger a pathological re-emergence of immature excitatory features of $GABA_A$ receptors (Galanopoulou, 2008). Moreover, TLE is often characterised by hippocampal sclerosis and thus depletion of GABAergic interneurons and glutamatergic hilar mossy cells, by mossy-fibre (with co-localization of GABA and glutamate receptors) sprouting and synaptic reorganization in the dentate gyrus (Jinde *et al.*, 2013). We hypothesise that in the epileptic brain, many modifications in GABA receptors and GABA-ergic neurons can occur, such that agents enhancing GABA neurotransmission (which decrease aggressive behaviours in subjects without epilepsy) can, depending on the brain region, have the opposite impact of triggering, rather than decreasing, aggression.

ii) Dose-dependent and opposite effects of NMDA receptor antagonists on epilepsy and aggression. The glutamatergic system, like the GABA system, may have dose-dependent opposite effects. Depending on the dose, NMDA receptor blockers such as PCP appear to have

both pro- and anti-epileptic as well as pro- and anti-aggressive properties (Leccese *et al.*, 1986; Belozertseva and Bespalov, 1999). In particular, PCP at low doses is antiepileptic but pro-aggressive, while the opposite is observed at high doses. Increased aggression might consequently occur when AEDs that have an NMDA receptor-inhibitory component to their action are used at doses that have minimal NMDA receptor antagonism. Some subtypes of epilepsy, such as temporal lobe epilepsy, can be associated with a reshaping of glutamatergic neurons and receptors in the hippocampus; consequently, drugs blocking glutamatergic receptors may have different or opposing effect in the epileptic brain than in non-epileptic brains.

iii) Genetic predisposition and decreased dopaminergic activity. A recent association study set out to explore whether there was a genetic basis that predisposes some patients to develop behavioural AEs during levetiracetam treatment. They identified several polymorphisms, all of which were associated with reduced dopaminergic activity (variations in dopamine-β-hydroxylase, catechol-O-methyltransferase, and an intracellular D_2-receptor binding protein), which seem to predispose epilepsy patients treated with levetiracetam to develop aggression (Helmstaedter *et al.*, 2013). It is not yet known whether this result is specific to levetiracetam, or whether reduced dopaminergic activity will predispose epilepsy patients to behavioural AEs with other AEDs

iv) Forced normalisation. Finally, the sometimes controversial forced normalisation theory is an attempt to explain the occasional observation of a paradoxical inverse relationship between epileptiform abnormality in the EEG and psychiatric symptoms. It was first described in 1953 by Heinrich Landolt who observed that EEGs paradoxically normalised and seizure activity was inhibited during psychotic episodes (Landolt, 1953). The “forced-normalisation” phenomenon is similar to but distinct from the concept of the “alternative psychosis” or “reciprocal psychosis”

(that psychosis is better when seizures are worse and psychosis is worse when seizures are better/controlled – also see later). This hypothesis was supported by epidemiological studies that found lower seizure frequency in epilepsy patients with psychosis, and studies reporting relatively few cases involving comorbid schizophrenia and epilepsy (Schmitz and Trimble, 1992). This observation can be extended to psychiatric phenomena other than psychosis, such as hypomania/mania, aggression, depression, and anxiety (Trimble and Schmitz, 1998). Therefore, the psychiatric adverse effects seen during AED treatment may not be a direct adverse psychotropic effect of the AED but rather a consequence of the suppression of seizures. This inverse link between seizure control and psychiatric symptoms (Flor-Henry, 1983), deserves further research, as it has far-reaching implications. Studies are needed to determine whether psychiatric symptoms seen with AEDs in epilepsy patients are side effects with no prognostic or clinical value, a necessary consequence of seizure control, or whether they could be a stage of a complex and progressive phenomenon leading to a chronic psychiatric disorder (Mula *et al.*, 2007). This is an important distinction, and future research should focus on clarifying the complex relationships between seizures and aggressive behaviour.

V. Antiepileptic drugs and aggression in adult patients with epilepsy

A. Introduction

We screened the literature for articles containing references to AED treatment and aggression-related behaviour (aggression, agitation, anger, assault, homicide/homicidality, hostility, impulsivity, irritability), and selected relevant reports in epilepsy populations (see Supplemental information A for search strategy and evaluation). The full listing of relevant studies retrieved for each AED, and brief data summary, are in Supplemental table S-1. Relevant information from previous systematic reviews, of individual drugs or of AEDs as a class, has been included where relevant. We also reviewed product labels for information about aggression-related behaviours, as an up-to-date source of relevant adverse reactions in both clinical studies and post-marketing experience (Table 3).

Our literature search and analysis captures only formally reported events of aggressive behaviour, and aims to identify large-scale, consistent patterns. As clinicians, we all have anecdotal experience of aberrant behaviours that appear in an individual patient after the addition of an AED, and which resolve on its removal. We have experienced this with all AEDs, including those which have no formal reports of aggression. Every patient is an individual, and each subtype of epilepsy is different, so while we have identified some broad trends we acknowledge that aberrant aggressive behaviour may develop in the occasional individual with an AED that is not usually associated with such behaviour. Additional confounding factors that may result in incorrect attribution of behavioural disturbance to a specific AED are discussed elsewhere in this paper and in previous publications (Besag, 2001b).

B. Review of data for each AED

The majority of studies we retrieved focused on one AED. Those that included a number of AEDs are discussed separately under each AED heading. One study included sufficient patients and AEDs to allow some comparisons of psychiatric side effects between the AEDs and merits discussion here. A retrospective chart review was conducted of adult outpatients seen between 2000 and 2005 at a US epilepsy centre; this included 1394 patients who had taken one of the newer AEDs (at the time): gabapentin, lamotrigine, levetiracetam, topiramate, tiagabine, vigabatrin, and zonisamide (Weintraub *et al.*, 2007). Overall, 16% of patients experienced psychiatric/behavioural side effects. The highest rates were seen with levetiracetam (16% incidence and 8% discontinuations, significantly higher than average, $p<0.001$) and tiagabine (not significant, probably due to low patient numbers); intermediate rates with topiramate and zonisamide; and low rates with gabapentin (0.6% incidence, significantly lower than average, $p<0.001$), lamotrigine (4.8% incidence, $p<0.001$), and vigabatrin, felbamate, and oxcarbazepine (not significant, probably due to low patient numbers). A past psychiatric history was the most significant predictor of AED-related behavioural/psychiatric side effects (Weintraub *et al.*, 2007).

1. Brivaracetam

Brivaracetam is included in this paper because it is currently under review for approval as adjunctive treatment of focal epilepsy with or without secondary generaliseation. Our searches retrieved no published studies with brivaracetam that included any of our key search terms.

Manual searches for brivaracetam RCTs identified three Phase III studies (Victor Biton *et al.*, 2014; Kwan *et al.*, 2014; Ryvlin *et al.*, 2014) and two Phase IIb studies (French *et al.*, 2010; Van Paesschen *et al.*, 2013) which reported AEs (Supplemental table S-1). Irritability was seen in ~5% of patients with 50 mg/day (*vs* 2–4% with placebo) in three of the four studies (Van Paesschen *et al.*, 2013; Biton *et al.*, 2014a; Ryvlin *et al.*, 2014). Discontinuation of brivaracetam was most often prompted by psychiatric AEs (including aggression and irritability) in two studies (Biton *et al.*, 2014a; Ryvlin *et al.*, 2014). A *post-hoc* meta-analysis across these Phase II/III studies reported that 6.8% of brivaracetam patients had non-psychotic behavioural AEs, compared with 4.2% in the placebo group. This incidence is lower than across the Phase III studies with levetiracetam (10.9% *vs* 4.8% with placebo) (D'Souza *et al.*, 2012).

2. Carbamazepine

One RCT with behaviour-specific measures was found. This study used a withdrawal design to show that in seizure-free epilepsy patients treated with AEDs (both overall, and in the carbamazepine subgroup), there was a small improvement in depression and in 'brooding' after withdrawal of AED, compared to the group that continued AEDs (Hessen et al., 2007), suggesting carbamazepine may negatively affect mood. No measures directly related to aggression, e.g. irritability, anger, were reported. However, anecdotal experience of this review's authors suggests that carbamazepine may have mood-stabilising properties in some epilepsy patients; we have observed deterioration in mood after withdrawal of carbamazepine.

No carbamazepine RCTs that reported aggression-related behavioural AEs were retrieved by our searches.

Four observational studies were retrieved: two showed slight evidence of aggression-related behaviours with carbamazepine in epilepsy patients (Shehata *et al.*, 2009; Wieshmann *et al.*, 2011), one showed positive behavioural effects (Pulliainen and Jokelainen, 1994), and one showed no behavioural worsening (Friedman *et al.*, 1992) (Supplemental table S-1). Using the Liverpool Adverse Event Profile to assess patient-reported AEs, one study reported that 16% of the 36 patients taking carbamazepine had feelings of anger (compared with 33% for levetiracetam, 19% for valproic acid, and 15% for lamotrigine) (Wieshmann et al., 2011). One study showed that epilepsy patients performed worse on several behavioural-specific measures compared with healthy controls, and that behaviour worsened in relation to dose and duration of AED treatment (with carbamazepine or valproic acid) (Shehata et al., 2009). A partially blinded, prospective, observational study which focused mainly on cognitive outcomes showed a slight improvement from baseline in negative mood after 6 months of phenytoin or carbamazepine (Pulliainen and Jokelainen, 1994). A small observational study in patients with developmental delay showed no increase in behavioural problems in patients receiving carbamazepine as an AED only, but worsening behaviour in patients receiving carbamazepine for either comorbid seizures and behavioural/psychiatric disorder, or for psychiatric disorders alone (Friedman et al., 1992).

3. Clobazam

No relevant studies in adult populations were retrieved.

4. Clonazepam

Our searches identified no RCTs for clonazepam in adults, either using behaviour-specific endpoints or AE reporting.

One observational study (published in 1979) with clonazepam in 40 patients aged 8–60 years with generalised or focal seizures, reported irritability as an AE in seven patients (17%) (Lander *et al.*, 1979). A 1974 review article reports "irritability or aggressiveness" in 5–20% of patients in previous studies, and "frank aggressiveness" requiring dose reduction in 20% of patients in that author's personal experience (Edwards, 1974).

5. Eslicarbazepine acetate

Our searches (including abstracts at key epilepsy congresses, See Supplemental Information A) identified no RCTs or observational studies with eslicarbazepine acetate in patients with epilepsy, which reported aggression-related data. One conference abstract on the incidence of psychiatric AEs with eslicarbazepine acetate did not mention any aggression-related AEs (Biton *et al.*, 2014b).

6. Ethosuximide

Our searches found no studies reporting aggression-related behaviours in adults with epilepsy treated with ethosuximide; however, psychosis has been reported. For example, Fischer et al. reported five episodes of psychosis in three adults treated with ethosuximide; although no aggression was reported in any of these cases, the patients were described as being "tense" (Fischer *et al.*, 1965). The psychosis occurred in clear time relation to the ethosuximide treatment; the authors suggested that this might have been a manifestation of "forced normalisation".

7. Felbamate

Our searches identified no RCTs with behaviour-specific endpoints. Rates of psychiatric/behavioural AEs were low with felbamate in the large observational study discussed

in section V (part B) (Weintraub *et al.*, 2007). One observational study of headache in 60 epilepsy patients taking felbamate, reported adverse effects of "agitation or restlessness" in 14 patients (23%), which caused discontinuation in six (12%) (Ettinger *et al.*, 1996). A case series of seven epilepsy patients with behavioural changes with add-on felbamate, reported that the changes included marked agitation/irritability in four patients and that the changes resolved on discontinuation in all seven patients (McConnell *et al.*, 1996) (Supplemental table S-1).

8. Gabapentin

Our searches identified no relevant studies with gabapentin in adults with epilepsy, other than the large observational study mentioned earlier (section V part B) – rates of psychiatric/behavioural AEs were significantly lower with gabapentin (0.6%) than the average ($p<0.001$) (Weintraub *et al.*, 2007).

9. Lacosamide

Our searches identified no relevant studies with lacosamide in adults with epilepsy. A manual search of lacosamide RCTs found no mention of aggression-related behaviours as AEs in individual epilepsy trials, where the threshold for reporting AEs ranged from ≥5% to ≥10%, nor in a pooled analysis of lacosamide epilepsy trials (Sake *et al.*, 2010), nor in a meta-analysis of AE data across 10 RCTs in epilepsy and other indications (Zaccara *et al.*, 2013).

