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Treatment issues for children with epilepsy transitioning to adult care

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ABSTRACT

This is the third of three papers that summarize the second symposium on Transition in Epilepsies held in Paris in June 2016. This paper focuses on treatment issues that arise during the course of childhood epilepsy and make the process of transition to adult care more complicated. Some AEDs used during childhood, such as stiripentol, vigabatrin, and cannabidiol, are unfamiliar to adult epilepsy specialists. In addition, new drugs are being developed for treatment of specific childhood onset epilepsy syndromes and have no indication yet for adults. The ketogenic diet may be effective during childhood but is difficult to continue in adult care. Regional adult epilepsy diet clinics could be helpful. Polytherapy is common for patients transitioning to adult care. Although these complex AED regimes are difficult, they are often possible to simplify. AEDs used in childhood may need to be reconsidered in adulthood. Rescue medications to stop prolonged seizures and clusters of seizures are in wide home use in children and can be continued in adulthood.

Adherence/compliance is notoriously difficult for adolescents, but there are simple clinical approaches that should be helpful. Mental health issues including depression and anxiety are not always diagnosed and treated in children and young adults even though effective treatments are available. Attention deficit hyperactivity disorder and aggressive behavior disorders may interfere with transition and successful adulthood but these can be treated. For the majority, the adult social outcome of children with epilepsy is unsatisfactory with few proven interventions.

The interface between pediatric and adult care for children with epilepsy is becoming increasingly complicated with a need for more comprehensive transition programs and adult epileptologists who are knowledgeable about special treatments that benefit this group of patients.

This is the third and final paper based on a symposium held in Paris in June 2016 about transition from pediatric to adult care for young people with epilepsy. The first paper [1] reviews the basic biological, sociological, and psychological issues that surround transition and the second paper [2] reviews the outcome of childhood onset epilepsy from adolescence to young adulthood with emphasis on transition issues for different epilepsy syndromes. This third paper summarizes issues that are important for successful transition related to drug and dietary therapy as well as psychiatric and psychosocial care.

1. Antiepileptic drugs used in pediatrics but rarely in adult medicine

Most antiepileptic drugs (AEDs) have been developed in adults with focal seizures and then transferred for use in children. This transfer is typically valid for focal seizures but has been disappointing for some specific epilepsy syndromes with onset in infancy and childhood. There is a lack of both efficacy and pharmacological data (pharmacokinetics, pharmacodynamics) for children, particularly infants. However,

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the methodology for introducing new AEDs is evolving with an occasional revolution when AEDs are first introduced for use in children. The following examples emphasize how a few drugs have been developed and registered for specific pediatric syndromes. Children receiving these AEDs will eventually transition to adult care at an age when there may not be much data about efficacy and pharmacokinetics.

Stiripentol is currently approved in many countries for children only, as adjunctive therapy with valproate and clobazam in Dravet syndrome. This AED was developed first for focal seizures and failed to show efficacy in phase 3 trials in adults. An exploratory open trial in pediatric pharmacoresistant epilepsies helped to identify Dravet syndrome as a potential target. Finally, a randomized double-blind trial of stiripentol in children with Dravet syndrome established its utility [3]. Presently, this AED is licensed in many countries as an orphan drug specifically for Dravet syndrome in children. Children with Dravet syndrome often enter adolescence and adulthood with stiripentol as part of their medication regime. Long-term studies show that efficacy is maintained up to late adolescence, but follow-up data in adulthood are still scarce [4,5]. It seems likely that adult patients with newly-diagnosed Dravet syndrome will also benefit from stiripentol, not only for seizures but also for cognitive enhancement [6]; however, the optimal dose and potential interactions with other AEDs and other classes of drugs remain to be determined in adults.

Vigabatrin was extensively used during the 1990s by adults with focal onset seizures, but its use has been markedly restricted due to retinal toxicity. Because this toxicity increases with the dose and duration of drug exposure, vigabatrin is currently a "third line" AED in adults with pharmacoresistant focal epilepsy. However, the specific efficacy of vigabatrin for infantile spasms, noted as early as 1990 [7], has meant that it continues to be the first-line treatment for infantile spasms, especially in patients with tuberous sclerosis complex due to a positive benefit-risk balance [8]. It is possible that vigabatrin-induced visual field defects occur more frequently in adults (36%) than in children (18%) [9] and infants (21%) [10]. The information in infants is based entirely on electroretinogram studies since visual field testing is not possible at this age.

