New epilepsy therapies for the 21st century – From antiseizure drugs to prevention, modification and cure of epilepsy, Special issue, Neuropharmacology

Why we urgently need improved seizure and epilepsy therapies for children and neonates

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Highlights

- Treatment of early onset seizures and epilepsies pose a clinical challenge to clinicians.
- Only very few drugs have been licenced due to lack of randomised controlled trials.
- Systematic reviews no good evidence for the choice of treatment.
- Precision medicine is so far only available for a small number of syndromes.

Abstract

In contrast to epilepsy in adolescents and adults, neonatal seizures and early onset epilepsy poses unique challenges with significant repercussion for treatment choices. Most importantly, high seizure burden and epileptic encephalopathy are associated with developmental, behavioural and cognitive problems. The causes are multifactorial and include etiology, seizure burden, epileptic encephalopathy, but also antiseizure medication. In contrast to adults and older children only very few drugs have been licenced for infants and neonates, and after a long delay. Very recently, extrapolation of adult data has become possible as a path to speed up drug development for younger children but this is not necessarily possible for infants and neonates. With the advances in understanding the molecular basis of many epilepsies, targeted therapies become available, for example for KCNQ2 mutation related epilepsies, Dravet syndrome or tuberous sclerosis complex. Drug trials in neonates are particularly challenging because of their inconspicuous clinical presentation, the need for continuous EEG monitoring, high co-morbidity, and poor response to antiepileptic drugs.

There is an urgent need for development of new drugs, evaluation of safety and efficacy of current antiseizure drugs, as well as for national policies and guidelines for the management of seizures and epilepsy in neonates and infants.

Effects of early onset epilepsy

In contrast to epilepsy in adolescents and adults, epilepsy in infants and young children poses unique challenges with significant repercussion for treatment choices. Most importantly, early onset epilepsy below the age of 1 year is a significant risk for developmental, behavioural and cognitive problems.

In this respect, adequate and aggressive treatment is warranted in order to try to stop the seizures as soon as possible. Waiting for 3 or 6 months to judge to efficacy of a treatment, as is often considered in adults, is not justifiable in an 8 month child, in his crucial phase of rapid developmental brain changes. There is also the ill-understood progression towards an "epileptic encephalopathy" in some infants and young children with epilepsy: Regardless of etiology, some children first present with seizures; at some point during the follow up become refractory and then move into a phase of severe and non-reversible encephalopathy with very little cognitive progression, stagnation or even regression. The problem remains that this evolution and especially this point-of-no-return cannot be predicted in an individual child. This common pathway into epileptic encephalopathy typically is associated with frequent generalized seizures (typically tonic, myoclonic or atonic) and with a-specific changes on the EEG, such as slow-spike and wave complexes (Auvin et al., 2016). The end phase of this negative evolution actually is the so called Lennox-Gastaut syndrome. A well-known example is the clinical observation that about one third of infants presenting with epileptic spasms (West syndrome) shows this evolution towards Lennox-Gastaut syndrome (Asadi-Pooya, 2018).

In addition to etiology and frequent early onset seizures, treatment itself, and especially some anti-seizure drugs (ASD) can be associated with negative side effects at the cognitive and behavioural level. Fortunately, the newer anti-epileptic drugs overall have a better tolerability profile and have less cognitive and behavioural sides effects. It is now well understood by the pharma industry that studying new ASDs in children should include a thorough assessment of cognitive and behavioural safety (Moavero et al., 2017, Lagae, 2017). It should also be mentioned that for some early onset epilepsies epilepsy surgery or ketogenic diet is the optimal treatment option. For instance, in severe structural hemispheric epilepsy syndromes (such hemimegalencephaly), surgery should be considered very early. In some metabolic diseases with epilepsy, ketogenic diet should not be postponed and is indeed first line treatment. The most common example is the Glut1 transporter disease, which can be treated best with the ketogenic diet. The latter example actually is a very good example of precision medicine (see below).

