Reflections in the rear-view mirror. Two decades of epilepsy

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For the first series of ACNR in 2001, I wrote a series of articles covering key areas in the management of epilepsy: diagnosis; first line treatment; refractory epilepsy; status epilepticus; women and epilepsy; social effects of epilepsy. Now, 20 years on, it is interesting to review progress. The differential diagnosis of epilepsy has not changed. The tools to aid diagnosis have improved in other areas but not for epilepsy itself. For the everyday management of cases, undoubtedly the most significant advance since 2001 is the mobile phone with video capability. This enables the differentiation of dissociative from epileptic events with more than 90% sensitivity and specificity.[1] Cardiologists have helped us by developing implantable new recorders, to detect cardiac arrhythmia. EEG is working on similar long-term monitoring but is not yet there. Once epilepsy has been diagnosed, we now have a new classification.[2] Every owner of a new house feels the need to stamp its identity by redecorating the property and so it is with each generation of epilepsy specialists and classification. The new classification does have some merit in recognising that seizures are a symptom of a complex disorder in which there may be a range of different causes and different associated characteristics. Since 2001, there has been an explosion of genetic diagnosis and some of these are starting to lead to greater understanding in treatments e.g. why Dravet syndrome might be exacerbated by sodium channel blocking medications. The identification that the mammalian target of rapamycin (mTOR) was upregulated in tuberous sclerosis has led to the first anti-epileptogenic (rather than anti-seizure) drug[3] and potentially represents a paradigm shift in epilepsy management. It remains to be seen if an analagous approach is more broadly applicable, but evaluation in patients with high risk pathologies e.g. severe brain injury, haemorrhagic stroke or encephalitis would need complex, long term longitudinal study in large numbers.

In 2001, I wrote that lamotrigine was gaining ground as a first line treatment in focal epilepsy, as a result of a favourable adverse effect profile compared to carbamazepine. That position was consolidated after SANAD 1 in 2007.[4] It was also gaining popularity in generalised epilepsy because of valproate side effects and teratogenicity. Equally SANAD and other studies[5] showed it is less effective than valproate in generalised epilepsies and the choices are therefore more complex in women of reproductive age. We knew about major teratogenicity of valproate long before 2001 although the structurally undetectable consequences of foetal exposure (autism ADHD and learning disability) were not fully established until more recently.[6,7] We have had the recent government response to a Europe-wide legal case, with a frankly clumsy and coercive system of regulation and it is to the profession's credit that this has been moderated to a more sensible monitoring system. At the core of the debate are some truly profound questions which have not yet been answered: Who is responsible for balancing the risks and choosing treatment of a medically serious condition? Does a woman have the right to choose to take a risk of having a disabled child, if they feel that valproate is their best option, or does society via its government, who may have to help fund the consequences have the right to enforce a choice? At the start of this process, the answer from government was women may not choose. Now it is a grudging acknowledgment of a partial right to choose, which is in marked distinction to conversations that might be had, for example in a genetics clinic, around other disorders affecting offspring. Clinicians have responsibilities here. The first is to identify risk, and the profession has been proactive with epilepsy and pregnancy registers, starting in the UK and adopted around the world, which may give early warning of risks. The second, in which we have been less good with valproate, as it was a staple of the armamentarium for so long before this process, is to keep track of our patients on these drugs, so that we can recall them if and when information becomes available. Finally, the lesson is clear that we have to be advocates of patient choice in the face of big government. Our current knowledge is that some drugs are fairly safe in pregnancy; levetiracetam, also lamotrigine, carbamazepine and oxcarbazepine (in dose dependent fashion), some are unsafe; valproate, topiramate and phenytoin for example and others are too new to know, but presumed unsafe. Hopefully more information will emerge from our registers.

Those born in 2001 are part of Generation Z, but epilepsy specialists might call it generation K. Keppra® (Levetiracetam) has been the commercial success story of the last twenty years. With a novel mechanism of action, (SV2A protein binding) no interactions, simple kinetics, low teratogenicity and rapid dose titration, it has found a role in focal epilepsies,

generalised epilepsies and status epilepticus. For many clinicians it has become the go to first line drug, although studies suggest it is less efficacious than valproate in generalised epilepsy and there is little evidence to compare it to lamotrigine in focal epilepsy. It also has a unique and not that uncommon tendency to cause irritability, often distressing to those around the patient and not always recognised by themselves "Keppra rage". Despite levetiracetam and the explosion in the numbers of new anti-epileptic drugs since 2001, the number of seizure-free patients remains stuck stubbornly at around 70%. The drug treatment of refractory epilepsy therefore becomes the balance of epilepsy and adverse effects in the maintenance of the best possible quality of life. The best we can say is we have slightly reduced adverse effects compared to old AEDs. Principles of combining AEDs largely centre around complementarity of adverse effect profiles and pharmacokinetics and that has not changed since 2001. Epilepsy surgery remains an option for a small number of those whose epilepsy does not respond to medication and the ability to identify them accurately increases over time but no step-change here. Vagus nerve stimulation has become a widely used treatment with significant benefits and none of the neurocognitive side effects of medication. We still don't really know how or why it works but then willow bark was used widely for centuries before we understood it.