10. Lamotrigine

Our searches identified one RCT with behaviour-specific endpoints. In adults with focal seizures treated with adjunctive lamotrigine or levetiracetam, anger and hostility improved (i.e. lessened) from baseline with lamotrigine, with a significant difference *vs* levetiracetam, based on anger-hostility subscale scores of the Profile of Mood States (POMS) scale (Labiner *et al.*, 2009).

Two observational studies designed to look at behaviour present good evidence that lamotrigine is not typically associated with behavioural/aggressive side effects. The large observational study mentioned earlier (section V part B) reported that rates of psychiatric/behavioural AEs were significantly lower with lamotrigine (4.8%, $p<0.001$) than average (Weintraub *et al.*, 2007). Kato *et al.* used the Buss-Perry Aggression Questionnaire (BAQ) and showed significant improvement from baseline in aggression overall (and the anger subscale), after 10 weeks of adjunctive lamotrigine in patients with temporal lobe epilepsy (Kato *et al.*, 2011). Other observational studies and case series are detailed in Supplemental table S-1, and the results differ among the different populations and comorbidities. In general lamotrigine has no detrimental effects with respect to aggressive behaviour, although there are some reports of aggressive behaviours in epilepsy patients with intellectual disability (Ettinger *et al.*, 1998). In this population, the possibility of the "release phenomenon" must be considered: releasing the individual from the additional handicap of ongoing seizures can lead to difficult behaviour as their abilities improve (Besag, 2001). Lamotrigine may also have an alerting effect which could lead individuals with intellectual disabilities to become much more reactive to their environment. In both eventualities, appropriate behavioural guidance can lead to longer-term positive outcomes (Besag, 2001).

11. Levetiracetam

RCTs with behaviour-specific endpoints (n=1)

We identified only one RCT that used a behaviour-specific endpoint (the aggression-hostility subscale of the POMS) to explore aggression with levetiracetam (Supplemental table S-1). This prospective study by Labiner *et al.* showed that anger/hostility subscale scores were significantly worse with levetiracetam relative to lamotrigine, after 20 weeks of add-on treatment and throughout the study (Labiner *et al.*, 2009). Scores were worse than baseline with levetiracetam

at 14 of the 20 weeks, whereas scores were improved at every week with lamotrigine (significant difference *vs* levetiracetam at 12 of these weeks, and overall). One RCT of levetiracetam *vs* placebo with a behaviour-specific endpoint was conducted in adolescents, and is reported in section VI (de la Loge *et al.*, 2010).

Observational studies with behaviour-specific endpoints or designed to explore aggression/behaviour (n=10)

Six observational studies explored behavioural effects of levetiracetam using behaviour-specific measures, and three additional observational studies used non-behaviour-specific endpoints (e.g. the Liverpool Adverse Event Profile) with the defined intent to explore adverse behaviour or aggression (Supplemental table S-1).

In a prospective open-label study in 71 epilepsy patients, Lee *et al.* saw significant improvement from baseline in the Beck Anxiety Inventory after adding levetiracetam, and no significant changes in most other measures and subscales (including a hostility subscale). However, five patients (6.5%) discontinued due to psychiatric symptoms (nervousness, irritability, anxiety, hostility, depression, and suicidal ideation or attempt) (J-J Lee *et al.*, 2011) .

In the large retrospective chart review already mentioned (Weintraub *et al.*, 2007), levetiracetam had the highest incidence of psychiatric/behavioural AEs (16%), leading to discontinuations in 8% of 521 epilepsy patients taking levetiracetam. These rates were significantly higher than average ($p<0.001$), and rates of individual AEs (irritability, 9%; behavioural change, 3.5%) were also significantly higher than average ($p<0.001$).

In an interview-based study, which included carers as well as patients, negative behaviour change was reported in 37% of levetiracetam patients, and positive change in 22%, whereas any

behavioural change was reported in only 9% of patients not taking levetiracetam. Patient reports agreed with carer reports of behaviour change in most cases (85%). Aggression was the most prominent negative feature of the symptom complex, and clustered with increased energy and improved concentration (Helmstaedter *et al.*, 2008). In a gene-association study based on these patients, polymorphisms in three genes related to dopamine activity and signalling were associated with negative psychotropic AEs with levetiracetam, suggesting that reduced dopamine activity may predispose epilepsy patients to developing psychotropic AEs with levetiracetam (Helmstaedter *et al.*, 2013). The mechanisms underlying this association are not yet understood (also see Section IV).

In a very short-term study (1 week), no differences were seen between levetiracetam and pregabalin on performance in several neuropsychological tests and anxiety questionnaires. Some improvements from baseline were seen with levetiracetam (e.g. improved anxiety), but no aggressive-behaviour-specific scales were used (Ciesielski *et al.*, 2006).

In a prospective chart review of 517 patients with various epilepsies treated with adjunctive levetiracetam, 10% developed psychiatric AEs, most commonly aggressive behaviour (3.5%). Risk factors were history of febrile convulsions, previous psychiatric history, and history of status epilepticus (M. Mula *et al.*, 2003). A related study looking just at patients with epilepsy and learning difficulties prescribed levetiracetam (N=118), reported that 15 (12.7%) developed psychiatric AEs (most commonly aggression, 7.6%), and levetiracetam was discontinued in 7.6%. Again, previous psychiatric history was a risk factor for psychiatric AEs (Mula *et al.*, 2004).

In a chart review of 108 patients with epilepsy treated with both levetiracetam and topiramate (at different times), overall 13% had psychiatric AEs with levetiracetam and 30% with topiramate (Mula *et al.*, 2007).

In a case–control study of 553 patients taking levetiracetam, 7% discontinued levetiracetam due to behavioural abnormalities (most commonly depression and irritability), and 10 patients (1.8%) were considered a danger to themselves or others (White *et al.*, 2003).

A study of patient-reported side effects from the UK antiepileptic drug register by Wieshmann and Baker, found that 49% of patients taking levetiracetam reported anger as always or nearly always being a problem, compared with 39% of patients treated with other AEDs, and 7% of controls (people with infrequent seizures and not taking AEDs) (Wieshmann and Baker, 2013). This highlights the high rate of anger when epilepsy patients themselves are asked the question directly, as well as the higher rate with levetiracetam than with other AEDs.

An earlier, smaller, study by the same group using the same registry, reported that of 100 epilepsy patients taking AEDs, 33% of the 12 patients taking levetiracetam said anger was always a problem, compared with 19% of the 21 patients taking valproic acid, 16% of the 36 patients taking carbamazepine, and 15% of the 20 patients taking lamotrigine (Wieshmann *et al.*, 2011).

A more recent observational study in 163 patients taking levetiracetam, reported aggressive behaviour as “always” a problem in 9.8% of the patients. These patients also had a 7-fold increased risk of being depressed as measured with the Neurologic Depression Disorders Inventory – Epilepsy (NDDIE) (Mula *et al.*, 2015)**.**

RCTs with aggression data extracted from overall AE reporting

A recent meta-analysis of 10 RCTs of add-on levetiracetam provides some useful information, although it does not capture all AEs across these studies (Mbizvo *et al.*, 2014). Each individual study reported only AEs occurring in ≥5% (in some studies ≥10%) of patients, so any AEs in the individual studies occurring below these thresholds were excluded from the analysis entirely. Hence, agitation was reported as an AE in one study in children (6/101, *vs* 1/97 placebo) and one study in adults (3/28, 11% *vs* 0% with placebo), and any agitation AEs below the reporting thresholds in the other studies were ignored to give an overall incidence of agitation of 9/1092, 0.82% (*vs* 0.14% with placebo). Similarly, one study (in adults) reported irritability as an AE (5/77, 6.5%, *vs* 0 with placebo), giving an overall incidence of irritability across the meta analysis of 0.46% (*vs* 0% with placebo).

Two earlier systematic reviews are more useful, as they included all AE data from the levetiracetam database of adjunctive use in focal seizures (French *et al.*, 2001; Cramer *et al.*, 2003); the French *et al.* review also includes healthy volunteers, elderly patients with cognitive decline, and anxiety patients. French *et al.* reported a rate of behavioural AEs of 13% with levetiracetam (*vs* 6% with placebo) in placebo-controlled epilepsy trials; 6.0% *vs* 4.1% in elderly patients in cognitive studies; and 5.1% *vs* 5.5% in anxiety studies (French *et al.*, 2001). Across all the levetiracetam epilepsy studies analysed by Cramer et al. (short-term placebo-controlled trials and long-term open-label extensions), affective-type behavioural AEs were seen in 25.4% of patients (*vs* 6.2% placebo). These included: agitation 1.6% (*vs* 0.2%); emotional lability 3.0% (*vs* 0.2%); hostility 3.3% (*vs* 0.9%); nervousness 7.3% (*vs* 1.8%) (Cramer *et al.*, 2003). Rates of behavioural AEs were lower in levetiracetam trials in non-epilepsy indications, suggesting that patients with epilepsy are biologically more vulnerable to behavioural/psychiatric AEs (French *et al.*, 2001; Cramer *et al.*, 2003).

The individual levetiracetam RCTs are not discussed here, and any RCTs we found which reported an aggression-related AE are listed in Supplemental table S-1.

Observational/open-label studies with aggression data extracted from side-effect reporting

Our searches retrieved eight such studies, which are detailed in Supplemental table S-1. One large, long-term study was comparative (N=828), reporting discontinuation due to behavioural adverse effects in 19% of the 196 patients taking levetiracetam, compared with 2–7% with oxcarbazepine, lamotrigine, topiramate, and zonisamide (Chung *et al.*, 2007). In the other studies we retrieved (see Supplemental table S-1), rates of individual behavioural AEs with levetiracetam ranged from 5% up to 24% – this highest rate being the incidence of irritability in a retrospective chart review of 568 patients treated with levetiracetam mono/polytherapy at a tertiary epilepsy centre (Kang *et al.*, 2013). These studies generally approximated normal clinical use of levetiracetam, although some excluded patients with a history of serious psychiatric disorders, and some expressly included patients with psychiatric history or mental handicap. Discontinuation due to aggression-related adverse effects was reported in 4.1–10% of the overall populations in these studies (4.1%–5.6%, if limited to studies with ~100 patients or more) and discontinuations due to behavioural adverse effects in general was reported in 19% (Kang *et al.*, 2013).

A number of case reports were retrieved, which in general we have excluded from this review. However, we selected one case series and one case study for a brief mention, with all the caveats that apply to interpreting case reports.

Dinkelacker *et al.* described a case series of 33 epilepsy patients who experienced aggressive episodes during levetiracetam adjunctive therapy; the authors estimated that 3.5% of all their

epilepsy patients experienced irritability or aggression attributable to levetiracetam. In 24 of the 33 patients they described, irritability was transient, none of the 24 patients had a history of unprovoked impulsive aggression, and ten patients required dose reduction or discontinuation of levetiracetam. In the remaining nine patients (1 woman, 8 men), the aggressive symptoms were severe (including physical violence), and in two cases necessitated emergency psychiatric treatment. In four of these nine patients, there was a history of irritability or aggression, and one patient had experienced aggressiveness with gabapentin treatment (Dinkelacker *et al.*, 2003).

In a case study of a homicide during post-ictal psychosis, in which the perpetrator had a complex psychiatric and seizure history, the authors stated that AED changes may have had a contributing role. Discontinuation of carbamazepine 9 months before the homicide may have "increased the propensity for post-ictal mood dysregulation", and the addition of levetiracetam at the same time "may have increased impulsiveness" (Eisenschenk *et al.*, 2014).

12. Oxcarbazepine

Two relevant studies in adults were retrieved. In the Weintraub study previously mentioned, 5.6% of oxcarbazepine-treated patients had behavioural/psychiatric AEs, slightly lower than the overall average, and no irritability was seen (Weintraub *et al.*, 2007). In a retention study by Chung *et al.*, only two of 97 patients discontinued oxcarbazepine due to behavioural AEs, the lowest rate of all the AEDs that were included (Chung *et al.*, 2007).

13. Perampanel

Our searches retrieved one of the three perampanel Phase III RCTs in epilepsy, the open-label extension, a meta-analysis of all perampanel double-blind RCTs (epilepsy and other indications), an observational study, and a case study. By searching reference lists (excluding duplicates, data

that had previously been published, or extension studies that had been superseded by more recent follow-up) and recent conferences (and excluding conference abstracts that had since been published in full), we ultimately retrieved 27 relevant articles (see Supplementary table S-1, and below).