New treatment discoveries

With regards to ASDs, the typical scenario is that a drug with anti-seizure properties is discovered, sometimes accidently, as the result of high throughput screening, or more dedicated screening. The drug is then tested in adults with focal onset epilepsy, mainly because this is the most frequent seizure type in adults. The regulatory trials are thus focusing on seizure type rather than on etiology and are done in adults in a first phase. If successful, studies in adolescents and younger children are set up. It is clear that this is not an optimal strategy and that years go by before newer drugs can be used in children and infants. Very recently, extrapolation of adult data (but only for focal epilepsy), has become possible, so that no extra efficacy studies for children down to 4 years have to be done. Only safety and pharmacokinetic studies are required (Arzimanoglou et al., 2018, Arzimanoglou et al., 2019). But extrapolation will not give earlier access to ASDs in generalized epilepsies and so far, children below the age of 4 are excluded from extrapolation. Newer study designs for young children and infants are being proposed (for instance 'time to N seizures' designs), with the aim to reduce long placebo exposure and to make the study shorter. Only recently suggestions for trial designs have been published for infants (Auvin et al., in press). This will eventually lead to earlier access to the newer ASDs.

In rare cases, drugs are first tested in children for specific indications, before they are considered for adults. For instance rufinamide was first tested in children with Lenox Gastaut syndrome (Striano et al., 2018). A very recent example are the studies with cannabidiol in Dravet syndrome and Lennox Gastaut syndrome (Devinsky et al., 2017, Devinsky et al., 2018). Here, the public opinion in a way forced the pharma industry to test cannabinoids in these severe childhood epilepsy syndromes. It is surprising to see that only 5 years were needed for cannabidiol to become FDA and EMA approved, after the first retrospective reports on the possible beneficial effects of cannabis derivates.

Considerations for neonatal seizures

Seizures are the most common neurological emergency in newborn babies, arising in around 2-3 per 1000 term live births and are more common in preterm infants (Ronen et al., 1999; Lloyd et al., 2017). The majority of neonatal seizures are acute symptomatic and are caused by perinatal brain injuries (hypoxic-ischaemic encephalopathy (HIE) and perinatal arterial ischaemic stroke in term infants and intracranial infection (Glass et al., 2016, McCoy and Hahn, 2013). In contrast, 10-15% of newborns with seizures have neonatal-onset epilepsy syndromes, mostly due to genetic disorders,

inborn errors of metabolism or congenital cortical malformations (McTague et al., 2016; Shellhaas et al., 2017, Axeen et al., 2018). Most of these are epilepsy syndromes which are difficult to treat with a poor prognosis and require a different approach to management (Cornet et al., 2018). It can be difficult or impossible to identify this group early although clinical presentation (Nunes et al., 2019), EEG findings (Vilan et al., 2017), neuroimaging can give early indications towards the aetiology of seizures and consequently prognosis. Recent advances in genetic testing, particularly the development of rapid whole-genome sequencing the can provide with a definitive genetic diagnosis (French et al., 2019) which may initiate targeted treatment as discussed above.

Challenges in the diagnosis and management of neonatal seizures

Clinical diagnosis of seizures is difficult and often impossible without EEG. Up to 70% of all neonatal seizures are electrographic-only (subclinical) depending on aetiology, co-morbidity and medication (Nash et al., 2011, Murray et al., 2008, Mizrahi, 1987). Electrographic seizures are particularly common in critically-ill neonates, HIE, and preterm infants. Treatment with antiseizure drugs such as phenobarbital or phenytoin can further increase the proportion of electrographic-only seizure due to uncoupling (Boylan et al., 2002, Scher et al., 2003).

