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CURRENT AWARENESS SERVICE

Psychogenic non-epileptic seizures (PNES): a refresher

There is no doubt that during and following the COVID pandemic, the nation has seen a marked increase in the incidence, and therefore the prevalence, of psychological and mental health disorders across all ages. This includes children in whom the manifestations of this psychopathology have included a range of what could be broadly termed, 'functional neurological disorders' or 'non-epileptic attack disorders'. This includes tics, psychogenic non-epileptic seizures (PNES), paralyses, mutism and visual loss. PNES is well-recognised as one of the most common neuropsychiatric disorders associated with epilepsy and has been acknowledged as such by the International League Against Epilepsy (ILAE). This led to the establishment of an ILAE PNES Taskforce and, predictably, a number of publications, including one on its diagnosis [LaFrance et al, 2013]. I thought it would be timely and relevant to write a brief refresher on PNES.

Terminology

Many terms have been used to describe PNES, including:

- 'Medically-unexplained symptoms' (*unhelpful, as 'seizures' should never be regarded as an 'unexplained symptom'. It also suggests that the doctor has no knowledge of the cause of the symptoms [i.e. that they are seizures]*)
- Non-epileptic attack disorder (NEAD) (*a useful umbrella term that also includes vaso-vagal and cardiac syncope and a range of other paroxysmal movement disorders but is probably too vague, as it does not describe the specific nature and origin of the 'attacks'*)
- Pseudo-seizures (*a very commonly-used term but one that is perjorative and inaccurate as the seizure itself is very real [for the individual] and not false or 'pseudo'*)
- Dissociative convulsions/seizures (*a recognised disease category in the International Classification of Diseases 10th Revision [Chapter V, block F44.5], where it is formally defined as a 'Psychologically-mediated impairment of awareness and/or control of neurological function' [World Health Organisation 1992]. Although this is clearly a medical definition, it may not be readily understood by most young people and their families*)
- Psychogenic-non-epileptic seizures (*this is probably the most accurate and appropriate terminology because it correctly identifies the seizures and their non-epileptic and psychologically-mediated origin. It is my preferred term*).

The following is a useful definition of PNES: "A disorder of paroxysmal motor, non-motor or behavioural response to internal or external triggers that superficially resemble epileptic seizures but that are not associated with the abnormal electrical activity on an EEG associated with

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the latter [adapted from Reuber and Elger, 2003]. There are two caveats with this definition. The first is that it implies that an EEG must be undertaken in every possible case of PNES, which is not always necessary; this is discussed later. The second is that epileptic seizures which originate from the medial inferior lobe may also show no changes during an EEG.

Epidemiology

Adult data suggest a prevalence rate of 2-30/100,000 people [Benbadis, 2000], but there are no equivalent reliable paediatric data. However, it is very likely that the prevalence is far lower in children and in the region of 2-5/100,000 (aged<16 years). A recent nationwide Danish study described the characteristics of 364 children aged 5-17 diagnosed with PNES between January 1996 and December 2014 [Hansen et al, 2020]. The incidence of PNES was found to be between five and 14 per 100,000 person-years and there was an increase in incidence over time [Hansen et al, 2020]. Those aged 15-24 are most likely to experience PNES and the majority (75-85%) are females [Lesser, 1996; Hansen et al, 2020]. In children, the peak age is between 10 and 15 years, but they have been reported to occur in children less than eight years of age [Hansen et al, 2020; Agarwal et al, 2021]. In those aged less than eight years, the incidence and prevalence are reported to be similar in girls and boys but this may simply reflect the very small numbers of all children at this age. In my experience, children less than 10 years of age were nearly always girls.