RCTs with behaviour-specific endpoints (n=0)

We found no studies in adults with behaviour-specific endpoints (see section 6.2 for a perampanel study in adolescents with behaviour-specific assessments). *Post-hoc* analyses specifically designed to explore aggression in perampanel RCTs are reported later in this section.

Observational studies with behaviour-specific endpoints or designed to explore aggression/behaviour (n=0)

We found no observational studies in adults with behaviour-specific endpoints.

RCTs with aggression data extracted from overall AE reporting (n=13 publications)

Of the five perampanel RCTs in epilepsy (three Phase III, two Phase II), two reported aggression-related AEs (French *et al.*, 2012, 2013), while one Phase III study and the two Phase II studies did not (Krauss *et al.*, 2012). A pooled analysis of all data from the Phase III trials showed that 30 of the 225 patients taking 12 mg perampanel (11.8%) reported irritability as an AE (*vs* 2.9% with placebo, and 3.9–6.7% with 2–8 mg perampanel), and aggression as an AE in 3% of patients taking 12 mg perampanel (*vs* 1% with placebo, 1% with 4 mg and 2% with 8 mg). No other aggression-related AEs occurred in ≥5% of patients in any treatment group (Steinhoff *et al.*, 2013). Serious psychiatric AEs were seen in 12 patients (1.2%) taking 12 mg perampanel (*vs* 0.9% placebo), with aggression being the most common (3 of 1038 patients taking perampanel, 0.29%, *vs* none with placebo). Because of the interest in aggressive behaviour with

AEs, a further analysis was conducted in the pooled Phase III clinical trial population, using both broad and narrow standard medical queries (SMQ) for events suggestive of hostility/aggression. The broad SMQ identified events broadly suggestive of hostility/aggression (e.g. including events like laceration, regardless of cause) in 6% of placebo patients, and 5% (4 mg), 12% (8 mg), and 20% (12 mg) of perampanel patients (Steinhoff *et al.*, 2013). Homicidal ideation and/or threat were exhibited in 0.1% of 4,368 perampanel-treated patients in controlled and open-label studies, including non-epilepsy studies (B Steinhoff *et al.*, 2014). A population PK/PD study using the pooled Phase III epilepsy population confirmed a significant association with perampanel plasma concentration and incidence of aggression (Gidal *et al.*, 2013). A meta-analysis of nine randomised controlled trials including studies in Parkinson disease (Zaccara *et al.*, 2013) reported on a total of 3947 patients, 2627 of whom had been randomised to perampanel. In this analysis, similar terms were merged (e.g. irritability and aggression). No AEs were significantly associated with doses of 2 or 4 mg/day; and the only behavioural AE significantly associated with any dose of perampanel was 'irritability' (which includes aggression) with 12 mg/day perampanel.

Several *post-hoc* analyses of the perampanel epilepsy and non-epilepsy clinical trial databases have been conducted; aggressive/irritable behaviour was seen only in epilepsy populations (Ettinger *et al.*, 2014; LoPresti *et al.*, 2014), and the incidence was not significantly different in patients taking concomitant levetiracetam (*vs* no concomitant levetiracetam) (Fain *et al.*, 2015) – see Supplemental table S-1 for details of these analyses. After our searches were completed, these conference abstracts have been published as a full article (Ettinger *et al.*, 2015).

The most recent analysis of the open-label extension study to the Phase III trials, which followed patients for a median of 1.5 years, reported irritability in 11.5%, and aggression in 5.1% of

patients over the entire exposure period (N=1216). Overall, 3.9% of patients had ≥1 psychiatric serious AE. Among these were two serious AEs of agitation (0.2%) and abnormal behaviour (0.2%) and 12 serious AEs of aggression (1.0%). Aggression resolved in five patients while remaining on perampanel, and seven patients discontinued (Krauss *et al.*, 2014). Irritability and aggression, respectively, led to the discontinuation of perampanel in 1.3% and 0.4% of patients.

The recently completed Phase III study of perampanel in patients with primary generalised tonic–clonic seizures (PGTC), reported irritability as the only individual AE with an incidence of ≥5% (11.1% with perampanel, vs 3.7% with placebo). The combined incidence of hostility/aggression-related AEs (as per the broad and narrow SMQ terms) was 18.5% with perampanel, vs 4.9% with placebo, and using just narrow SMQ terms (i.e. AEs very likely to be related to aggression or hostility), the rates were 2.5% with perampanel, and 0% with placebo (French *et al.*, 2015).

Observational/open-label studies with aggression data extracted from side-effect reporting (n=13)

We identified two published observational studies. In one, (a prospective, multi-centre clinical audit of adjunctive perampanel in refractory epilepsy) low rates of aggression (2.8%) and irritability (2.1%) were reported (BJ Steinhoff *et al.*, 2014). In the other (a single-centre case-series of 47 patients), the median dose taken by patients was 8 mg. The most common AEs requiring withdrawal of perampanel were behavioural: aggressive behaviour in two cases (4.3%), suicidal ideation in two cases (4.3%), and aggressive behaviour together with suicidal ideation in one further patient (2.1%) (Coyle *et al.*, 2014). Another 11 observational studies (n=16 to n=111) were reported in conference abstracts, with populations ranging from institutionalised adults with highly-refractory epilepsy, to less severe patients in general neurology practice (See

Supplemental table S-1). Aggression, irritability, and/or behavioural disturbance were reported as AEs in most (but not all) abstracts, ranging in incidence in those reports from 8% to 36% (Supplemental table S-1).

Case studies (n=1)

In a patient with moderate intellectual disability, a history of challenging behaviour, and severely refractory epilepsy, addition of perampanel 8 mg significantly improved seizure frequency and duration, but worsened aggressive behaviour and resulted in the patient being unable to live at home, despite reducing the perampanel dose and the addition of antipsychotics (Dolton and Choudry, 2014).

14. Phenobarbital

Our searches retrieved only one relevant study with phenobarbital – the authors of this case report suggested that phenobarbital may cause behavioural AEs or exacerbate maladaptive behaviours, which may mask or suppress the effectiveness of neuroleptics (in this case chlorpromazine) in treating aggressive behaviour in patients with seizures and comorbidities (Hanzel *et al.*, 1992). Because data with phenobarbital was scarce in patients with epilepsy, data in healthy patients was considered. In 49 healthy adults who underwent a battery of neuropsychological tests, scores in the anger subscale of the POMS were significantly worse (increased anger) than baseline after 1 month taking phenobarbital 15 mg/day (but not with phenytoin [30–100 mg/day] or valproate [250 mg/day] (Meador *et al.*, 1995).

15. Phenytoin

Only one relevant study with phenytoin was retrieved. In this observational study in 43 newly diagnosed epilepsy patients, a small decrease in irritability (assessed with the POMS scale) was seen after phenytoin treatment was commenced (Pulliainen and Jokelainen, 1994).

16. Pregabalin

One study with pregabalin specifically investigated the neuropsychological and psychiatric impact of pregabalin and levetiracetam in 20 epilepsy patients, but only over the course of one week of treatment, so the results have very limited utility. No major neuropsychiatric effects were seen (Ciesielski *et al.*, 2006). Two observational studies in refractory epilepsy – one in inpatients with intellectual disability and one in outpatients, showed infrequent behaviour-related AEs (Huber *et al.*, 2008; Valentin *et al.*, 2009) (Supplemental table S-1).

17. Retigabine

Our searches revealed no relevant retigabine studies in adults. Neither the pivotal trial publications, nor a pooled analysis of these three trials, reported any aggressive or behavioural AEs above the 5% (in one case 10%) reporting thresholds (Porter *et al.*, 2007, 2012; Brodie *et al.*, 2010; French *et al.*, 2011). Searches of epilepsy congress abstracts for retigabine revealed no further relevant data.

18. Stiripentol

Only one relevant study was retrieved – an observational study in Japanese adults and children with Dravet syndrome (Inoue *et al.*, 2009). Irritability was observed in three of the eight patients aged ≥13 years in the early and intermediate period, but resolved, and no adults discontinued due to irritability.

19. Tiagabine

We retrieved two observational studies that examined behaviour with tiagabine. The largest was the observational study by Weintraub *et al.*, which showed high rates of psychiatric/behavioural AEs (15.8% with tiagabine, *vs* 8.4% average), and irritability (10.5%), depression (5.3%), anxiety (5.3%), and psychosis (5.3%) with tiagabine, but the data are based on only 19 patients (Weintraub *et al.*, 2007). A small controlled study used a mood and behaviour rating scale, and found no significant impact of tiagabine on these scores (Sveinbjornsdottir *et al.*, 1994). Adverse event reporting from this study showed that three of the 19 patients withdrew early due to aggression; aggression/irritability was reported in three of 11 patients taking tiagabine in the double-blind portion of the study, *vs* none of the 11 patients in the placebo period (Sveinbjornsdottir *et al.*, 1994). The only other relevant publication was a report of two cases in which addition of tiagabine controlled postencephalitic seizures and improved behaviour (including aggressive outbursts) (Kaufman *et al.*, 2002).

20. Topiramate

We retrieved no RCTs and four observational studies that focused on behaviour/aggression, as well as five observational studies from which behaviour/aggression rates can be extracted from side-effect reporting (Supplemental table S-1). The Weintraub *et al.* observational study concluded that topiramate had intermediate rates (6.3% overall) of psychiatric/behavioural AEs compared with other AEDs (Weintraub *et al.*, 2007). A retrospective analysis by Mula *et al.* reported psychiatric AEs in 24% of the 431 patients assessed, with aggressive behaviour in 5.6% (Marco Mula *et al.*, 2003). In a chart review of 108 patients with epilepsy treated with both levetiracetam and topiramate (at different times), overall 13% had psychiatric AEs with levetiracetam and 30% with topiramate (Mula *et al.*, 2007). A case series that explored in detail

103 patients who developed psychiatric AEs with topiramate, found that nearly half of the sample had affective disorder, with aggressive behaviour the next most common (23%). The aggression resolved in the majority of patients with discontinuation (or reduction) of topiramate (Mula and Trimble, 2003). Aggressive behaviour was associated with seizure worsening, suggesting it was a direct expression of the epileptic state (ictal, pre-ictal, or post-ictal – see earlier).

In a retention-rate study by Chung *et al*., topiramate had the lowest retention rate (44.2%), but few of the discontinuations were due to behavioural AEs (5 of 156 patients) (Chung *et al.*, 2007). In the other observational studies we retrieved, irritability was reported in a wide range of patients, from <1% up to 20%, and discontinuation due to irritability/aggression/agitation in 5–12%; see Supplemental table S-1 for details (Tartara *et al.*, 1996; Stephen *et al.*, 2000; Bootsma *et al.*, 2004; Voronkova *et al.*, 2007).

21. Valproic acid

We identified one prospective, controlled study in adults that used aggression-specific endpoints, and one small observational study (Supplemental table S-1). In a prospective study using cognitive and behavioural endpoints, both treated (seizure-free) and untreated (newly diagnosed or never treated) epilepsy patients had worse aggression (total and verbal) compared to healthy controls, and total aggression scores were worse in patients treated with valproic acid compared with carbamazepine (Shehata *et al.*, 2009). In a small observational study (N=55) conducted in 1978, aggressive behaviour was seen in one patient (Ruuskanen *et al.*, 1979).

22. Vigabatrin

Our searches identified one individual RCT with vigabatrin that reported behaviour-related AEs (Loiseau *et al.*, 1986), and one pooled analysis across all vigabatrin trials (randomised, double-blind, placebo-controlled studies of add-on vigabatrin) that aimed to explore psychiatric AEs (Levinson and Devinsky, 1999). The small cross-over study reported irritability as an AE in two patients during the placebo phase and one during the vigabatrin phase (Loiseau *et al.*, 1986), and the pooled analysis showed an odds ratio of >1 for incidence of aggressive reaction and for agitation, but this was small and not significant (Levinson and Devinsky, 1999). We manually identified a Cochrane Review of vigabatrin clinical trial data up to October 2012 (n=747), and this meta-analysis did not report any behavioural events significantly associated with vigabatrin (Hemming *et al.*, 2013). Therefore, we did not extend our manual searches any further, to evaluate any individual vigabatrin clinical studies.

We identified one small observational study in adults with refractory epilepsy and severe learning difficulties. Aggression was reported in 4/22 (18%) and agitation in 2/22 (9%) of patients treated with add-on vigabatrin (Armour *et al.*, 1992).