Cannabidiol use in epilepsy is very recent. Several small open studies suggested that it might be useful for pharmacoresistant pediatric epilepsy and epileptic encephalopathies. An open-label study of 137 patients with Dravet syndrome, Lennox-Gastaut syndrome, and other drug-resistant epilepsies in childhood suggested that "motor" seizures decreased by a median of 37% (CI 0–65%) over 13 weeks of treatment [11]. Preliminary results from randomized placebo-controlled trials in Dravet syndrome and Lennox-Gastaut syndrome suggest efficacy in both conditions [12]. Cannabidiol has been shown to be of some value in the adult treatment of pain and multiple sclerosis; however, optimal dose and drug interaction profile need to be more extensively studied. A possible interaction with clobazam (increased serum levels) through CYP450 inhibition has been reported but requires further evaluation.

Other molecules to treat rare epilepsies are currently in phase 2 and phase 3 trials aiming to be registered as orphan drugs. As the pathophysiology of early-onset epilepsies is better understood, there will be encouragement to develop highly targeted therapies. It is likely that the first trials of these drugs will be in childhood. Therefore, in the future, youth with epilepsy transitioning from pediatric to adult care will increasingly be receiving AEDs that are not familiar to adult caregivers.

2. Antiepileptic drug treatment differences in children compared with adults

The etiology of epilepsy that begins in childhood may be very different than in adult epilepsy, which raises an important question for transition - do different AEDs have different effects in children than adults [13,14]? Most randomized clinical trials of AEDs include patients with a restricted age range (such as age 4–16, age 16–65 or >65 years), which makes it impossible to know relative drug effects at different ages. The famous SANAD (Standard And New Antiepileptic Drugs) study randomized 1721 newly-diagnosed patients including children over 4 years of age up to the elderly [15]. The AEDs studied were carbamazepine, gabapentin, lamotrigine, and oxcarbazepine. Children (<16 years of age) were more likely to experience treatment failure than adults, but also more likely to experience a 12-month remission. There were no differences in rates of response between AEDs in children and adults. On the basis of numerous trials in focal epilepsies of the same AED showing no difference in effect between adult and pediatric trials, the European Medicines Agency (EMA) concluded: "Focal epilepsies in children older than 4 years of age have a similar clinical expression to focal epilepsies in adolescents and adults. In refractory focal epilepsies … the results of efficacy trials performed in adults could to some extent be extrapolated to children provided the dose is established …" [16]. More recently Dr. Jack Pellock and colleagues, in collaboration with the University of Maryland, performed a PK-PD analysis as part of the FDA critical path initiative, to determine if the serum exposures necessary to control seizures in adults produced a similar degree of seizure reduction in children [17]. On the basis of this analysis, the FDA determined that results of adjunctive clinical trials in focal epilepsy in adults can be extrapolated to children 4 years and older. Most "specific" AED safety issues occur in children more than adults. These include increased rash from lamotrigine, increased liver toxicity from valproate, and probably increased behavioral issues from levetiracetam, topiramate, gabapentin, pregabalin, and others. These issues will have resolved or have been avoided by late adolescence and therefore are not of special concern in the context of transition.

In the USA, of eight new AEDs approved since 2004 (pregabalin, lacosamide, rufinamide, ezogabine, clobazam, perampanel, eslicarbazepine, brivaracetam) only two have pediatric indications (clobazam and rufinamide). As emphasized above, there are some AEDs in development where the goal will be approval for children before adults. These AEDs include cannabidiol for Dravet syndrome and Lennox-Gastaut syndrome, fenfluoramine for Dravet syndrome, triheptanoin for Glut1 deficiency, anavex-273 for Rett syndrome, and everolimus for tuberous sclerosis. If these and similar drugs are effective then there will be a new issue for transition – do they continue to work in adults?

3. Strategies to deal with AED polytherapies (rarely simplified prior to transfer in severe epilepsies)

Not surprisingly, many of the epilepsy syndromes that begin in childhood and persist into adulthood are characterized by poor seizure control. Polytherapy is very common for these patients and at its best provides satisfactory seizure control without significant side effects. At its worst there are many seizures and sedation. In adult care, simplifying these complex medication regimes may be challenging. Based on clinical experience, we propose four strategies.

First, it is important to confirm that the events described by the patient (or parents/caregivers) are indeed seizures. Some epilepsy syndromes are associated with only one seizure type that is very typical, stereotyped, and unchanging through the pediatric years. Other epilepsies may present with different seizure types as the infant/child grows which may be a source of confusion. For instance, patients with severe epilepsy with very early onset (especially with intellectual disability) may have seizures with very subtle manifestations such as pupil dilatation or facial flushing. After these subtle types of seizures disappear, parents and caregivers may still interpret autonomic signs as seizures in their teenage child. The adult epileptologist now caring for this patient should be aware of this misinterpretation. Other paroxysmal events may also be confused with seizures: mannerisms, agitation, screaming episodes, and aggressive outbursts (especially in patients with moderate/severe intellectual disability). Movement disorders (tremor, myo-clonus, dystonia) and sleep disorders, may also be mistaken for seizures [18,19]. Video-EEG may be challenging in these patients but very helpful to clearly define which activities are seizures, thereby AED polytherapies.