Patients with PNES show an exaggerated physiological response to stressors when compared to control populations. They also exhibit dysregulation in the autonomic nervous system, and display differences in brain networks that involve areas of the brain related to cognitive, emotional, and executive functions. There is no single aetiological theory to explain the development of PNES; it is more likely that a number of factors operate and lead to their manifestation and onset. These include:

- **Predisposing factors** (including genetic, behavioural or psychiatric factors, neurological co-morbidities and early life traumas)
- **Precipitating factors** (stressful physical or emotional events)
- **Perpetuating or sustaining factors** (lack of social support, avoidance, isolation and ongoing and un-resolved traumas and precipitating factors)

Co-morbid disorders

Psychogenic non-epileptic seizures may clearly arise in isolation but are more commonly seen in teenagers (particularly girls) who also have epileptic seizures. It is very rare for a child (particularly a girl) aged less than 11 to develop PNES without a pre-existing diagnosis of epilepsy. The prevalence of coexisting epilepsy and PNES across all ages ranges from 10 to 65% [Benbadis et al, 2001; Devinsky et al, 2011]. In children, the coexistence is lower, at between 10 and 30% [Hansen et al, 2020; Agarwal, 2021]. In those with both epilepsy and PNES, the epilepsy invariably precedes the onset of the PNES. It is important to acknowledge that patients with PNES may also present as psychogenic status epilepticus and even be admitted to intensive care [Walker et al, 1996], although this is rare in children. In the recently-published Established Status Epilepticus Treatment Trial (ESETT) study, 10% of 384 patients that were enrolled into this double-blind, randomised controlled trial (RCT) were considered to have psychogenic CSE [Kapur et al, 2019]. Treating these patients with ASMs, and certainly escalating treatment to rapid sequence induction with an anaesthetic carries a high risk of iatrogenic complications.

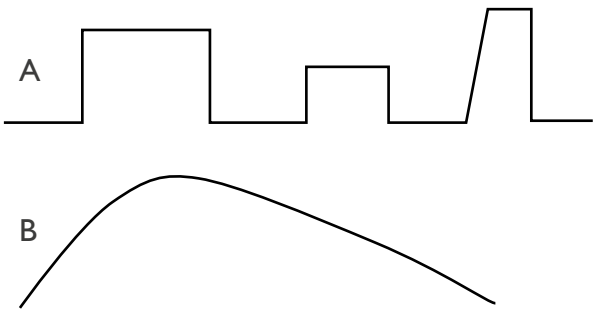
Children with PNES show a higher prevalence of psychiatric disorders, both prior to, and following the onset of PNES [Hansen et al, 2021]. Multiple psychological and social factors have been implicated in the development, onset, and maintenance of PNES in children. Common comorbid psychological conditions include anxiety, mood and adjustment disorders, somatic symptoms, conversion disorder, behavioural problems and a family history of epilepsy or mental illness. However, there are very limited data that have shown a clear causal relationship between these conditions and PNES.

Presentation and clinical features

The majority of PNES resemble a tonic-clonic seizure, less commonly a tonic or atonic seizure and rarely a focal and absence seizure. One of the reasons for this is that a focal or absence seizure is less dramatic and less 'eye-catching' than a tonic-clonic or tonic seizure. The language used by patients, and less commonly the parents of children with PNES, can be useful in discriminating between PNES and epileptic seizures [Reuber and Brown, 2017]. There are also a number of features that should readily identify apparent tonic-clonic seizures as being non-epileptic, and psychogenic, in origin. In PNES:

- They typically occur in public places and with many people around
- They do not occur during sleep – unless the child has woken first. Young children who present with paroxysmal episodes that arise directly from sleep or that are bizarre or difficult to characterise should not be considered to have PNES until epileptic seizures (particularly of frontal lobe origin) have been seriously considered and excluded
- Their onset and offset is sudden rather like a square wave pattern and this may be repeated at regular or irregular intervals over a number of minutes (see **A** on the next page). The episodes last from seconds up to many (even >10-15) minutes. This is in marked contrast to an epileptic tonic-clonic seizure which builds up, peaks and then gradually ends like a gentle curve (see **B** on the next page), with most

Figure 1. PNES and epileptic tonic-clonic seizure onset and offset. A - PNES tonic-clonic seizure with sudden onset and offset and repeated over a number of minutes. B - epileptic tonic-clonic seizure with gradual build-up, peak and end in the shape of a curve.