Even if seizures have a clinical correlate, the ability of healthcare professionals to correctly identify clinical seizures is poor owing to discreet clinical manifestations similar to non-seizure behaviour (Malone et al., 2009). Continuous video EEG (cEGG) is therefore considered gold standard in the diagnosis of neonatal seizures (Palegrin et al, in press, Shellhaas et al., 2011, Soul et al., 2019). However, EEG monitoring is a sparse resource due to high costs of specialized equipment and staff as well as need for specialised expertise. Even in high income counties EEG monitoring is often not available or only during working hours. While amplitude integrated EEG (aEEG) with single or two-channel EEG recording is more readily available, it has limitations in the reliable and accurate detection of seizures. As well as being subject to misinterpretation, some seizures will not be detected, in particular very focal, short or low amplitude seizure. A recent systematic review (Rakshasbhuvankar et al., 2015) showed that aEEG has a relatively low and variable sensitivity and specificity suggesting that, based on the available evidence, aEEG value has limited usefulness for diagnosis of neonatal seizures, particularly as outcome measure for clinical trials. In clinical practice, aEEG has the advantage of being more widely accessible with acceptable seizure detection rate. A recent observational study of neonatal seizures in 6 European centres suggested that even with access to continuous EEG monitoring, neonatal seizures are difficult to diagnose in a timely manner and treatment is often delayed (Rennie et al., 2018). Another study suggested that in a setting of a

neuro-critical care program, continuous EEG monitoring improved seizure detection and timely treatment which was in turn associated with an overall decreased use of antiseizure medication (Bashir et al., 2016). This is in keeping with findings of a study looking at the benefits of standardised and timely treatment of neonatal seizures n which adherence with protocol was associated with fewer patients progressed from seizures to status epilepticus, reduced phenobarbital concentrations and shorter length of hospital stay (Harris et al., 2016). These studies suggest that neonatal seizures become more difficult to treat the longer they last.

Neonatal seizures are associated with adverse effects on cognitive and behavioural outcome, with up to 50% infants with seizures in the neonatal period exhibiting significant sequelae (Pinchefsky and Hahn 2017; Kharoshankaya et al., 2016b; Massey, Jensen, and Abend 2018). The causers for this is multifactorial (figure 1) and include aetiology (Pisani and Spagnoli 2015), and seizure burden (Kharoshankaya et al., 2016a; Payne et al., 2014). Although debated in the past, there is now mounting evidence that both electro-clinical and electrographic-only seizure are associated with adverse outcomes (Srinivasakumar et al., 2015; van Rooij et al., 2010; Miller et al., 2002). In addition there is increasing concern that antiseizure medication can have long-term effects on neuro-development. Animal studies suggest that even short term administration of many anti-seizure drugs can increase apoptosis of immature neurons (Bittigau, Sifringer, and Ikonomidou 2003; Kaindl et al., 2006; Kim et al., 2007). In addition, fatal exposure to several antiepileptic can impair cell proliferation and inhibit neurogenesis in the immature brain (Yanai et al., 1989; Stefovska et al., 2008). In humans, off-springs of mothers exposed to antiseizure drugs (in particular sodium valproate) are at increased risk of neurodevelopmental deficits and behavioural disorders (Kellogg and Meador 2017).

Evidence base of current neonatal seizure treatment

For several decades phenobarbital is the first-line antiseizure drug for neonatal seizures as shown by a number of national and international surveys (Glass, Shellhaas, et al., 2016; Vento et al., 2010; Bartha et al., 2007). This is in contrast to older children and adults where phenobarbital is rarely used because of adverse effects. There is little consensus among clinicians and experts regarding second-line treatment for neonatal seizures (Table 1) with considerable variability between countries and centres. So far three systematic reviews evaluated the evidence of antiseizure drugs from clinical trials in neonates (WHO 2011; Booth and Evans 2004; Slaughter, Patel, and Slaughter 2013), in addition to one systematic review on the pharmacokinetics of second line antiepileptic drugs in neonates (Tulloch, Carr, and Ensom 2012). The Cochrane review of 2004 (Booth and Evans 2004) only identified 2 randomised controlled trials meeting methodological quality criteria: 1.