Behavioural disturbances and aggression were reported with vigabatrin in a number of case reports soon after its approval – e.g. in seven of 145 patients in one letter to the editor in Lancet, and nine of 119 patients in another – and the outbursts were occasionally extreme and violent (Robinson *et al.*, 1990). A follow-up of 136 patients in whom behavioural problems were reported with vigabatrin to either the authors or the manufacturers, found sufficient detail for 81 of these patients, and found depression in 22 patients and psychosis in 28. There was no mention of aggression-related behaviours in this report (Thomas *et al.*, 1996). A study of cognitive and

behavioural effects in healthy volunteers found no effects of vigabatrin on cognition or mood/behaviour, although this was only with short-term use (Thomas and Trimble, 1996).

23. Zonisamide

Our searches retrieved no studies that used aggression- or behaviour-related endpoints, but one RCT and one meta-analysis reported aggression-related AEs (Sackellares *et al.*, 2004; Carmichael *et al.*, 2013), and two observational studies reported aggression-related AEs (Chung *et al.*, 2007; Weintraub *et al.*, 2007), one of which was specifically designed to explore psychiatric/behavioural effects of AEDs (Supplemental table S-1).

The recent meta-analysis of zonisamide studies (studies published up to February 2013), found a significant association between zonisamide and agitation/irritability (relative effect *vs* placebo 3.25, 95% CI 1.05–5.27). The individual study retrieved by our searches (Sackellares *et al.*, 2004) was included in this meta-analysis, so it is not discussed separately here. The observational studies we retrieved have been discussed earlier in this review. Weintraub *et al.* concluded that zonisamide had an intermediate rate of psychiatric/behavioural AEDs (9% *vs* 8.4% average), and Chung *et al.* reported few discontinuations due to behavioural AEs with zonisamide (9.8%, *vs* 19% with levetiracetam).

C. Conclusions

A previous review of the psychotropic effects of AEDs concluded that "There is a need for large-scale, prospective, randomised, double-blind, placebo-controlled studies that are properly designed to assess psychotropic effects of AEDs so as to control for confounding factors" (Piedad *et al.*, 2012). Our review of the data, focusing just on aggression-related behaviours, must come to a similar conclusion: that few well-designed and reliable studies have been

performed. Although it did not use behaviour-specific assessments and does not include all currently available AEDs, the comparative, observational study by Weintraub *et al.* gives perhaps the most useful information. This found levetiracetam to have the highest rates of behavioural AEs, and gabapentin to have the lowest (Weintraub *et al.*, 2007).

Information from regulatory drug trials should be treated with caution, as the majority do not include behaviour-specific endpoints, and interpreting AE reporting across the spectrum of aggression-related behaviours is fraught with difficulties. More information is available on the newer AEDs, as with each new approval scrutiny of psychotropic side effects is increasing, but equivalent scrutiny is not possible for older AEDs often because the questions were not asked of their regulatory trial data. Another gap in the literature regards the relationship between adverse events (e.g. aggression) and efficacy. Reports suggest that AEDs may have different side-effects when the drug is efficacious (i.e. patients come into remission) and when the drug fails in efficacy (Shih and Ochoa, 2009), but none of the studies we reviewed included any information on the relationship between anti-seizure effects and aggressive behaviours. This relationship is further complicated by the fact that uncontrolled epilepsy may impair behaviour in similar ways to the side effects of AEDs (Baker and Marson, 2001).

Based on available data, levetiracetam, perampanel and topiramate seem to be associated with increased rates of irritability, hostility and/or aggression, particularly in patients with a previous history of psychiatric symptoms. For such patients, these drugs should be used with caution. Product labels are generally consistent with this conclusion, and provide a useful benchmark. From US labels, 13% of adults taking levetiracetam (pooled, all doses) have non-psychotic behavioural symptoms; 12% of patients taking perampanel 8 mg have hostility/aggression-

related AEs (20% with 12 mg); and 2–10% of adults taking topiramate have aggression-related AEs (Table 3).

There are mixed data for vigabatrin, valproic acid, and zonisamide. Early vigabatrin case reports of sometimes violent aggressive behaviour are not supported by evidence of increased rates in pooled analyses, although very high rates of irritability (23%) are reported in the vigabatrin US label (Sabril USPI, 2013). One controlled study with valproic acid showed significantly worse aggression than with carbamazepine, but we found no other data supporting a risk of aggressive effects. Data from zonisamide clinical studies show an increased rate of agitation/irritability *vs* placebo, but low rates in observational studies and no evidence for aggression in studies using behaviour-specific measures.

There are reasonable data supporting no specific risk of aggression-related behaviour with carbamazepine, eslicarbazepine acetate, gabapentin, lamotrigine, oxcarbazepine, and retigabine.

There are insufficient data for any conclusions for clobazam, clonazepam (although the clonazepam US label reports behaviour problems in ~25% of epilepsy patients (Klonopin USPI, 2013), ethosuximide, felbamate, gabapentin, phenobarbital, phenytoin, pregabalin, and tiagabine. Because the developmental AED brivaracetam has only been used in clinical trial populations to date, there is insufficient available evidence, although the incidence of non-psychotic behavioural AEs appears to be ~7% (D'Souza *et al.*, 2012).

VI. Aggression with antiepileptic drugs in children and teenagers with epilepsy.

A. Introduction

The most striking aspect of the literature search in this area is, once again, the lack of high-quality data. There are almost no blinded, controlled studies using accepted measures of behavioural disturbance or providing adequate information either on the nature of the aggressive behaviour itself or on factors that would allow a reasonable evaluation of causation. As stated earlier, a more comprehensive discussion of the confounding factors that could lead to false attribution of behavioural disturbance to a specific antiepileptic drug has been published elsewhere (Besag, 2001). The lack of data is surprising, considering the size of the problem. A 1994 questionnaire survey by Brown found that 60% of the 896 children and teenagers surveyed felt that the antiepileptic medication caused tiredness and over 50% viewed it as being responsible for poor concentration. About 50% reported that that they were "cross/irritable" and about 30% as being "angry" as a result of the medication (Brown, 1994). Although this survey was on a highly-selected population (namely members of the British Epilepsy Association), and lacked a control group, the results are striking, and highlight the need for attention to aggressive adverse effects of AEDs.

B. Review of data for each AED

The evidence for aggression associated with each of the antiepileptic drugs (in alphabetical order) is presented. In general, data in very young infants (e.g. those with infantile spasms) is not

included, because AEs of 'irritability' in these babies cannot be interpreted as aggressive behaviours, but where infants formed part of a larger population that cannot be separated, the data are reported (with caveats).

1. Acetazolamide

No evidence found.

2. Carbamazepine

No evidence found.

3. Clobazam

We identified one double-blind, randomised trial with clobazam that included behaviour-specific measures (Paolicchi *et al.*, 2015). Using data from a trial of clobazam to treat Lennox-Gastaut syndrome, Paolicchi et al. carried out a *post-hoc* analysis of all randomised paediatric patients (aged ≤18 years) treated with at least one dose of study drug or placebo. Of the 146 clobazam-treated patients, aggression-related AEs were seen in 23 (15.8%), compared with 8.3% of placebo patients. In patients taking high- and medium-dose clobazam, most of the aggression-related AEs occurred during the three-week titration period, whereas in the low-dose and placebo group they were evenly distributed during the 15-week study. The aggression-related AEs included the following MedDRA-preferred terms: aggression, irritability, abnormal behaviour, perseveration and negativism (although no patients fell into the perseveration category and only one into the negativism category). Three patients discontinued clobazam because of aggression-related AEs. There was no significant difference between clobazam and placebo in the behaviour item scores on the Achenbach child behaviour checklist (CBCL), although there was a trend towards worsening scores in the aggression domain with clobazam in patients with a history of

aggressive behaviour (Supplemental table S-2). The authors concluded that the overall rate of aggression was low with clobazam, was dose-dependent, resolved by study end and was independent of the history of aggression/behavioural problems (Paolicchi *et al.*, 2015). The other clobazam studies we retrieved did not use behaviour-specific measures, but reported behaviour-related AEs in varying degrees of detail (Supplemental table S-2). Bawden *et al*., in a small, randomised, blinded (double dummy) study, compared 24 patients taking clobazam with 17 receiving standard monotherapy (nine carbamazepine and eight phenytoin). Three of the patients taking clobazam exhibited externalising behavioural AEs compared with three on standard monotherapy; three taking clobazam exhibited internalising behavioural AEs compared with two on standard monotherapy (Bawden *et al.*, 1999). The rate of behavioural AEs was very similar between the two groups but it is difficult to draw any conclusions from such small numbers. Sheth and colleagues reported that seven of 63 children (11%) treated with clobazam for refractory epilepsy developed severe behavioural disturbance. "Aggressive agitation" was reported in the seven children, mean age 6.4 years. The aggression was described by parents as being "animal-like" and included biting, kicking, head-banging, tantrums and hyperactivity, all of which were said to be out of character (Sheth *et al.*, 1994, 1995).

Jan *et al.* reported a small, open, uncontrolled study of 31 children with refractory epilepsy, aged 2 months to 15 years, in whom clobazam was added to the existing antiepileptic medication in doses of up to 2 mg/kg/day. Seven of the 31 had adverse effects, including behavioural change in two (Jan and Shaabat, 2000). The clobazam had to be withdrawn in three children because of repeated vomiting or behavioural changes but it was not clear, from the report, whether it had to be withdrawn in both the children with the behavioural change.

Klehm et al. reported a large retrospective chart review in 300 children (mean age 9.1 years) with refractory epilepsy, who were prescribed clobazam. The children had variety of seizure types (many had multiple seizure types), and the vast majority of patients (97%) were taking at least 1 other AED. The median starting dose was 0.2 mg/kg/day and the average dose at last follow-up was 0.73 mg/kg/day (range 0.05–3.3 mg/kg/day). The median seizure reduction was 80%; the 50% responder rate was 67.7%; and 84 patient (28%) were seizure-free at the last follow-up. Twenty-three patients (7.7%) experienced AEs related to mood or behaviour change (Klehm *et al.*, 2014).

4. Clonazepam

None of the clonazepam studies used behaviour-specific measures; two observational studies and two reviews of previous studies were included (Supplemental table S-2). Mikkelsen *et al* carried out a single-blind, placebo-controlled trial of clonazepam in 10 patients with simple absence seizures and 10 patients with myoclonic-atonic seizures (Mikkelsen *et al.*, 1976). Most of the patients (17/20) were under 18 years of age. Clonazepam had to be withdrawn from two of the patients, in one case because of severe irritability, dysphoria and aggressiveness; in the second case because of somnolence, behavioural disturbance and lack of efficacy. Further details in this report were sparse.

Lander *et al.* reported that 22 of 40 patients treated with clonazepam for refractory epilepsy had "undesirable effects" attributable to the clonazepam, the commonest of which were drowsiness, loss of concentration, irritability and aggression (Lander *et al.*, 1979).

Kalachnik *et al.* reviewed behavioural adverse effects of benzodiazepines, including clonazepam, diazepam and lorazepam, commenting that these are easily overlooked and under-recognised

(Kalachnik *et al.*, 2002). They stated that behavioural adverse effects occurred in 13% of 446 individuals with mental retardation prescribed these AEDs for behavioural, psychiatric or medical conditions. The rate of behavioural disturbance in the 208 individuals who had epilepsy was 15.4%.

Browne, in a review of clinical trials of clonazepam, commented that behavioural disturbance occurred in a minority of patients, usually children (Browne, 1976). In some cases this represented an exacerbation of the previous disorder but in others did not. The behaviours were variously described as irritable, aggressive, excitable, irrational, antisocial, temperamental, violent, disobedient, noisy and hard to discipline. In 10 studies, the percentage of behavioural disturbance ranged from 2% to 50% (median 17%). The behavioural disturbance sometimes resolved with a reduction in dosage but in other cases required discontinuation of the clonazepam.

5. Eslicarbazepine acetate

In a prospective, open-label study of 29 children between two and 17 years of age, aggressive behaviour was reported in one child, and one other had "aggression aggravated" (Almeida *et al.*, 2008).

6. Ethosuximide

The only evidence retrieved for ethosuximide was two case studies. Yamamoto *et al.* reported that an 11-year-old boy with refractory myoclonic epilepsy and severe psychomotor delay had complete control of myoclonic seizures with ethosuximide but had "behavioural changes, more of the manic type". This was attributed to the forced-normalisation phenomenon because the EEG was said to be almost normal during the episode (Yamamoto *et al.*, 2001).