(approximately 80-90%) ending spontaneously within four minutes after the onset

- The movements are either random 'thrashing' or, if regular, are of a much faster frequency than the clonic movements in a tonic-clonic seizure
- The face and mouth are rarely, if ever, involved; it is extremely rare for a child to faithfully and convincingly mimic or reproduce the tonic or clonic movements that involve the face in an epileptic tonic-clonic seizure
- The eyes remain closed and when an attempt is made to passively open them, the child resists; the eyes are often open in a tonic-clonic seizure
- The tongue or inside of the cheek is rarely bitten
- Urinary incontinence is rare; its occurrence in PNES is often associated with chronic PNES or a significant underlying and un-resolved psychological issue
- Faecal incontinence is extremely rare and if it occurs, would indicate the seizure was epileptic
- Physical injuries, and specifically a fractured limb or tooth or carpet (friction) burns, are extremely rare in children but may occur in adults and usually when there is a comorbid psychiatric disorder
- The recovery is often rapid – but often followed by one or more 'on-and-off' recurrences (**A**) with similar or very different intensities and durations

Diagnosis

As might be expected, a detailed account of the episodes (seizures) must be obtained from a reliable eye-witness (or witnesses). The history must include when, where and what time they occurred; who was with the child; how long the episode lasted; how did the episode end; and what was the child like immediately following the end of the seizure. Video-footage of the seizures can be extremely helpful, if not diagnostic. Some young people and their families may benefit from seeing the video-footage and having it explained by the paediatric team with or without a psychologist.

Where there is significant doubt over the diagnosis or when the family is initially non-accepting of the diagnosis, video-EEG telemetry may be required. However, this will only be informative (and usually diagnostic) if the child or young person experiences their typical event(s) during it. The exception is with frontal lobe seizures, where an ictal EEG (an EEG recorded during a seizure) may be normal. Finally, telemetry should be undertaken as an inpatient because of the importance of being able to simultaneously record the EEG as well as the clinical episodes on high quality (including infrared) CCTV. The ILAE initially suggested that video-EEG telemetry was mandatory in all individuals in whom PNES was a possible diagnosis [LaFrance et al, 2017]. However, they subsequently and appropriately revised the use of telemetry from being 'mandatory' to 'recommended', in recognition that not all countries would have access to this investigation [Kanemoto et al, 2017].

A detailed educational and social and family history should also be obtained, including a family history of any mental health disorders. This is in an attempt to begin to identify any predisposing and precipitating factors. In my experience, high-achieving teenage girls seemed to be a particularly high-risk group. Taking on just one more in- or out-of-school commitment(s) seems to act as the final straw. In those cases, PNES seems to represent an acceptable, 'escape' or 'get out' illness behaviour rather than being perceived as not being able to cope or failing at what they are doing. The identification of any recent emotional or physically traumatic event (including face-to-face or on-line bullying) is important because adolescents and adults with post-traumatic stress disorder (PTSD) are well-recognised to be at a high risk of developing PNES. It is important to understand although PNES may be inaccurately diagnosed as tonic-clonic or focal seizures, the converse is true, in that epileptic seizures may be misdiagnosed as PNES.

There is often a considerable delay in the correct diagnosis of PNES. A review published almost 20 years ago found a mean delay of 7.2 years between the initial manifestation and the eventual confirmed diagnosis of PNES [Reuber and Elger, 2003]. The delay is likely to be longer in adults than in children, largely because of the better access that children have to specialist paediatric neurology services. One would expect (and hope) that the diagnosis would be established far more quickly in 2022/3. A delay may result in the child undergoing unnecessary hospital admissions and investigations and receiving numerous anti-seizure medications (ASMs), often as 'polypharmacy' with adverse side effects. An additional consequence of a delayed diagnosis is that any underlying stressors or provoking or perpetuating factors (and resulting abnormal behaviour) may become entrenched and therefore more challenging and resistant to a successful resolution. This is compounded further if the child or young person and their family have received

inconsistent and particularly overtly contradictory explanations of the seizures from different medical and nursing staff.