(Painter et al., 1999) studied the efficacy of phenobarbital versus phenytoin as first line drug showing that both controlling seizures in less than 50% of neonates. 2. (Boylan et al., 2004) evaluated efficacy of 2nd line treatment (lidocaine, midazolam and clonazepam) in neonates not responding to phenobarbital numbers of included babies were too small for statistical analysis. Overall the authors concluded that there was little evidence to support the use of any antiseizure drugs in the neonatal period. The guidelines published by the World Health Organisation (WHO 2011) formulated guidelines on the basis of the quality of evidence, taking into account feasibility, benefit and harm, as well as preferences of policy makers, health care providers and parents. Due to lack of evidence, most of the final recommendations were based on expert consensus and only one recommendation about ASDs was regarded as strong (phenobarbital as first line drug) but based on very low quality of evidence. Furthermore, the choice of second-line ASDs in the neonatal period was found to be highly empiric. Similarly, in the most recent systematic review by Slaughter in 2013 (Slaughter, Patel, and Slaughter 2013) 16 studies were identified meeting inclusion criteria but only two were randomized trials (same as mentioned in the 2 previous systematic reviews) and a further three studies had comparison groups but either were retrospective (Castro Conde et al., 2005; Shany, Benzaqen, and Watemberg 2007) and/or used only aEEG (Shany, Benzaqen, and Watemberg 2007; Hellstrom-Westas et al., 1988). The only systematic review concentrating on second line drugs is on pharmacokinetics (Tulloch, Carr, and Ensom 2012). They found only limited pharmacokinetic data for the use of carbamazepine, lidocaine, paraldehyde, topiramate, valproic acid, and vigabatrin for neonates with seizures refractory to treatment with first-line antiepileptic agents. All of these reviews emphasize the lack of evidence for any drugs in the management of neonatal seizures, old or new.

Consequently, there is high frequency of off-label drug therapy in neonates despite a lack of information about their safety or efficacy in this population (Silverstein and Ferriero, 2008). As these have not been tested in clinical trials for the indications, drug formulation and excipients doses, routs of administration, safety or efficacy, this poses a significant risk to a vulnerable patient group which are more likely than adults to experience adverse reactions (Turner et al., 2014).
Examples are the premature use of bumetanide (Pressler et al., 2015; Vanhatalo et al., 2009; Kharod et al., 2019) or topiramate (Kundak et al., 2012; Filippi et al., 2017; Courchia et al., 2018) in the treatment of neonatal seizures.
More recently levetiracetam has been recognised as a promising drug for the treatment of neonatal seizures. Levetiracetam has a favourable pharmacokinetic profile with a wide therapeutic range and few adverse events reported in paediatric population (Egunsola et al., 2016). A number of retrospective (for example (Abend et al, 2011; Neininger et al., 2015; Rao et al., 2018) and open

perspective studies (for example (Falsaperla et al., 2017, Gowda et al., 2019, Ramantani et al., 2011, Sedighi et al., 2016) have indicated that levetiracetam may be as effective or even be superior than phenobarbital for the treatment of seizures in the neonatal period. However, the majority of these studies did not use EEG as an outcome measures, tested a variety of different doses (ranging from 5-80mg/kg for the loading dose and 5-100mg/kg for maintenance) and did not control for poly-therapy. Overall efficacy ranged from 30 to 86% in uncontrolled studies (Loiacono et al., 2016, McHugh et al., 2018). There are in fact three current randomized controlled trials comparing efficacy of levetiracetam with phenobarbital as first line medication (NCT03107507 NCT02550028, NCT01720667) but only one using continuous EEG monitoring to evaluate seizure burden (NCT01720667). This study has been completed but results have not yet been published in a peer reviewed journal. As presented at the American Epilepsy Society Meeting, in New Orleans 3rd Dec 2018 results of this trial may not support findings of the retrospective or open trial.
The lack of ASD development for newborn infants is in vast contrast to adults, in whom around 20 new drugs have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in the past 3 decades. This compares to less than a handful of approvals for children less than 2 years of age and none for newborn infants.