A case study by Chien described a 10-year-old boy who developed acute mania with psychotic symptoms and suicidal ideation with ethosuximide (Chien, 2011).

7. Gabapentin

Two observational studies were identified, which reported aggression from AE data, and two case studies (Supplemental table S-2). Khurana *et al.* carried out a chart review of 32 children treated with gabapentin. Behavioural AEs occurred in 15 patients. Physician intervention was required in four children: one became more withdrawn and the other three became more hyperactive and more aggressive with violent outbursts and mood swings (Khurana *et al.*, 1996). In three of the four, the behaviours returned to baseline after the gabapentin was stopped.

Lee *et al.* reported seven children who developed behavioural adverse effects in association with gabapentin. It is not clear how these children were selected from the larger pool of 55 children treated at this centre (Lee *et al.*, 1996). In some cases the behaviours were present before treatment but exacerbated when the child was treated with gabapentin. New behaviours included oppositional defiant disorder (58%) and conduct disorder (33%). Again, because of the small numbers, it is difficult to draw any firm conclusions.

The results of studies carried out by one of the current authors and his colleagues on 14 teenagers, using a standard instrument for monitoring behaviour (the Rutter Behavioural Scales) before and during treatment with gabapentin did not confirm these results. There were no significant behavioural changes with gabapentin: two subjects moved from the “non-disturbed” to the “disturbed” behavioural range and one moved from the “disturbed” to the “non-disturbed” range. In a further behavioural study on the same pool of patients, six female and 10 male subjects were matched for sex, and as closely as possible, for age and other parameters.

Examination of the changes in the Rutter scale scores revealed no significant differences between the gabapentin-treated group and the comparison group (Besag, 1996).

A case study by Tallian *et al.* reported two children who had aggressive behaviour with gabapentin (Tallian *et al.*, 1996). The first case was a 16-year-old boy in whom the seizures were fully controlled but his appetite decreased and he had problems sleeping. He then developed aggressive behaviour with biting, slapping, scratching, growling and "acting like an animal". The gabapentin was discontinued and the behavioural disturbance resolved. When the gabapentin was recommenced and the dose increased, the aggression became marked. When the gabapentin was subsequently discontinued the problem resolved again. The second patient was a 6-year-old girl with intellectual disability and ADHD but no history of aggressive behaviour. When gabapentin was commenced she stopped interacting socially and, when confronted socially, she became physically aggressive, assaulting other children. When the gabapentin dose was decreased a moderate improvement in behaviour occurred; it was continued because her parents judged her behaviour as being tolerable and she remained seizure free.

A case series described by Wolf *et al.* reported behavioural problems in three children with learning disability when treated with gabapentin (Wolf *et al.*, 1995). The behaviours described included unprovoked outbursts of anger in case one, episodes of hyperactivity and oppositional behaviour in case two and outbursts characterised by throwing food, screaming and fighting in case three.

It is difficult to assess the causative role of the gabapentin itself in all of these reports, not only because of the small numbers and open nature of the studies but also because of confounding factors such as drug interactions and changes in seizure control.

8. Lacosamide

Our searches for lacosamide data in children retrieved only small observational studies (Supplemental table S-2).

Gavatha *et al.* reported a study in 18 children (10 male, 8 female, aged 3–18 years) with intellectual disability. No aggression was specifically reported but there were two cases of irritability. No further details were provided (Gavatha *et al.*, 2011).

Guilhoto *et al.* analysed results from a retrospective study of 16 young people with treatment-resistant epilepsy (7 male, 9 female, aged 8–21 years, mean age 14.9 years). Lacosamide was withdrawn in one boy (8.4 years old) because of severe behavioural outbursts (Guilhoto *et al.*, 2011).

Heyman *et al.* carried out a retrospective study of medical records of 17 children (10 male, 7 female, aged 1.5–16 years, mean age 8 years) with epilepsy taking lacosamide. Restlessness was reported in two patients but no other behavioural disturbance was reported (Heyman *et al.*, 2012).

Kim *et al.* described a retrospective study of medical records that included 21 children (16 male, 5 female, aged 1.2–17.9 years, median age 13.9), two of whom discontinued lacosamide because of AEs (aggressive behaviour and depression) (Kim *et al.*, 2014).

9. Lamotrigine

Two observational studies were retrieved (Supplemental table S-2). In a long-term, open-label extension study, Piña-Garza *et al.* followed 204 infants (1 to 24 months of age), treated with lamotrigine following Phase III studies. The only AE that they considered could be reasonably

attributable to lamotrigine in >2% of patients was irritability, which occurred in 10 patients (5%) (Piña-Garza *et al.*, 2008).

Cardenas *et al.* carried out a retrospective review of patients who developed "neurobehavioural adverse reactions to lamotrigine" (Cardenas *et al.*, 2010). They identified nine children (7 male, 2 female, mean age 5 years) who became hyperactive and agitated, over a wide range of doses from 0.7 to 14 mg/kg/day. Five patients developed self-injurious and violent behaviours, two had severe insomnia and the most affected, a six-year-old boy, developed "extremely volatile mood and affect", with visual and auditory hallucinations together with insomnia. All nine patients improved markedly after discontinuation or dose reduction of the lamotrigine. These authors said that severe, reversible neurobehavioural disturbance associated with lamotrigine therapy had not previously been reported in the literature.

It should be noted that lamotrigine is now widely acknowledged as an AED that can improve mood significantly; large studies have established this in adults and the positive psychotropic effects of improving mood/behaviour in young people with or without epilepsy have also been confirmed (Frye *et al.*, 2000; Cramer *et al.*, 2004; Biederman *et al.*, 2010).

10. Levetiracetam

There are several reports of aggression in children with epilepsy treated with levetiracetam, including two RCTs with behaviour-specific measures, but there are also several reports of improved behaviour (Supplemental table S-2).

Our searches identified one study that specifically explored the behavioural effects of levetiracetam in a randomised, placebo-controlled study, using standardised measures – the CBCL and the Child health questionnaire – parent form 50 (CHQ-PF50) (de la Loge *et al.*,

2010). Patients received adjunctive levetiracetam (N=64) or placebo (N=34) for 12 weeks. The CBCL separates scores into a Total Problems Score, and a Total Competence Score. Among the per-protocol population (levetiracetam N=46, placebo N=27), there was no difference between treatment groups in the Total Competence Score, but a significant difference in the Total Problems Score (p=0.020) between levetiracetam (worsening) and placebo (improvement). In the Problems component of the CBCL, there was a significant worsening of aggression with levetiracetam *vs* placebo (p=0.013), which drove the overall difference in the Problems Score. In the Competence component of the CBCL, there was a small improvement with levetiracetam *vs* placebo in the Activities subscale (p=0.049). The CHQ-PF50 score showed little change during treatment, and no significant between-group differences. A long-term extension that included 80 patients who continued from this study, and 23 additional patients, found no significant change from baseline CBCL score (or aggression subscale scores) with levetiracetam (Schiemann-Delgado *et al.*, 2012). From AE reporting in this study, aggression was seen in 7.8%, irritability in 7.8%, and abnormal behaviour in 3.9% of patients.

One other study with levetiracetam specifically studied aggressive behaviour but did not use standardised measures. In 12 children with epilepsy with continuous spikes and waves during slow sleep and pervasive developmental disorder, parents reported the frequency of seizures and frequency of episodes of panic or aggressive behaviour. In the eight patients whose seizures improved with addition of levetiracetam to existing AEDs, six patients also had a ≥50% reduction in the frequency of episodes of panic or aggression; there was no change in episode frequency in the other two responders (Kanemura *et al.*, 2014).

There have been many RCTs and observational studies with levetiracetam in children and adolescents, and rather than review them all here, the results of a recent systematic review and

meta-analysis of the behavioural effects of levetiracetam are presented (Halma *et al.*, 2014). These authors included studies in children aged from 1 month to 18 years with a diagnosis of epilepsy, taking oral levetiracetam as monotherapy or add-on therapy, with follow-up of at least 2 weeks, and which reported behavioural side effects. They excluded case studies or case series with fewer than 10 patients, studies of neonatal convulsions, and studies that included adults and did not have separate subgroup analyses for patients aged <18 years. Their review identified 13 studies in 727 patients. In the three randomised controlled trials they identified, the most frequent behavioural AEs with add-on levetiracetam (N=165) were hostility (7.3%), nervousness (6.1%) and aggression (4.9%). A meta-analysis of these studies revealed a statistically significant increased risk of behavioural AEs with levetiracetam: risk ratio *vs* placebo = 2.18 (95% CI 1.42–3.37). Ten observational studies met their selection criteria and these reported both worsening and improvement of behaviour with levetiracetam. Levetiracetam add-on therapy was associated with behavioural AEs of irritability (4.7%), hyperexcitability (4.4%) and aggression (2.7); monotherapy was associated with behavioural problems in general (19%), and irritability (2.6%). No meta-analysis was possible across the observational studies.

Our searches identified the majority of the studies included by Halma *et al.* in their systematic review and meta-analysis, and also a number of additional studies that were excluded by their selection criteria. Details of all these studies can be found in Supplemental table S-2; the rates of behavioural AEs they report are broadly in line with those reported by Halma et al.

Mbizvo *et al.* performed another meta-analysis of levetiracetam studies, which was also discussed earlier (Section V part B.11; Mbizvo *et al.*, 2014). This meta-analysis only included two RCTs in children/adolescents (whereas Halma *et al.* included three), and when all the captured behavioural AE terms were combined across these two studies for the child/adolescent

populations, an incidence of 40.6% (*vs* 21.4% with placebo) was found. This seems remarkably high – especially considering the fact that the analysis excluded behavioural AEs that were not reported in the original publications because they were below the reporting thresholds (≥5 or ≥10%); however, it is broadly consistent with the doubling of risk (i.e. a risk ratio of ~2 *vs* placebo) as reported by Halma *et al.* The terms included by Mbizvo *et al.* were hostility, personality disorder, nervousness, depression, aggression, agitation, emotional lability, psychomotor hyperactivity, irritability, abnormal behaviour, altered mood, anxiety, and dissociation. It was not clear, from their paper, whether they excluded "double-counting", for example, adding together reports of AEs of aggression and agitation when these occurred in the same subject; if they did not exclude double-counting, this could explain the very large percentages of behavioural AEs in both the levetiracetam and placebo groups.

11. Oxcarbazepine

Very little evidence of any aggression-related features was found for oxcarbazepine, just one open-label study (Supplemental table S-2). Northam *et al.* carried out a prospective, open-label study of 24 young patients (aged 2–45 months). Oxcarbazepine was associated with irritability in 5/24 (21%) in the treatment phase (up to 30 days) and in 7/20 (35%) in the six-month extension phase (Northam *et al.*, 2005). The oxcarbazepine was discontinued in one of the patients with irritability (who also had fatigue and ataxia). The usual comments about the reliability of findings from small, open, uncontrolled studies apply.

12. Perampanel

Our searches identified one study with perampanel in adolescents that used standardised measures to assess behaviour, one pooled analysis of Phase III clinical trials, and several observational studies (Supplemental table S-2). Lagae *et al*. reported a Phase II, randomised,

placebo-controlled trial of add-on perampanel in 133 adolescents with refractory focal-onset epilepsy; behaviour was assessed with the CBCL. There was no significant difference between perampanel and placebo in the change from baseline in CBCL Total Problem or Total Competence scores, or in any of the subscales (e.g. aggression). AEs related to hostility or aggression occurred in 17.6% (n=15) of the perampanel-treated subjects (7 aggression, 6 irritability, 2 anger, 1 laceration) and 4.2% (2) of the placebo group (1 aggression, 1 irritability).

Rosenfeld *et al.* reported pooled AE data for the 143 adolescents in the three Phase III trials of perampanel. The most common AEs included aggression in 8.2% of adolescents, *vs* 0% for placebo; this was more frequent than in the overall perampanel-treated population (1.6%). Furthermore, aggression was reported as being one of the most common reasons (6.6%) for interruption or dose adjustment of the perampanel among adolescents during the extension phase (Rosenfeld *et al.*, 2015).

The other perampanel reports come from observational studies. Biró *et al.* published a retrospective analysis of 58 children (mean age 10.3 years, range 2–17 years) treated with perampanel (Biró *et al.*, 2015). Aggression was reported in eight (13.8%). Philip *et al*., in a retrospective study of 18 patients (age range 4–19 years), reported behavioural change in only one patient (5.6%) (Philip *et al.*, 2014).