Management

The most important points in the management of PNES are:

- To correctly diagnose them as soon as possible. The longer the diagnosis is missed or avoided, the more difficult it will be to not only identify, but also address the underlying precipitating and perpetuating factor(s) causing the seizures. It also makes it more difficult to work effectively with the child and family. This may be more challenging when the child has both epileptic seizures and PNES.
- There should be no need to undertake video-EEG telemetry if the diagnosis is established early and without difficulty. However, the longer the diagnosis is delayed, often accompanied by parental anxiety or anger, telemetry has a role. As stated above, this will only be informative if the child has their typical event(s) during it.
- To be honest with the child and family – recognising that the events are genuine events or seizures, but that they are not epileptic seizures.
- To avoid the use of a confrontational and judgemental approach (this may be difficult for some family members to do…)
- To assure the child and the family that help is available and the seizures can be treated successfully but that this may take some time, often months
- To seek early advice and input for the child from clinical psychology or child and adolescent mental health services (CAMHS). It is often very helpful for initial consultations to be joint ones with the psychologist/psychiatrist and paediatrician, paediatric neurologist or epilepsy nurse specialist.
- If all of the child's seizures are PNES (i.e. the child does not also have epileptic seizures), any ASM must be withdrawn slowly. Some families will want to stop the ASM (or ASMs) immediately and usually when their response to the correct diagnosis of PNES has been anger. Although it is unlikely that an abrupt discontinuation will lead to acute withdrawal seizures, it would be wise to withdraw the ASM over four to six weeks.

The more detailed and in-depth psychological or psychiatric approaches to the management of PNES can be found in a number of recent reviews [LaFrance et al, 2013; Brown and Reuber, 2016; Kozlowska et al, 2018; Gasparini et al, 2019].

Prognosis

The course and outcome of PNES varies depending on a number of factors, including:

- The age of the individual
- Its cause
- Its duration
- The persistence of, and failure to address the factors that precipitated or sustained the PNES, or both
- Early acceptance of a diagnosis of PNES in the child and family
- Early and sustained engagement with, and co-operation of the child and family with psychological support

In contrast to adults, there is relatively little information on the outcome of PNES in children. A study published in 1991 compared 18 children (mean duration of PNES of 5.5 months, range one month to two years) with 20 adults (mean duration of 5.5 months, range a few months to 20 years). Three years after the diagnosis of PNES, 81% of children but only 40% of adults were free of PNES. The seizures stopped 'immediately' after the diagnosis was made in 44% of children and 20% of adults. This difference largely reflected the later diagnosis in adults [Wylie 1991]. A much more recent study was undertaken in 70 adult patients with PNES and without comorbid epilepsy (age: 41.1 ± 13.5 years; 74 % female) and with a follow-up period of 5.2 ± 4.2 years. Perhaps surprisingly (for 2020), the mean delay to the correct diagnosis was still long at 6.7 years (median: 4.3; range: 0.1–32 years). Of the 70 patients, 23 (33%) had experienced no PNES during the last 12 months. Those who were PNES-free were younger at PNES onset ($p<.01$) and at diagnosis ($p<.01$) and had a higher education ($p<.05$) [Walther, 2020]. Finally, an observational study of 34 children showed that almost 77% became and remained free of PNES after a short follow-up period of 9.8±7 months [Rawat et al, 2015]. In my experience, the younger the child (particularly <12 years) and the quicker the diagnosis of PNES is made, the better the outcome with most becoming and remaining free of PNES.

Conclusion

As we all know, 'not everything that jerks or causes a fall' is an epileptic seizure. Psychogenic non-epileptic seizures are often missed or wrongly diagnosed and, through a delayed diagnosis, this may make their management more challenging and difficult. Recent evidence also indicates that the coexistence of PNES and psychiatric disorders cannot be explained by chance alone; find one and then consider or look for the other. The management of PNES should be initiated as soon as possible, involve psychological input and use a non-confrontational and non-judgemental approach.