Our appreciation of psychological and social comorbidities of epilepsy has deepened. Accelerated forgetting has been identified as a common and recognisable association and, much as in many other complex neurological disorders, behavioural and cognitive changes are recognised as organic associations, for example with the identification that these neurobehavioural disorders may affect siblings of those with generalised epilepsy.[8] Epilepsy is therefore a complex neurological disorder with seizures as one manifestation, hence the new classification. In my decades managing patients with epilepsy, sadly I have not discerned any significant change in prejudice towards them, especially from employers and my heart still sinks at the struggles I fear my patients frequently face, whose tribulations are often disproportionate to the occasional hours of inability to work that their seizures may cause. With additional tragic irony, my experience is that nurses and teachers with epilepsy have particular difficulties.

In the management of status epilepticus, the greatest advance has again come from outside epilepsy, with the identification of immune mediated encephalitides, which respond to immunotherapy, rather than to AED. What did we think was going on before we knew about them? Drug treatment of status remained without new good quality evidence from 1998 until very recently, with studies now showing that Levetiracetam, Valproate and Phenytoin are not significantly different in managing status epilepticus in children and adults;[9] research following practice in the move to levetiracetam as an easier drug to manage and one that the clinician does not have to change when leaving the acute setting to long term management. We have also learned how in status epilepticus, GABA receptors are rapidly down-regulated and glutamate receptors up-regulated, explaining the loss of efficacy of benzodiazepines soon after the onset of status.[10] Buccal midazolam in the community is a major advance in reducing the risk of hospital admission and refractory status in those with recurrent episodes. In 2001, we had already started to understand the frequency and some of the risk factors for Sudden Unexplained Death in Epilepsy (SUDEP). The U remains stubbornly refractory to detailed analysis although autonomic mechanisms affecting the heart and respiration seem likely. SUDEP has risen up the priorities for clinicians, driven by patient groups and the hope is seizure detection technologies, which are becoming more reliable, will further reduce risk and give patients and their parents more control over their condition.

My wish-list for the next 20 years. Long term EEG at home; utilising AI for diagnosis and to deliver drugs, including by vector driven drug delivery for refractory epilepsy; anti-epileptogenic medicines for high-risk brain pathologies; better recognition and management of comorbidities; technologies to help prevent SUDEP; softening of social attitudes to epilepsy; World Peace and never to hear about Coronavirus or Brexit ever again. My best wishes to the next generation. It will be an exciting time as new technologies mature and others emerge.

REFERENCES

1. Ramanujam B, Dash D, Tripathi M. *Can home videos made on smartphones complement video-EEG in diagnosing psychogenic nonepileptic seizures?* Seizure. 2018;62:95-98. https://doi.org/10.1016/j.seizure.2018.10.003
2. Scheffer IE, Berkovic S, Capovilla G, et al. *ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology.* Epilepsia. 2017;58:512-521. https://doi.org/10.1111/epi.13709
3. French JA, Lawson JA, Yapici Z, et al. *Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study.* Lancet 2016;6736:1-11. https://doi.org/10.1016/S0140-6736(16)31419-2
4. Marson AG, Al-Kharusi AM, Alwaidh M, et al. *The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial.* Lancet (London, England) 2007;369:1000-15. https://doi.org/10.1016/S0140-6736(07)60460-7
5. Marson AG, Al-Kharusi AM, Alwaidh M, et al. *The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial.* Lancet (London, England) 2007;369:1016-26. https://doi.org/10.1016/S0140-6736(07)60461-9
6. McVearry KM, Gaillard WD, VanMeter J, Meador KJ. *A prospective study of cognitive fluency and originality in children exposed in utero to carbamazepine, lamotrigine, or valproate monotherapy.* Epilepsy Behav. https://doi.org/10.1016/j.yebeh.2009.09.024
7. Christensen J. Prenatal Valproate *Exposure and Risk of Autism Spectrum Disorders.* JAMA 2013;309:1696-1703. https://doi.org/10.1001/jama.2013.2270
8. Iqbal N, Caswell HL, Hare DJ, et al. *Neuropsychological profiles of patients with juvenile myoclonic epilepsy and their siblings: A preliminary controlled experimental video-EEG case series.* Epilepsy Behav. 2015;14:516-521. https://doi.org/10.1016/j.yebeh.2008.12.025
9. Kapur J, Elm J, Chamberlain JM, et al. *Randomized trial of three anticonvulsant medications for status epilepticus.* N Engl J Med. 2019;381:2103-2113. https://doi.org/10.1056/NEJMoa1905795
10. Naylor DE. *Glutamate and GABA in the balance: Convergent pathways sustain seizures during status epilepticus.* Epilepsia. 2010;51:106-109. https://doi.org/10.1111/j.1528-1167.2010.02622.x