13. Phenobarbital

Four studies were identified for phenobarbital (Supplemental table S-2). Willis *et al.* carried out a neuropsychological and EEG study of 11 children with epilepsy aged 7 to 14 years treated with phenobarbital and mephobarbital (Willis *et al.*, 1997). They stated that parents reported clear behavioural changes in six of 11 subjects, including irritability, oppositional attitude and

overactivity. In four of the six the changes were relatively mild and the barbiturate was not discontinued.

In a large observational study that used parent questionnaires, Domizio *et al.* compared 197 children (66 male, 37 female, mean age 5.3 years) treated with phenobarbital, with 103 children (66 male, 37 female, mean age 6.4 years) who were treated with other antiepileptic drugs. In the phenobarbital group, 150 children (76.1%) had one or more behavioural disturbances, compared with 32 (31%) in the other group ($p<0.0001$). Hyperactivity was the most frequent behavioural disorder (Domizio *et al.*, 1993).

In a randomised study of four antiepileptic drugs: phenobarbital, phenytoin, carbamazepine and sodium valproate, de Silva *et al.* discontinued the phenobarbital arm after six of the first 10 children taking this drug had unacceptable AEs, which were primarily behavioural (de Silva *et al.*, 1996). In contrast, Pal *et al.* found no behavioural effects of phenobarbital (N=47) in a study in 94 children in India (Pal *et al.*, 1998).

14. Phenytoin

Although anecdotally phenytoin is associated with behavioural disturbance in young people, no firm published evidence for this was found (Supplemental table S-2). In the study in India referred to above, Pal *et al.* also found no behavioural effects of phenytoin in 47 children (Pal *et al.*, 1998). Krishnamoorthy *et al.* reported three cases of phenytoin-induced choreoathetosis associated with agitation/restlessness in three young children: two were two years of age and one was 15 months of age (Krishnamoorthy *et al.*, 1983).

15. Pregabalin

No evidence found.

16. Primidone

Despite the fact that primidone is partly metabolised to phenobarbital, no evidence of aggression in children and teenagers with primidone was found.

17. Retigabine

We identified only one study: Groening *et al.* treated 17 patients (1 year 10 months to 19 years) with retigabine for pharmacoresistant seizures (Supplemental table S-2). Results were analysed for 12 patients, and AEs included hallucinations, agitation and personality changes. Further details were not provided in this conference abstract (Groening *et al.*, 2012).

18. Rufinamide

In a recent consensus paper on rufinamide in childhood epilepsy by Coppola *et al.*, aggression and related behaviours were not reported among the adverse effects (Coppola *et al.*, 2014). There have been few other reports of behavioural adverse effects with rufinamide (Supplemental table S-2).

Coppola *et al.,* in a multicentre, prospective, add-on, observational study of rufinamide in 43 children, adolescents and adults with Lennox-Gastaut syndrome (26 male, 17 female, aged 4–34 years, mean 15.9 years), reported irritability/aggressiveness in three patients (6.9%) (Coppola *et al.*, 2010). In a separate observational study, the effects of rufinamide in encephalopathies other than Lennox-Gastaut syndrome were reported in 38 patients (19 male, 19 female, aged 4–34 years, mean age 13.7 years). Irritability/aggressiveness was seen in two patients (5.3%) (Coppola *et al.*, 2011).

Cusmai *et al.*, in a prospective, open-label, add-on trial in refractory epilepsy in 69 children and adolescents, reported irritability in 11 patients (15.9%) (Cusmai *et al.*, 2014). Lee *et al.*, in a

retrospective study in 23 patients in Korea (age range 4–22 years), reported aggressive behaviour in two patients (8.7%) (Lee *et al.*, 2013).

19. Stiripentol

One observational study was identified (Supplemental table S-2). Inoue *et al.* reported clinical results using stiripentol to treat Dravet syndrome in patients aged 1 to 22 years. Of 23 patients, six had hyperactivity/irritability early in treatment, which resolved with continued treatment or dose reduction. One patient (a 15-year-old girl) discontinued stiripentol because of early irritability (Inoue *et al.*, 2009).

20. Tiagabine

No evidence found.

21. Topiramate

Two large retrospective studies, together with several smaller studies and case studies were identified (Supplemental table S-2). Reith *et al*. reported data in 159 patients with epilepsy aged <18 years and taking topiramate. Follow-up was possible in 127 patients (0.5–17.9 years); aggression/psychosis was a treatment-limiting AE in 10 (7.9%) of these patients (Reith *et al.*, 2003). Grosso *et al.* treated 59 children aged ≤2 years with topiramate for localisation-related and generalised epilepsies. Irritability was listed as one of the most frequent AEs, but precise rates were not given (Grosso *et al.*, 2005). During topiramate treatment, Lee *et al.* reported that four of 28 infants (14.3%) aged 2–18 months with West syndrome developed irritability (GM Lee *et al.*, 2011), and Endoh et al. reported that five of 33 children (15.2%) aged ≤12 years with epileptic spasms developed irritability (Endoh *et al.*, 2012).

Metabolic acidosis is a known adverse effect of topiramate, and this can be associated with irritability/aggression (Ko and Kong, 2001). In patients taking topiramate who present with hyperpnoea or mental status change, metabolic acidosis must be excluded as a possible cause.

22. Valproic acid

Two studies were identified with sodium valproate in adolescent epilepsy populations (Supplemental table S-2). In a retrospective study of 100 children with epilepsy treated with sodium valproate, Egger and Brett reported aggressive behaviour in four (4%) (Egger and Brett, 1981).

Ronen *et al.* studied eight children (6 male, 2 female, aged 6–12 years), without clinical seizures but with abnormal EEGs and significant developmental learning disorder. While taking sodium valproate, the children were more distractible, had increased delay in response time and had lower memory scores. Their parents also reported higher internalising scores on the CBCL while the children were taking valproate (Ronen *et al.*, 2000). In contrast, sodium valproate and divalproex sodium are used extensively as mood-levelling drugs in both adults and children in non-epilepsy populations; for example, Hollander *et al.* reported that impulsivity and aggression were decreased in 14 patients with autism taking divalproex sodium as a psychotropic medication (Hollander *et al.*, 2000).

23. Vigabatrin

We found no RCTs of vigabatrin with behaviour-specific endpoints, and one observational study in children and adolescents that focused on behaviour (Supplemental table S-2). Sheth *et al.* reported that in 31 patients aged 1–22 years (mean age 12.6 years) with refractory focal and generalised seizures, add-on vigabatrin was associated with negative behaviour change in six

children (based on parent reports), with discontinuation in one patient with severe aggressive agitation, and positive behaviour change in one patient (Sheth *et al.*, 1996).

The remaining studies we identified relied on AE reporting from five observational studies, three case reports, and six studies in babies with infantile spasms (Supplemental table S-2). Gobbi *et al.* carried out a prospective study of vigabatrin monotherapy in the treatment of focal epilepsies in 40 children (mean age at last visit 7.5 years) compared with 40 children treated with carbamazepine monotherapy (Gobbi *et al.*, 1999). They stated that tolerability was good in the vigabatrin group but four of 37 patients had mild irritability at the end of the trial (*vs* none in the carbamazepine group). Raucci *et al.* studied 61 children with various types of epilepsy, treated with vigabatrin, 12 as monotherapy and 49 as add-on therapy (Raucci *et al.*, 1994). Vigabatrin was discontinued in six children because of adverse effects, including irritability.

In the first of three case studies, Weber et al. reported psychosis associated with vigabatrin in an adolescent girl with refractory symptomatic epilepsy following an early middle cerebral artery insult (Weber *et al.*, 2012). The onset of the psychosis was seven weeks after the vigabatrin was commenced, when she had been seizure-free for two weeks. They attributed this to the phenomenon of "forced normalisation", although it should, more accurately, be termed "alternative psychosis" or "reciprocal psychosis" – the situation when the psychosis is likely to occur when the seizure control has improved (see earlier). Two of the teenage patients of one of the current authors also developed psychosis with vigabatrin, which resolved with dose reduction or discontinuation (F Besag, personal communication). Cánovas Martínez *et al.* published a case of a seven-year-old boy with refractory epilepsy who developed an acute psychosis three days after rapid introduction of vigabatrin (Cánovas Martínez *et al.*, 1995). The psychosis resolved within 48 hours of discontinuing the vigabatrin. Re-commencement of the vigabatrin two months

later, using a slower dose escalation, was well tolerated with no return of the psychosis. Chiaretti *et al.* also published a single case report of psychosis with vigabatrin in a child (Chiaretti *et al.*, 1994).

The data in infantile spasms are not presented here, as AEs such as 'irritability' in young infants cannot be interpreted as aggression-related behaviours, but studies are listed in Supplemental table S-2.

24. Zonisamide

We identified one study with behaviour-specific outcomes, and five additional studies reporting behavioural AEs (Supplemental table S-2).

Eun *et al.* studied the neuropsychological and behavioural effects of low-dose and high-dose zonisamide, using a Korean version of the CBCL, in children aged 2–16 years receiving zonisamide monotherapy for newly diagnosed epilepsy (Eun *et al.*, 2011). Data were available on 63 patients (27 on low-dose and 36 on high-dose), and were presented as group data, so it is not possible to determine whether some patients became more aggressive and others less aggressive. Overall, they saw a significant improvement ($P<0.05$) in various parameters, including aggressive behaviour, in the low-dose group and a non-significant improvement in the high-dose group. No aggression-related or behaviour-related AEs were reported.

Cross *et al.* carried out a pooled analysis of 17 zonisamide studies in patients aged 16 years or younger, including four randomised, double-blind trials (Cross *et al.*, 2014). Irritability was reported in 5.8% of the 391 zonisamide-treated patients but was not among the AEs commonly leading to discontinuation. Irritability was somewhat more common (7.5%) in patients aged 6-11 years than in patients aged 12–16 years (<5%).

A Phase III study by Guerrini *et al.* was included in the meta-analysis by Cross *et al.,* so is not discussed in detail. No aggression-related AEs were reported in the zonisamide-treated group but one patient in the placebo group discontinued due to aggression (Guerrini *et al.*, 2013). In the subsequent long-term extension study, there were no behavioural AEs in patients continuing on zonisamide from the Phase III study but there were two cases of aggression (2.8%) in patients who switched from placebo to zonisamide during the extension (Guerrini *et al.*, 2014).

Coppola *et al.* carried out a prospective, add-on, open-label study of 82 young patients (45 male, 37 female, aged 3–34 years, mean age 13.1 years). Irritability was reported in nine patients (11.0%) but resolved in most cases with dose reduction. No other behavioural adverse effects were reported (Coppola *et al.*, 2009).

Hirai *et al.* treated 27 children who had idiopathic epilepsy with zonisamide in a prospective study, observing behavioural disturbance in two cases (7.4%) (Hirai *et al.*, 2002). One of the cases developed an obsessive-compulsive disorder. The other case, a 14-year-old girl with focal seizures, whose seizures were treated effectively with zonisamide from six years of age, developed selective mutism, violent behaviour and lack of concentration at 10 years of age. Decreasing the zonisamide dose was said to have maintained adequate seizure control while resolving the behavioural disturbance. Because of the long time-interval between the prescription of zonisamide and the development of the violent behaviour, the direct role of the antiepileptic drug is questionable in this case; a more likely explanation might be that the violent behaviour was an interaction between seizure control and developmental factors.

C. Conclusions

In most cases there is inadequate evidence to draw any firm conclusions about the aggression-related behavioural AEs associated with AEDs in children and teenagers. From the evidence that is available, however, it is suggested that children and adolescents who are treated with gabapentin, levetiracetam, perampanel (especially at higher doses), phenobarbital, sodium valproate, topiramate, and zonisamide are monitored closely for possible behavioural AEs. The most extensive evidence is for levetiracetam but the reports of both improvement and deterioration with this drug emphasise the need for monitoring each individual patient for positive or adverse effects of AEDs. Although there is credible evidence for psychosis developing with vigabatrin, this is more likely to be the phenomenon of "alternative" or "reciprocal" psychosis that might have occurred with any AED that achieved rapid seizure control and could probably have been avoided by starting at low doses and escalating the dose slowly. This emphasises the importance of excluding the confounding factors that have been described in detail elsewhere (Besag, 2001) before attributing behavioural or aggression-related AEs to an AED.