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Adding and changing anti-seizure medications: a practical guide

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Approximately 50-60% of individuals with epilepsy across all ages will respond to the first anti-seizure medication (ASM) they are started on. However, in children with a more severe epilepsy syndrome, including developmental and epileptic encephalopathy (DEE) or symptomatic focal epilepsy, this figure will be much lower, at 10-30%, depending on the epilepsy syndrome. Consequently, in many people, and particularly in children, the ASM will need to be changed, or another ASM added. This may be either because of a lack of efficacy or because of unacceptable adverse side effects or severe adverse drug reactions (ADRs), or sometimes both.

Starting or changing ASMs may be challenging for less experienced prescribers and advice from books, scientific papers and colleagues can be confusing and even contradictory. This article describes a personal practice and rational approach to this issue. It reflects one, but not the only, way of managing ASM changes successfully. How one defines 'success' is open to debate, but a useful definition may be whereby a patient's seizure control shows a significant and sustained improvement with no or only minor and acceptable side effects. Clearly, one has to appreciate and understand that any change to an ASM regimen may actually make the situation worse. Using a rational approach avoids the often perceived scenario of 'going round in circles', which can be frustrating for the child, their family, their GP and the epilepsy clinic team. It would be reasonable to regard the process of starting or changing an ASM as 'hypothesis-testing', although for many families this may simply be regarded as a 'trial and error' approach.

From the outset, it is important to try and agree a clear and realistic treatment goal with the child and family. This must be tailored for the individual child within the context of the known natural history of the child's epilepsy syndrome or epilepsy and its underlying cause. It will also be important to discuss the child's and their family's expectations when establishing a treatment goal, as these may occasionally be completely unrealistic. Examples at either end of the spectrum of the goals could be:

1. to stop or control all epileptic seizures and have no adverse drug reactions, or

2. to have only brief and infrequent seizures but to be able to remain alert or awake for at least a few hours in the day and to be able to be discharged home from hospital.

Clearly, in children, these goals may need to change and keep pace with the evolving (changing) natural history of their epilepsy syndrome/epilepsy. Generally, a reduction in epileptic seizure frequency of 50% or more is considered worthwhile (a good treatment response) and is an outcome that has, and remains, the most commonly-used one in randomised controlled trials (RCTs) of a new ASM. Further useful and practical information can be found in some excellent publications by the International League Against Epilepsy (ILAE). This includes articles on drug resistant epilepsies [Kwan et al, 2010] and on seizure freedom [Westover et al, 2012].

It is important to document the baseline seizure frequency that is to be used. This can be done from a seizure diary, or, if not available or not feasible (e.g. with absence, atonic or myoclonic seizures that occur many dozens of times a day), document an approximate impression, such as 'seizures every minute/hour/day/week/month'. On this ordinal scale, a good treatment response may be represented by a reduction from, for example:

- 'one seizure per hour on average' to 'several a day', or
- 'seizures on most days' to 'only a couple a week', or
- 'a seizure a week' to 'a couple a month on average', or
- 'one a month' to 'a few a year'.

However, it is also important to not 'give up' on trying to achieve a significant period of seizure freedom. This could be having no seizures for six months or being seizure free for a period at least three times as long as the child's previous seizure free period. The ILAE defines this latter outcome as a criterion or 'definition' of a good response to a recently introduced ASM in an individual's drug regimen. Data from adults suggest that even when numerous combinations of ASMs have been tried, success (in terms of seizure control) may still be achieved in some people [Luciano and Shorvon, 2007].

