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Practical approach to anti seizure medications, an update

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Seizures are unpleasant, may cause injury and contribute to societal impairments such as cessation of driving privileges. Critically even seizures that stop by themselves, and are not unduly prolonged, may be fatal.[1] All adults who have a first seizure should be referred to their local 'First Seizure Service' where someone with expertise will identify if there is a seizure mimic present, such as reflex vasovagal syncope, dissociative seizures and rarely cardiogenic syncope. Following a second seizure, or now the first – if there is a strong indicator of seizure recurrence, such as a major scan abnormality – anti-seizure medications (ASM) are initiated.[2] Safety advice and avoidance of lifestyle factors known to trigger seizures are important, but for the majority of people with epilepsy, the mainstay of their treatment is medication. Anti-seizure medications are the preferred term to reinforce an important point – these medications reduce the likelihood of seizures occurring, but they are not disease modifying (not 'anti-epilepsy drugs') and there is more complexity than just grand mal seizures (not 'anti-convulsants').[3]

The Getting it Right First Time report for Neurology (2021) identified epilepsy as the second most common neurological reason for admission, after headache, with 83/100,000 in 2018.[4] Whilst only 4% of people in England are admitted to hospitals with no neurological presence, 28% of admissions (66,781 emergency admissions/year) are to district general hospitals with a visiting neurologist only and so it is important that all acute medics are familiar with manipulating ASMs.

Anti seizure medication choice

The dogma is that identifying the seizure type(s) and putting this in the context of the age of onset, EEG and MRI findings, co-morbidities, allows for an epilepsy classification that then facilitates ASM choice. Whilst this is undoubtedly correct this is much less important for acute medics, as the vast majority of people that they see and almost all of de novo epilepsy in adults will be of focal onset. This presents with two main seizure types – major convulsive seizures, now technically called 'focal to bilateral tonic-clonic seizures' and smaller 'focal seizures with loss of awareness'. The latter seizure type has been known as petit mal, complex partial seizures and focal dyscognitive seizures and patients still commonly call them absences. Furthermore, the two most commonly started ASMs for focal onset seizures are very reasonable choices for the other type of epilepsy, idiopathic generalised. This pragmatic view is further strengthened by the fact that the 'odd one out' of the major ASMs, sodium valproate (meaning it is primarily used for seizures associated with idiopathic generalised epilepsy, rather than focal onset seizure) is increasingly hard to prescribe safely (see valproate below).

Adherence matters – the most common reason someone with epilepsy will attend with breakthrough seizures will be accidental or deliberate under-dosing. This may because we have not recommended a sufficient dose (answer; increase dose as per Table 1) or they have not absorbed, vomited their last dose, or there is an adherence issue. Acute medics have a critical role to play in identifying medication non-adherence, it is only the initial blood tests that can be used to identify sub-optimal ASM levels, as all subsequent bloods will represent the supervised treatment as an inpatient. All ASMs can be assayed by the DTM unit at Chalfont,[5] but pragmatically it is unusual for someone to be taking some of their ASMs religiously and others haphazardly and so it is defensible if you choose to only assay the ASMs that you have ready access to (likely to be the five drugs in Table 1, plus phenobarbital).

Identifying adherence is crucial as the episodic seizures seen with indifferently taking ASMs are a very good mimic of a drug-resistant epilepsy and so medication doses may be increased unnecessarily, or people might be swapped on to other, often inferior ASMs.

The route of medication is important to know; Table 1 identifies that lamotrigine and carbamazepine lack an intravenous formulation. It is vitally important that people with epilepsy do not miss doses and so options here include i) a nasogastric tube; ii) a short-term levetiracetam or benzodiazepine bridge. This latter strategy utilises the fact that levetiracetam, lorazepam, diazepam, and clonazepam are available intravenously and are rapidly therapeutic.[6]

There are five ASMs that all acute medics should know, and know well (Table 1). Lamotrigine has high-quality pragmatic randomised trial evidence from the UK to support its role as the first choice for focal onset epilepsy; this is based on comparison with levetiracetam and zonisamide, where it had good efficacy, tolerability and was inexpensive.[7] There is a lag of weeks before it becomes therapeutic as it is started slowly (typically starting at 25 mg od and going up by 25 mg a fortnight). This strategy is important to combat skin reactions which can be mild to severe when escalated quickly. If seizure control is needed sooner, consider co-prescribing clobazam (perhaps 10 mg bd) for the first 6 weeks until lamotrigine is close to therapeutic. The slow escalation helps with avoiding initiation side effects, but may also contribute to under-dosing. Lamotrigine trough levels are helpful as a guide; these are best before the next dose is due, or at least 6 h or more post dose so a 'near trough' late in the afternoon is convenient.