VII. Avoidance and management of AED-induced aggression

Although there is a limited amount of good-quality clinical data on aggression with AEDs in children, adolescents, and adults with epilepsy, it is becoming clear that there is increased propensity for some patients to develop aggression-related behaviour during treatment with some AEDs. In a recent survey, for example, 49% of 158 people with epilepsy treated with levetiracetam reported aggression as sometimes or always being a problem, whereas 39% of 260

patients taking other AEDs were aware of anger issues, and only 9% of 41 controls admitted to ever losing their temper (Wieshmann and Baker, 2013). Based on the evidence collected in this review (in sections V and VI), we can conclude that there is reasonable evidence of an increased risk of aggressive behaviours occurring in epilepsy patients treated with levetiracetam, perampanel and topiramate, and in children/adolescents that use of gabapentin, phenobarbital, sodium valproate, and zonisamide also carries some risk. What can we do to anticipate, identify and ameliorate aggressive-type behaviours that can occur with these AEDs?

When it comes to anticipating which patients may develop aggressive behaviours with AEDs, the evidence is very limited. Previous psychiatric history is a predictive factor in some studies, but certainly not all patients with a history of psychiatric illness or aggressive behaviour will go on to develop aggressive behaviour with higher-risk AEDs. However, when initiating treatment with any AED, a personal and, if possible, a family history of psychiatric disorders should be explored and documented. All patients should be asked whether or not they have a short temper, how often they lose it and what is the likely outcome. A similar question to accompanying partners and family members often elicits a different response, since some people are not aware that they have this problem or appreciate its extent. Any history of physical violence is of particular concern in this context. If the patient has had serious anger management issues in the past or has regularly demonstrated hostile or aggressive behaviour, it does not necessarily completely preclude using AEDs that have evidence for increased risk of aggressive behaviours, but such AEDs should be used with extreme caution or avoided altogether based on clinical judgement. The decision will involve weighing the risks of aggressive behaviours and their possible impact, against the risks of inadequate seizure control, and will be influenced by the other treatment options available to the patient. Alcohol and other stimulating agents can

exacerbate aggression and their effects should also be discussed with the patient, partner and family (Heinz *et al.*, 2011). Providing patients and/or carers with a medical contact number to call if inappropriate behaviour occurs is a sensible precaution, particularly in patients who admit to frequently losing their temper or to exhibiting aggressive behaviour. Regardless of the individual patient history, the potential for aggressive behaviour should be explained to patient and/or caregivers starting an AED associated with risk to aid early detection of any problems. Finally, documentation of this discussion in the case notes and in the correspondence with the patient's general practitioner should be considered as an integral part of good practice and as an essential precaution. The possibility of later medico-legal repercussions if a serious assault subsequently occurs underlines the importance not only of following good practice but also documenting it.

In general, slow titration should be used when possible, particularly when the patient is considered at risk of aggressive behaviour based on their psychiatric history or selection of AED.

Certain groups of patients require special attention. When introducing AEDs in teenagers, particularly those with juvenile myoclonic epilepsy, be aware that some patients will have a tendency to exhibit impulsive behaviour (Crespel *et al.*, 2013). Particular attention should also be paid to patients with intellectual disability , who cannot easily express their frustrations in an acceptable way, and those with dementia, who may demonstrate unexpected violent behaviour (Newman, 2012). The possibility of 'release phenomena' in patients with intellectual disability should also be considered (Besag, 2001). Some AEDs, such as the sodium channel blockers, carbamazepine, oxcarbazepine and, particularly, lamotrigine (Labiner *et al.*, 2009) or valproic acid, may be better choices in these situations (Comai, Tau, Pavlovic, *et al.*, 2012).

Another possibility to help anticipate aggressive responses is to use questionnaires to screen patients. There are a number of published and validated scoring systems for measuring aggression that could be used in patients with epilepsy (Silver and Yudofsky, 1991; Buss and Perry, 1992; Harris, 1995). An instrument for measuring irritability in people with epilepsy has also recently been published (Piazzini *et al.*, 2011).

If irritability, anger, hostility or aggressive behaviours do develop or worsen, managing these depends on their severity and the extent of the positive pharmacological response to the implicated AED. This consideration is particularly important in patients with severe pharmacoresistant epilepsy where other treatment options may be limited. Dose reduction of the most recently added AED should be considered. Reducing alcohol intake can also be a helpful step in ameliorating aggression. Often, however, the aggressive behaviour can only be stopped by discontinuing the AED. The decision whether or not to maintain AED treatment in this setting should be made in discussion with the patient, partner and family; again, this discussion should be documented in the patient's case notes. If the AED is continued, improvement in anger-related symptoms can occur with time, although this appears to be relatively uncommon, and anger management programmes can also be a helpful addition to the therapeutic regimen particularly in seizure-free patients. It is important to make the patient's general practitioner fully aware of the situation, stating which AED is implicated.

If the AED is continued, and/or the aggressive behaviour continues, then pharmacological management of the behaviour may be warranted. There is, however, no single pharmacological strategy recommended for the management of anger and aggression (Newman, 2012).

Antipsychotic, antidepressant and other psychotropic agents have all been used to ameliorate these behaviours (Alper *et al.*, 2002; Nevels *et al.*, 2010), and there is also evidence that mood stabilisers, such as carbamazepine, oxcarbazepine, phenytoin and lithium, are significantly better than placebo in reducing aggressive behaviour (Jones *et al.*, 2011). Pharmacological management of aggression can be complicated by pro-seizure effects of some psychotropic medications, particularly in higher doses (Varma *et al.*, 2011). Existing treatment for psychiatric comorbidities, particularly depression, anxiety, psychosis, panic attacks, bipolar symptoms and attention deficit disorder should be reviewed.

If the comorbid psychiatric symptoms are chronic and severe, it is advisable that the patient also remains under the care of an experienced psychiatrist. Managing psychiatric comorbidities is not always an attractive option for the neurologist, but this should be attempted if prompt management from a psychiatrist is not available and the symptoms are relatively mild and amenable to standard pharmacological intervention with widely used mood-stabilising drugs.

VIII. Overall summary

One of the major areas of interest in the management of epilepsy is the effect of psychiatric comorbidities on the choice of and response to AED therapy (Hitiris *et al.*, 2007). There is, of course, substantial overlap among their clinical presentations in the setting of newly diagnosed and refractory epilepsy (Lin *et al.*, 2012). There has been particular concern recently regarding the potential for some of these drugs to cause or worsen hostility and aggression with possible medicolegal consequences. This evidence-based review discusses for the first time the relationship between epilepsy, antiepileptic drugs and aggression, covering a wide range of

issues including definitions, psychiatric comorbidities and epilepsy, the neurobiology and pharmacology of aggression, evidence for each AED in causing or exacerbating this problem in children, adolescents and adults, and finally some suggestions for prevention and management. The main conclusion must be that better quality evidence and comparative studies are needed to clarify the link between AEDs and aggressive behaviour in patients with epilepsy. But based on the available evidence, some AEDs seem to be associated with higher risk than others, including clobazam, clonazepam, levetiracetam, perampanel, phenobarbital, tiagabine, topiramate, vigabatrin, and zonisamide, (in alphabetical order). The potential for aggressive behaviour should be explained to every patient starting on any of these drugs, particularly patients with known anger management issues. The AEDs with strongest evidence for a risk of aggressive behaviours are levetiracetam, perampanel and possibly topiramate, but the majority of patients taking these, and any other AEDs, will have no problems with aggressive behaviours. Involvement of partners and families is important, since many people are not aware that they have a short temper or that their demeanour could be perceived as aggressive. These issues should be taken into consideration when making the choice of AED therapy for all patients with newly diagnosed and chronic epilepsy. Future research should clarify the neurobiology of aggression and epilepsy and may help clinical decision-making and treatment selection to avoid problems with aggression in patients with epilepsy.

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Authorship contributions

Conceived of the review concept and scope: Brodie. Wrote or contributed to the writing of the manuscript: Brodie (Introduction, Avoidance and management of AED-induced aggression, Overall summary), Ettinger (Aggressive behaviour in epilepsy: definitions), Mula (Aggressive behaviour in epilepsy: clinical aspects), Comai and Gobbi (Neurobiology and psychopharmacology of epilepsy and aggression), Aldenkamp and Steinhoff (Antiepileptic drugs and aggression in adults with epilepsy), Besag (Antiepileptic drugs and aggression in children and teenagers with epilepsy). Reviewed and proof-read the manuscript: Besag.

Disclosures

MJB has received honoraria for activity on scientific advisory boards for Eisai, UCB pharma, GlaxoSmithKline, Lundbeck, Bial, GW Pharmaceuticals and Takeda. He is on the speakers' bureau for Eisai, UCB pharma, GlaxoSmithKline and Lundbeck and has accepted travel grants for scientific meetings from Eisai, UCB pharma and Lundbeck.

ABE has received honoraria for advisory board activity from Eisai and Sunovion Pharmaceuticals.

MM has received honoraria from UCB Pharma, Eisai and Pfizer. He has also received supports from Special Products Ltd and is currently serving as Associate Editor of Epilepsy & Behavior.

GG has received honoraria for speaking engagements from Merck, Lilly and Astra-Zeneca. GG has also received grants from the Canadian Institutes of Health Research (CIHR), the Canada Foundation for Innovation (CFI), and Fonds de recherche du Québec – Santé (FRQS).

SC has no relevant disclosures.

APA has received speaker fees from UCB pharma.

FB has attended a consensus meeting on rufinamide sponsored by Eisai. In the past (at least two years ago), he has attended and organised conferences supported by unrestricted educational grants from various pharmaceutical companies and has carried out research partly sponsored by a pharmaceutical company producing benzodiazepine drugs and by the company then producing lamotrigine.

BJS has received honoraria for speaking and/or advisory board activity from Braun Melsungen, Desitin, Eisai, GlaxoSmithKline, Marinus Pharmaceuticals, Medtronic, OmniaMed, Pfizer, PPD, UCB Pharma and Viropharm. His institution has participated in clinical trials supported by Bial, Cerbomed, Desitin, Eisai, GlaxoSmithKline, Marinus Pharmaceuticals, Novartis, Pfizer, SK Life Science, and UCB Pharma, and Upsher Smith.

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Tables

Table 1. Classification of aggressive symptoms according to their temporal relationship with seizures.

Peri-ictal	**Pre-ictal**	Not reported
	Ictal	Aggressive conduct in 1/1000 seizures recorded in monitoring units (Delgado-Escueta *et al.*, 1981)
	Post-ictal	Post-ictal delirium/confusion Post-ictal psychoses (22.8% present with aggressive behaviours)
Para-ictal	**Forced normalisation**	Rarely reported
Inter-ictal	**Inter-ictal**	Up to 7% in unselected groups but due to the underlying psychiatric comorbidity

Table 2. AED targets and impact on aggression in non-epilepsy patients

AED	**Main system targeted**	**Other possible systems targeted**	**Epigenetic mechanisms/ gene expression**	**Anti-aggressive in psychiatric patients**[a,b,c]
Carbamazepine	Na^+ channels		X	X
Eslicarbazepine acetate	Na^+ channels		X[d]	
Lacosamide	Na^+ channels			
Lamotrigine	Na^+ channels	Glutamate (AMPA R)	X	X
Oxcarbazepine	Na^+ channels			X
Phenytoin	Na^+ channels		X[e]	X
Rufinamide	Na^+ channels			
Zonisamide	Na^+ and Ca^{2+} channels	GABA	X[f]	
Ethosuximide	T-type Ca^{2+} channels			
Gabapentin	Ca^{2+} channels	GABA, glutamate (NMDA R s)		X
Pregabalin	Ca^{2+} channels	GABA		
Retigabine	K^+ channels	GABA[h]		
Felbamate	Mixed	Ca^{2+} channels, NMDA Rs, GABA Rs		
Topiramate	Mixed	$GABA_A$ Rs, AMPA/kainate Rs,	X	X

		Na^+/Ca^{2+} channels		
Phenobarbital	GABA			
Clobazam/ clonazepam	GABA ($GABA_A$-R)			X
Vigabatrin	GABA		X[g]	
Tiagabine	GABA			X
Stiripentol	GABA			
Levetiracetam	Neurotransmitter release (via SV2A)		X	X
Brivaracetam	Neurotransmitter release (via SV2A)			
Perampanel	Glutamate (AMPA Rs)			
Valproic acid	Mixed	GABA, Glutamate (NMDA, AMPA, and kainate Rs), Na^+ channels	X	X

R: receptor.