The reasons for this are the ethical and logistical challenges of performing drug trials for neonatal seizures. It is no doubt difficult to balance the potential risks and benefits of research against harm from inadequately studied treatments and the risk of withholding potentially effective treatments for lack of evidence. Due to differences in age dependent mechanisms of neurotransmission explaining a higher predisposition to seizures (Katsarou et al., 2018) but also why drugs developed for adults may not be as effective (Hernan and Holmes, 2016). Logistic difficulties include definition of a valid EEG outcome measure, timing of evaluation, challenges in repeated blood sampling, recruitment problems, consent issues and many more (Soul et al., 2019), all of which making these drug trials time consuming and expensive to perform. In particular the need for EEG monitoring hampers the setting up of clinical trials as there is a lack of EEG expertise in many neonatal centres. Although aEEG is sufficient for clinical management, experts agree that its diagnostic accuracy is not sufficient for clinical trials that aim to prove efficacy (Soul et al., 2019; Stevenson et al., 2016).

Precision medicine

Overall, however, these traditional approaches in drug development will still render only 70 % of the patients seizure free, and most likely this number in infants and young children is even lower. Newer treatment options therefore should be explored. The discovery of genetic variations/mutations as the

cause of epilepsy in many young children with epilepsy is a doorway to precision treatment (Ellis et al. 2019, Sisodiya et al., 2019, Orsini et al., 2019, Kearney et al., 2019, Fitzgerald et al., 2019, Truty et al., 2019, Milh et al., 2016). With the advances in understanding the molecular basis of many epilepsies, targeted therapies become available, in contrast with the broad-spectrum non-specific efficacy of most existing drugs. The hope is that this will lead to better and especially earlier efficacy. One prerequisite of course is that the genetic diagnosis should be made as early as possible. This is still the bottleneck in many centers. Although it is early enough realized that genetic studies should be done, it takes sometimes several months before the results become available.

A game changer in this respect is the treatment of (rather frequent) potassium channel epilepsies in neonatal and infant epilepsies. It was shown in an early case series that sodium channel blockers such as carbamazepine are very effective in KCNQ2 mutation related epilepsies (Pisano et al., 2015). Five years ago, sodium channel blockers were barely used in neonates and young children, but nowadays it has become first or second line therapy in non-structural early onset epilepsies, while waiting for the genetic results to become available. Clinical presentation, normal neuroimaging and a typical aEEG pattern (Vilan et al., 2017) can point towards KCNQ2 encephalopathy and thus influence treatment choice. In clinical practice we do see a considerable number of KCNQ2 infants becoming seizure free and not progressing to an epileptic encephalopathy. An even more compelling example are the mTOR inhibitors (such as everolimus) in the treatment of tuberous sclerosis complex. In tuberous sclerosis, the loss of inhibition of the mTOR pathway can be restored by administration of these mTOR inhibitors. In theory, this specific treatment should be effective for all symptoms of tuberous sclerosis complex (TSC), such as skin problems, renal cysts, brain tumours and also epilepsy. While different studies did show a dramatic effect on tumour growth, the effect on epilepsy was in the line with the efficacy of other ASDs used in TSC: about 50% of the patients show a 60% reduction of seizures, with very few becoming seizure free (French et al., 2016). Most likely, this can be explained by a too late treatment start. Epileptogenesis in TSC is already going on from conception and dysfunctional brain connectivity is already established at the start of the epilepsy. As the regulatory study only started at the age of 2 years, one might have missed the optimal time window to get much better results.

As we know that about 80 % of all TSC children will develop epilepsy before the age of 2 years and that many of these children will develop infantile spasms and West syndrome with a devastating effect on cognition and behaviour, we need to consider an even more radical approach: preventive treatment. This refers to anti-epileptic treatment before the start of clinical seizures. The aim is straightforward: by interfering early on, it is hoped that clinical epilepsy will not start or will occur later with less risk for age dependent West syndrome and that the developmental outcome therefore would be better. There is one small pivotal trial published showing that this might indeed be a future

