

## Seizures exacerbated by antiepileptic drugs in children

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### Abstract

There is growing evidence that antiepileptic drugs used in children that are meant to control seizures can actually cause seizure exacerbate instead. To minimize this problem, clinicians should be familiar with the epilepsy syndromes and the appropriate choice of antiepileptic drugs, avoid certain antiepileptic drugs which consistently aggravate specific seizure types and maintain a high index of suspicion of those at high risk as seizure exacerbation can present in diverse forms.

All physicians treat patients on the basis of “first do no harm”. Antiepileptic drugs (AED) are prescribed for children with epilepsy to control their seizures and hopefully improve their quality of life. Hence, complaints that the medication prescribed is making the child worse instead of better is often met with disbelief and distress.

Clinicians should be aware that AEDs used in children can cause seizure exacerbation. Many reports are anecdotal; there are a few case series but no population studies, hence there are no accurate estimates of this phenomenon. This is confounded by the possibility of an underlying progressive neurodegenerative disorder, spontaneous fluctuation of the epilepsy disorder itself or change in comedication. The highest level of proof that the AED is responsible for seizure exacerbation is to reintroduce the AED, but the family is often unwilling to do so.

There is thus a need to standardise criteria for reporting these events as in other adverse drug reaction reporting. At least one of the following criteria must be present<sup>1</sup>:-

- i) A clear cut increase in seizure frequency associated with administration of the AED and reversible on discontinuation/reduction of dose
- ii) A consistent adverse effect of specific AED in a specific seizure type or syndrome
- iii) Identification of any other factor (eg EEG features) that would be predictive of AED induced seizure deterioration
- iv) Appearance of new seizure type showing a clear cut temporal association with a change

The types of seizure aggravation include worsening severity or frequency of existing seizures, emergence of new seizure types and precipitation of status epilepticus, often of the non convulsive type. There are four clinical situations in which AED induced seizure exacerbation can occur<sup>2</sup>: (i) Drug toxicity; (ii) Drug induced encephalopathy; (iii) Inappropriate choice of AED; and (iv) True paradoxical effect.

In drug toxicity, the mechanism could be a non specific manifestation of drug toxicity (sedation or sleep disturbances) or true proconvulsant effect at toxic doses. This is mainly seen in children with malignant epilepsy syndromes already on polytherapy. There are often associated adverse events (sedation, irritability, sleep disturbances) and it is more likely to occur with sedative AEDs like benzodiazepines and phenobarbitone. Phenytoin (with its non linear pharmacokinetics) and carbamazepine (due to its 10,11 epoxide metabolite) can have true proconvulsant effect at toxic levels. Lamotrigine in high doses can cause myoclonic status.<sup>3</sup> Tiagabine at high doses is associated with non-convulsive status epilepticus in focal epilepsies and absence status in idiopathic generalized epilepsy.<sup>4</sup>

The most common example of a drug induced encephalopathy is valproic acid.<sup>5</sup> In this situation, seizures are part of the encephalopathy occurring at non toxic levels. Hyperammonemia with or without liver dysfunction has been reported. The encephalopathy can occur with valproic acid alone or during comedication with phenobarbitone, benzodiazepine, or topiramate. Carbamazepine and vigabatrin have also been implicated in AED induced encephalopathy.

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There is a growing body of evidence that some AEDs used in certain seizure types or epilepsy syndromes can actually exacerbate seizures; i.e. the inappropriate choice of AED. Carbamazepine used in idiopathic generalised epilepsies and myoclonic epilepsies can aggravate existing seizure types or induce new seizure types (absence status, atonic, myoclonic, generalized tonic clonic seizures), often associated with more severe generalised paroxysmal discharges on EEG.<sup>6</sup> Oxcarbazepine has similar effects. Other examples include lamotrigine in severe myoclonic epilepsy in infancy (SMEI), vigabatrin in myoclonic and partial epilepsies, gabapentin in absence and myoclonic seizures.

If seizure exacerbation occurs when the AED is usually effective or is the appropriate choice, then it is a true paradoxical reaction. Carbamazepine is the AED of choice for partial epilepsies; yet in some partial epilepsies (Frontal lobe epilepsy, benign childhood epilepsy with centrotemporal spikes, Landau –Kleffner syndrome, benign epilepsy of childhood with occipital paroxysms, Angelman syndrome), its use is associated with the appearance of new seizure types like negative myoclonus and atypical absences. Intravenous benzodiazepines have been reported to precipitate tonic status epilepticus in Lennox-Gastaut syndrome.

The pathophysiology is unclear. Clinically, AEDs with multiple mechanisms of action seem less likely to cause seizure exacerbation than AEDs with single mechanism of action and narrower spectrum of action. Epilepsy syndromes with multiple seizure types (usually young children, high seizure load, epileptic encephalopathy, polytherapy) are at higher risk, although some benign syndromes can be affected.

Several mechanisms have been postulated.<sup>1</sup> Firstly, the increased GABA transmission resulting in hyperpolarisation of thalamic neurons accentuate prolonged spike wave discharges in vigabatrin, tiagabine and gabapentin. Secondly, the secondary loss of efficacy due to tolerance with upregulation of receptor sensitivity and density in benzodiazepines. Thirdly, in sodium dependent channels, enhanced neuronal activity within thalamocortical circuits responsible for slow spike wave activity in carbamazepine, oxcarbazepine, phenytoin and lamotrigine. Lastly, pharmacogenomics may be the reason why some children are vulnerable to AED seizure exacerbation while others are not.

Clinicians can minimize the problem by the following measures.<sup>8</sup> Firstly clinicians should

delineate the syndrome diagnosis as soon as possible and be aware of the clinical and EEG pitfalls. For example, in juvenile myoclonic epilepsy, long or atypical absence may sometimes be mistaken for partial seizures. The epileptiform discharges of benign childhood epilepsy with centrotemporal spikes in sleep can be generalised, while focal elements in childhood absence epilepsy and Juvenile myoclonic epilepsy can result in misinterpretation. Secondly, clinicians should avoid starting certain AEDs in specific epilepsy syndromes, especially in idiopathic generalised epilepsies.

If seizures occur despite prescribing the appropriate AED, clinicians should reassess diagnosis and exclude pseudoseizures or other paroxysmal non epileptiform phenomenon. Other causes should be excluded, such as overdose, withdrawal of comedication, compliance issues, and metabolic or encephalopathic complications. Possible culprit AED should be withdrawn, rapid if recently introduced, gradual if longstanding AED with partial effect especially benzodiazepines. If paradoxical effect is suspected, should challenge under close clinical and EEG supervision.

In conclusion, it is important to remember that the AED treatment can cause seizure exacerbation. To minimise this problem, clinicians should be familiar with the epilepsy syndromes and the appropriate choice of AED, avoid certain AEDs which consistently aggravate specific seizure types and maintain a high index of suspicion in those at high risk of AED-induced seizures.

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