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Table 1
Commonly prescribed ASMs that all acute medics should be confident with. Ranges BNF (2023).[14]

Generic	Trade	Formulations	Smallest tablet	Titration dose	Maximum dose
lamotrigine	Lamictal	Tablet, dispersible	25 mg (2 mg dispersible)	50–100 mg bd	250 mg bd
levetiracetam	Keppra	Tablet, liquid, granules, IV	250 mg	As per effect - 750 mg bd	1,500 mg bd
carbamazepine	Tegretol	Tablet, liquid, PR	100 mg	400–600 mg bd	1,000 mg bd (rarely tolerated)
phenytoin	Epanutin	Capsules, tablet, liquid, IV	25 mg capsules	100–250 mg bd (200–500 mg od)	As per blood levels
valproate	Epilim	Tablet, liquid, granules, IV	200 mg standard (100 mg crushable)	500–1,000 mg bd	1,250 mg bd

Levetiracetam is a widely adopted anti-seizure medicine with indications for children and adults, for urgent seizure control (such as status epilepticus) as well as long-term prophylaxis. It is renally excreted and so doses need to be adjusted with significant renal disease, but is much used partly because it has an absence of clinically meaningful drug-drug interactions. Of less importance to acute medics, but commonly seen in neurology clinics, it has no mood stabilising properties and is the ASM most commonly stopped for mood aggravation; irritability and anxiety aggravation is common, psychosis is rare.[8] Some neurologists recommend supplementary vitamin B6 to mitigate against this side effect[9] whilst others swap to a mechanistically similar medication, brivaracetam, which can be done immediately overnight with a conversion ratio of approximately 15:1 (so levetiracetam 1,500 mg bd becomes brivaracetam 100 mg).[10] There is little concerning pregnancy safety data for lamotrigine or levetiracetam and so these are our preferred choices if pregnancy is possible.

Carbamazepine is a legacy drug meaning that it is much less likely to be initiated now, and in many ways has been superseded by mechanistically similar medications such as oxcarbazepine, elsicarbazepine. Long-term use of this liver metabolised drug can contribute to osteoporosis.[11] Higher doses or moderate doses in vulnerable individuals, such as the elderly, commonly cause ataxia.

Phenytoin is a medication best retained for emergency use to terminate prolonged seizures, or for expert use only for patients in whom nothing else has worked. There is a dual concern that the long-term somatic side effects (many of which are cosmetic such as hirsutism, gum hypertrophy but others are more cryptic such as osteoporosis), may outweigh the seizure-control benefit. Alongside this is that phenytoin is difficult to prescribe reliably in the long-term with drug-drug interactions and complex zero-order pharmacokinetics.

Sodium valproate is a drug in the headlines because it is a recognised physical and cognitive teratogen. Concordantly there is a pregnancy prevention programme with a standardised process of annual consenting for all people taking valproate who may become pregnant.[12] In most circumstances it would be unwise for a non-specialist to start valproate, but were you to do so, be aware that you need to do a pregnancy test, complete a shared-care document for the GP and give the patient medication until their GP can take over this role. The committee for human medicines (CHM) reviewed data regarding safety of valproate for children born to fathers taking the medication; now for all new valproate prescriptions in men and boys under 55 years, patients need formal counselling and documentation.[13] Irrespective of this controversy there are a plethora of reasons why long-term valproate use may be best avoided, primarily the weight gain can be egregious and contribute to premature metabolic syndrome.

Newer anti seizure medications

Proportionally fewer people are taking newer ASMs, however because these are more likely to be prescribed to people with more frequent seizures and or more complex needs, they may be disproportionately represented in emergency admissions. All people taking a newer medication should have seen a neurologist recently and almost certainly should have access to an epilepsy specialist nurse, either of whom, when contacted could provide advice and support. Some of the newer drugs have longer half-lives than previously available medications which helps prevent breakthrough seizures due to adherence issues. For example cannabidiol (56–61 h), cenobamate (50–60 h), perampanel (70–110 h), zonisamide (50–68), and in contrast levetiracetam is 6–8 h.[15] A practical advantage of this is that if a patient presents with side effects in keeping with drug toxicity from one of these medications, it may be safe to omit a dose and then amend the regular regimen, whereupon previously this was not an option. Cenobamate is increasingly used because it appears to be more likely to control seizures in people with multi-drug refractory epilepsy, however with this benefit comes a cost, there are a host of clinically meaningful and theoretical drug-drug interactions, including monoclonals and some anaesthetic agents, so care must be taken when prescribing for anyone of cenobamate.[16]

Declaration of competing interest

R Thomas has received honoraria from Arvelle/Angelini, Bial, Biocodex, Eisai, Jazz, LivaNova, Neuraxpharm, Sanofi, Takeda, UCB Pharma/Zogenix and UNEEG.

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