treatment option in TSC (Jozwiak et al., 2011). The advantage in TSC is that neonatal or even prenatal diagnosis is possible so that follow up can be started early. In the published trial, an EEG was done every 4 weeks with the assumption that occurrence of epileptic EEG activity is a hallmark of ongoing epileptogenesis. Whenever multifocal spikes were seen during follow up, preventive treatment with vigabatrin was started in a subgroup of the patients. At the age of 2 years, the outcome in this subgroup was significantly better than in the control group which was treated in the standard way (only ASDs when clinical seizures occurred): significantly less refractory epilepsy, less intellectual disability and less autism. These results were promising enough to start a multicentre randomized controlled trial (EPISTOP) and the first results confirm that preventive treatment is beneficial in TSC (Moavero et al., 2019). This rather extreme treatment option illustrates again that early intervention is key to better outcome. Preventive treatment can also become a treatment option in other conditions with a high prevalence of early onset epilepsy and a high risk for developmental problems. Examples are Sturge-Weber syndrome and hypoxic ischemic encephalopathy in neonates Therapeutic hypothermia which is now standard of care for hypoxic ischemic encephalopathy, reduces the total seizure burden in the acute stage (Low et al., 2012), but decreases possibly also the risk for subsequent epilepsy (Liu et al., 2017, Pisani et al., 2015).

Another route to more precision medicine is the use of repurposed drugs for specific indications. A recent example is the use of fenfluramine in Dravet syndrome. Fenfluramine was used as an anti-obesity drug and works through increased serotonin availability. Case reports suggested that fenfluramine could also be used in obsessive compulsive behaviour associated with photosensitive seizures. Careful study of the patients who responded best to fenfluramine showed that these were patients with Dravet syndrome. Larger and placebo controlled studies confirmed that low dose fenfluramine is indeed effective in Dravet syndrome with an efficacy which is much higher than seen with the usual standard drugs for Dravet syndrome (Ceulemans et al., 2012; Schoonjans et al., 2017). It is hypothesized that fenfluramine, by increasing serotonin, has a positive effect on the dysfunctional GABA interneurons in Dravet syndrome. In a high throughput study in a zebrafish model of Dravet syndrome these finding were confirmed and other potential drugs for Dravet syndrome were discovered involving other brain pathways. One of the future candidates is clemizole, known as an antihistaminergic drug but also involved in serotonin metabolism (Griffin et al., 2017). Since Dravet syndrome is a genetic condition with a mutation in the SCN1A gene in the large majority of patients, there is also realistic hope the genetic treatment can be developed to treat this devastating epilepsy syndrome. Different options are being explored, such as upregulation of the normal allele (hoping for more functional protein) or adenovector mediated gene delivery systems and other genetic interference techniques as currently successfully used in neuromuscular diseases (Keeling et al., 2014).

Again, the challenge will be to interfere as early as possible and not to wait until refractory epilepsy develops. A typical problem for this early genetic approach is that it is still difficult to predict the final phenotype from the actual SCN1A mutation. Some children with the same mutation only develop innocent febrile seizures while others develop Dravet syndrome.

Guidelines for drug development in neonatal seizures and early onset epilepsy

Despite all these challenges it is now recognised that research about the medicines used in newborn infants is an ethical requirement (Turner 2015). Even though there has recently been an increasing interest in neonatal seizures and their management with increasing studies and publications we still do not know which drugs we should use and for how long. In 2015, the FDA's Critical Path Institute launched the International Neonatal Consortium (INC), a global collaboration formed to forge a predictable regulatory path for evaluating the safety and effectiveness of therapies for neonates "by uniting stakeholders from research institutions, drug developers, regulatory agencies, patient advocacy and other organisations," with the ultimate aim to improve drug development for neonates (Turner et al., 2016). The INC neonatal seizure working group has just published recommendation for neonatal seizure treatment trials based on available literature and expert consensus, pharmacokinetic analyses, ethical considerations, and parental concerns (Soul et al., 2019). In 2009, the EMA's Committee for Medicinal Products for Human Use (CHMP), and the PASDiatric Committee (PDCO) published guidelines on the investigation of medicinal products in the term and preterm neonate' [Doc. Ref. EMEA/536810/2008], which addresses the considerations and requirements for the design and conduct of clinical trials in premature and term neonates using medicinal products of relevance for the use by this population. They are also currently updating their current guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98 Rev.3 2) which will include sections on drugs for children and for neonatal seizures.