Missing data from the table does not necessarily imply that there is no action on a specific target. In particular, research on the effects of novel and recent AEDs on epigenetic regulation and/or gene expression is still ongoing.

Unless otherwise specified, mechanism of action details may be found in the text of this review, in review articles (Rogawski and Löscher, 2004; Brodie, 2010; Comai, Tau, Pavlovic, *et al.*, 2012), and/or in the Summary of Product Characteristics for each individual AED.

[a](Comai, Tau, Pavlovic, *et al.*, 2012); [b](Gallagher and Herrmann, 2014), [c](Huband *et al.*, 2010); [d](Dezsi *et al.*, 2013); [e](Hassel *et al.*, 2010); [f](Ueda *et al.*, 2012); [g](Tran *et al.*, 1999); [h](Treven *et al.*, 2015)

Table 3. Summary of aggression-related behaviour incidence and warnings, from AED labels

AEDs are listed in alphabetical order.

AED	**Aggression-related AEs (and incidence)**	**Other related text, warnings, or precautions**	**Epilepsy-specific?**	**Source**
Carbamazepine	**Aggression**, **agitation** (rare: 0.01–0.1%)	*"The possibility of activation of a latent psychosis and, in elderly patients, of confusion and* ***agitation*** *should be borne in mind"*	No	(Tegretol SPC, 2014; Tegretol USPI, 2014)
Clobazam		*"****aggressive behaviour*** *towards self and others may be precipitated"*	No	(Frisium SPC, 2014; Onfi USPI, 2014)
	Irritability (7% with clobazam *vs* 5% with placebo) **Aggression** (8% with clobazam *vs* 5%) **Aggression** (1 of the 6 AEs leading to clobazam discontinuation)		Yes (LGS)	(Onfi USPI, 2014)

AED	Aggression-related AEs (and incidence)	Other related text, warnings, or precautions	Epilepsy-specific?	Source
Clonazepam	No incidence reported for aggression-related AEs	*"Clonazepam generally has a beneficial effect on behaviour disturbances in epileptic patients. In certain cases, paradoxical effects such as* ***aggressiveness****, excitability, nervousness,* ***hostility****, anxiety, sleep disturbances, nightmares, vivid dreams,* ***irritability****,* ***agitation****, psychotic disorders and activation of new types of seizures may be precipitated."*	Yes	(Clonazepam SPC, 2014)
	No incidence reported for aggression-related AEs	*"****131ehaviour problems*** *have been noted in approximately 25% of patients"*	Yes	(Klonopin USPI, 2013)
Eslicarbazepine	**Agitation**, **irritability** (uncommon: 0.1–1%)		Yes	(Zebinix SPC, 2014)
Ethosuximide	**Aggression**, **irritability** (uncommon: 0.1–1%), psychiatric AEs are seen *"particularly in patients who have previously exhibited psychological abnormalities"*		Yes	(Zarontin USPI, 2012; Zarontin SPC, 2014)
Felbamate	**Aggressive behaviour**, **agitation** (common: ≥1%)		Yes	(Felbatol USPI, 2012)

AED	Aggression-related AEs (and incidence)	Other related text, warnings, or precautions	Epilepsy-specific?	Source
Gabapentin	**Hostility** (common: 1–10%) In children, **aggressive behaviour** is also common (1–10%)		Yes	(Neurontin SPC, 2013; Neurontin USPI, 2013)
Lacosamide	**Irritability** (common: 1–10%) **Aggression**, **agitation** (uncommon: 0.1–1%)		Yes	(Vimpat SPC, 2014; Vimpat USPI, 2014)
Lamotrigine	**Aggression**, **irritability** (common: 1%–10%)		No	(Lamictal SPC, 2014)
	Irritability (3%, *vs* 2% with placebo, adjunctive use) **Irritability** (2–5%, monotherapy)		Yes	(Lamictal USPI, 2014)
Levetiracetam	**Hostility/aggression**, **nervousness/irritability** (common: 1–10%) **Anger**, **agitation** (uncommon: 0.1–1%) Behavioural AEs were more common in children/adolescents than adults: **agitation** (3.4%); **aggression** (8.2%); **irritability** (11.7%, children aged <4 years)		Yes	(Vimpat SPC, 2014)(Keppra SPC, 2010)

AED	Aggression-related AEs (and incidence)	Other related text, warnings, or precautions	Epilepsy-specific?	Source
	Non-psychotic behavioural symptoms (LEV *vs* placebo): Adults (13.3 *vs* 6.2%) Paediatric (37.6 *vs* 18.6%)	Warnings and precautions: *"Behavioral abnormalities including psychotic symptoms, suicidal ideation, irritability, and aggressive 133ehaviour have been observed. Monitor patients for psychiatric signs and symptoms"*	Yes	(Keppra USPI, 2014)
Oxcarbazepine	**Agitation** (1–2%, *vs* 1% placebo)		Yes	(Trileptal SPC, 2013; Trileptal USPI, 2014)
Perampanel	Adjunctive perampanel, occurrence in epilepsy clinical trials: **Aggression**, **anger**, **irritability** (common: 1–10%)	*"Aggressive and hostile behaviour has been reported in patients receiving perampanel therapy. In perampanel-treated patients in clinical trials, aggression, anger and irritability were reported more frequently at higher doses. Most of the reported events were either mild or moderate and patients recovered either spontaneously or with dose adjustment. However, thoughts of harming others, physical assault or threatening behaviour were observed in some patients (< 1% in perampanel clinical studies)."*	Yes	(Fycompa SPC, 2015)

AED	Aggression-related AEs (and incidence)	Other related text, warnings, or precautions	Epilepsy-specific?	Source
	Adjunctive perampanel, occurrence with 12 mg *vs* placebo in epilepsy clinical trials: **Irritability**: 12% *vs* 3% **Aggression**: 3% *vs* 1% **Anger**: 3% *vs* <1% Total incidence of **hostility- and aggression-related adverse reactions**: 20% with 12 mg; 12% with 8 mg; 6% with placebo	*"Serious or life-threatening psychiatric and 134ehaviour134l adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA. These reactions occurred in patients with and without prior psychiatric history, prior aggressive behaviour, or concomitant use of medications associated with hostility and aggression"*	Yes	(Fycompa USPI, 2014)
Phenobarbital	AE rates are not given. The listing of undesirable effects includes: *"paradoxical reaction (unusual excitement)"* *"behavioural disturbances in children"*		Yes	(Phenobarbital SPC, 2013)
Phenytoin	No mention of aggression-related behaviour in the SPC or USPI			
Pregabalin	**Irritability** (common: 1–10%) **Agitation**, **aggression**, **hostility** (uncommon: 0.1–1%)		No	(Lyrica SPC, 2015)(Lyrica USPI, 2014)

AED	Aggression-related AEs (and incidence)	Other related text, warnings, or precautions	Epilepsy-specific?	Source
Retigabine	Aggression-related behaviours reported only in overdose		Yes	(Potiga USPI, 2013; Trobalt SPC, 2014)
Rufinamide	No aggression-related behaviours or adverse reactions are listed in the SPC		Yes	(Inovelon SPC, 2013)
	Aggression (3%, *vs* 2% with placebo)		Yes	(Banzel USPI, 2015)
Stiripentol	**Aggressiveness**, **irritability** (common: 1–10%)		Yes (children)	(Diacomit SPC, 2014)
Tiagabine	**Hostility** (2–5% *vs* 1–2% with placebo) **Agitation** (1% *vs* 0%)		Yes	(Gabitril USPI, 2010; Gabitril SPC, 2014)
Topiramate	**Irritability** (>5%) **Aggression**, **agitation**, **anger**, **abnormal behaviour, irritability** (common: 1–10%)	**Aggression** was more common in children than in adults	Mostly*	(Topamax SPC, 2013)

AED	Aggression-related AEs (and incidence)	Other related text, warnings, or precautions	Epilepsy-specific?	Source
	Aggression, **agitation** (3%, *vs* 2% with placebo, clinical study in adults) **Aggression** (2% *vs* 0% with placebo, clinical study in adults) **Aggression** (9%*vs* 4%, paediatric trials)		Yes (individual epilepsy clinical trial data)	(Topamax USPI, 2014)
Valproic acid	**Aggression**, **agitation** (common: 1–10%), predominantly in children		Yes	(Epilim SPC, 2013)
	No terms of interest are listed in the epilepsy clinical study tables in the USPI. **Aggression**, **hostility**, and **irritability** are listed as adverse reactions reported in post-marketing experience (no incidence given)		Yes	(Depakene USPI, 2015)

AED	Aggression-related AEs (and incidence)	Other related text, warnings, or precautions	Epilepsy-specific?	Source
Vigabatrin	*Paediatric:* **Agitation** (very common: ≥10%) *Adults:* **Aggression**, **agitation**, and **irritability** (common: 1–10%)	"Vigabatrin should be used with caution in patients with a history of psychosis, depression or behavioural problems. Psychiatric events (e.g., **agitation**, depression, abnormal thinking, paranoid reactions) have been reported during vigabatrin treatment. These events occurred in patients with and without a psychiatric history, and were usually reversible when vigabatrin doses were reduced or gradually discontinued."	Yes	(Sabril SPC, 2014)
	Adults: **Irritability** (23% with 6000 mg *vs* 7% with placebo) *Adolescents:* **Aggression** (5% *vs* 0% with placebo) *Infantile spasm:* **Irritability** (16–23%)		Yes	(Sabril USPI, 2013)
Zonisamide	*Adjunctive use:* **Agitation**, **irritability** (very common: >10%) **Anger**, **aggression** (uncommon, 0.1–1%) *Monotherapy:* **Agitation** (common: 1–10%); **aggression** (uncommon)		Yes	(Zonegran SPC, 2014)
	Adjunctive use: **Agitation/irritability** (9% *vs* 4% with placebo)		Yes	(Zonegran USPI, 2014)

AED	Aggression-related AEs (and incidence)	Other related text, warnings, or precautions	Epilepsy-specific?	Source
**Predominantly epilepsy studies, but a minority of studies in migraine prophylaxis*				

Figure legends

Figure 1. Schematic representation of brain targets common to the neurobiology and pharmacology of epilepsy and aggression.

All of the targets illustrated in the figure are described in the main text. (A) Example of a prototypical excitatory (glutamate)/inhibitory (GABA) synapse modulating the activity of a forebrain postsynaptic neuron. Postsynaptic targets include glutamate (NMDA, AMPA and kainite receptors) and $GABA_A$ receptors. SV2A is a membrane glycoprotein that regulates neurotransmitter release from secretory vesicles. Voltage-gated K^+, Na^+, Ca^{2+} channels modulate the action potential and resting membrane potential thus controlling neuronal firing activity. GABA transaminase catabolizes GABA into succinic semialdehyde.

(B) Schematic representation of synaptic interactions between serotonin, norepinephrine, and dopamine neurons with their projections to the forebrain postsynaptic neurons. On the presynaptic level, the autoreceptors mediating the inhibitory action of these three neurotransmitters are indicated. Notably, autoreceptors are targets for aggression treatment. The α_2-adrenoceptor agonist clonidine is used to manage aggression; the D_2 autoreceptor antagonist haloperidol is an antipsychotic with anti-aggressive properties, and the 5-HT_{1A} autoreceptor agonist eltoprazine has demonstrated potent antiaggressive properties in preclinical studies. The enzyme monoamine oxidase (MAO), which catabolizes the monoamines dopamine, norepinephrine, and serotonin, is located on the outer membrane of mitochondria, and MAO inhibitors are widely used in mood disorders. On the postsynaptic level, the monoaminergic receptor subtypes implicated in the pathophysiology and pharmacology of epilepsy and aggression are indicated.

C) A schematic simplification of the Akt/GSK3 and mTOR signaling pathways is shown; these pathways are regulated by G-protein-coupled receptors, which may be involved in the neurobiology and in the treatment of both aggression and seizures. Furthermore, processes in the nucleus have also been implicated in aggression and epilepsy: DNA transcription, and epigenetic modifications of DNA such as methylation (Me) of the C-5 position of the cytosine ring, and histone modification (deacetylation of histones by histone deacetylases [HDAC]).

Figure 2. Brain regions that are important in both epilepsy and aggression

Schematic rendering of brain regions and nuclei involved in the neurobiology of both epilepsy and aggression. The role of each highlighted brain region/nuclei in epilepsy and aggression is discussed in the main text.