Conclusion

The crucial point in treating neonatal seizures and early onset epilepsy is early and effective treatment. We definitely need more precision drugs which target directly the pathophysiology of the seizures and/or epilepsy. The classical anti-epileptic drug arsenal will not suffice for this goal. In addition, also an early and correct etiological diagnosis is necessary in order to be able to identify and start the most adequate treatment. Only this approach will lower the risk for the developmental problems seen in early onset refractory epilepsies and following neonatal seizures.

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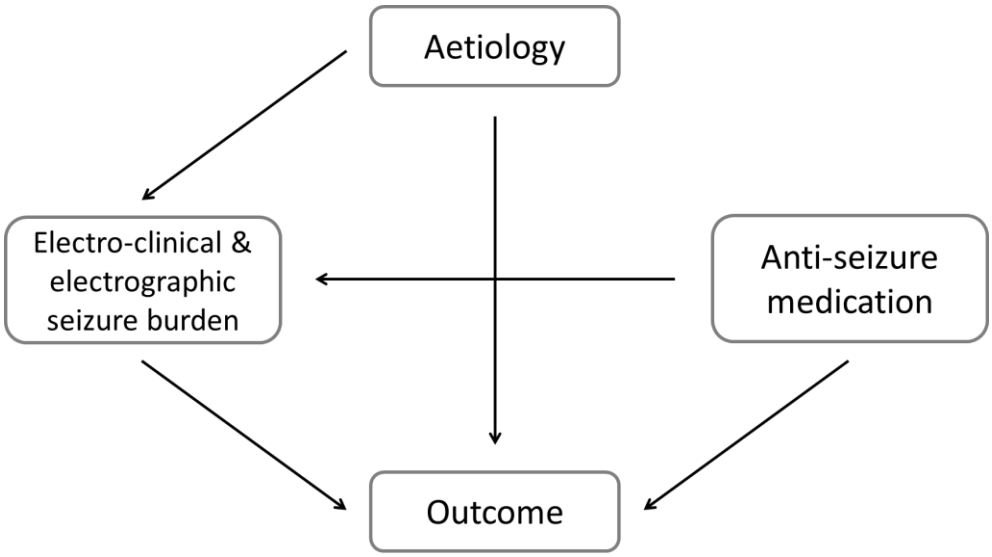
Table and figures

Table 1. Use of antiseizure drugs in neonatal period and evidence based (Booth and Evans 2004) (WHO 2011)

Drug	Randomised controlled trials with cEEG to evaluate outcome measure	Other prospective studies with cEEG to evaluate outcome measure	Use in neonates (WHO 2011)
Phenobarbital	As 1st line (Boylan et al., 2004); as 1st and 2nd line (Painter et al., 1999)	(Bye and Flanagan, 1995)	1st line "Standard of care“
Levetiracetam	None published but first RCT study indicating poor efficacy as 1st line (Sharpe, presented at AES 2018)	As 2nd or 3rd line but cEEG only in some neonates (Falsaperla et al., 2017) or no EEG in others (Gowda et al., 2019; Ramantani et al., 2011; Sedighi et al., 2016)	2nd or 3rd line Off-label
Phenytoin	As 1st line and 2nd (Painter et al., 1999)	As 2nd line (Bye and Flanagan, 1995)	2nd or 3rd line Off-label
Midazolam	As 2nd line but too few neonates to evaluate efficacy (Boylan et al., 2004)		2nd or 3rd line Off-label
Clonazepam	As 2nd line but too few neonates to evaluate efficacy (Boylan et al., 2004)	As 3rd line (Bye and Flanagan, 1995)	
Lidocaine	As 2nd line but too few neonates to evaluate efficacy (Boylan et al., 2004)	As 2nd or 3rd line but cEEG only in some neonates (Hellstrom-Westas et al., 1988)	2nd or 3rd line Off-label
Carbamazepine	None	None	
Topiramate*	None	None	No evidence for efficacy, safety concern
Bumetanide	None	As 2nd line (Pressler et al., 2015)	No evidence for efficacy, safety concern

Figure 1


Aetiology
Electro-clinical & electrographic seizure burden
Anti-seizure medication
Outcome