Once a child has a confirmed diagnosis of epilepsy, the first question is to decide whether starting an ASM is the most appropriate management option. This must take account of the epilepsy syndrome, seizure frequency and the child's 'quality of life' (safety, ability to function and participate to the best of their potential in things like school, family, peer groups and social activities). For the vast majority of

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children with epilepsy, prescribing an ASM will be the most appropriate management option. The next issue is to choose an ASM that is likely to be efficacious and well-tolerated (with a low risk of serious ADRs) and, at least theoretically, meet the agreed treatment goals. The ASM should be introduced at a low dose and increased at the usual and recommended titration rate for the individual medication. A dose and dose escalation regimen that is easy to give should be chosen. This must take into consideration the child's weight and the concentration of liquid formulations or the tablet or capsule strengths available. It is important to try and make the dose increments large enough to make a difference. For most ASMs, the escalation from the initial dose to the mid-maintenance dose should only take three to six weeks although it may need to be more slowly for some ASMs, and particularly with lamotrigine and perampanel. Dose increments should be made every two or three weeks for these two latter medications.

In out-patients the principle is to 'start low and go slow' to gradually increase the dose. However, if effective or high levels of ASMs are needed quickly, then it is reasonable, if not appropriate to use an intravenous loading dose so that 'steady state' levels are achieved almost immediately. This may happen in the Emergency Department (ED) or the Paediatric Intensive Care Unit (PICU), for example in the management of convulsive status epilepticus. This applies to not only the old ASMs, phenobarbital and phenytoin, but more relevantly to the newer ASMs, levetiracetam and sodium valproate [Dalziel et al, 2019; Lyttle et al, 2019; Chamberlain et al, 2020].

Discontinuing an ASM that has not been effective is always a good idea, but may have to be delayed. The withdrawal regimen can mirror the one used in its escalation, or if the AED definitely has not worked, it could be a little faster. However, an ASM should not be stopped suddenly unless there has been a serious ADR. It important to understand that the anti-seizure effect of some medications may last for up to four to eight weeks after the drug has been discontinued (e.g. sodium valproate, topiramate, phenobarbital). However, the anti-seizure effect of other medications (e.g. gabapentin) may last less than a week after it is discontinued.

In most situations, the ineffective ASM will be replaced with another one, providing the agreed treatment goals have not changed. As it may be difficult to tell if an ASM has been partially effective, it is often safer to introduce the new medication up to a reasonable maintenance dose before then gradually withdrawing the first one. This allows a simpler withdrawal of the new ASM if new side effects or ADRs develop, or if it is not effective. However, sometimes it is better to go faster and withdraw the first AED at the same time as the new one is introduced. This is particularly appropriate if the child is already receiving two ASMs, one of which is causing adverse side effects or if the child is experiencing frequent (i.e. at least weekly) seizures, particularly tonic-clonic or atonic. In the latter situation, a slower substitution may be frustrating or worrying for the family.

An example

Carbamazepine: start at 5 mg/kg/day (in one or two divided doses, as always, rounded up to a dose that is easy to administer) for one or two weeks. This is followed by 10 mg/kg/day for at least one week and then up to 15-20mg, depending on the child's response, both in terms of seizure control and the development of any adverse side effects. If the drug seems to be effective in a lower dose on the incremental regimen, it would be reasonable if not wise to remain on that dose for a number of weeks. If seizure control deteriorates, the dose can then be increased. If there are possible or probable dose-related ADRs (specifically, nausea, dizziness or ataxia) then the dose should be reduced down one step. If the child develops a possible or probable idiosyncratic ADR (specifically an acute rash), then the dose should either be rapidly withdrawn or stopped immediately. If the medication seems to show no benefit at all and the child has not developed any adverse side effects or ADRs on the top maintenance dose (i.e. 15 or 20mg/kg), then a serum or plasma level should be measured. If the level is absent or very low, consider the possibility that the child has been spitting it out, not taking it regularly, or has not been given it regularly. If the level is in the low or mid-target range, increase the daily dose again to aim for a non-trough, non-peak representative serum or plasma level near the top of the target range (e.g. top of target range +/- 10%). If the level is near the top of the target range, further dose increases will probably not significantly improve seizure control and may cause dose-related side effects, specifically nausea, dizziness and double vision. In this situation, the plan should be what is termed 'substitution monotherapy', in which one ASM is withdrawn whilst another is started, and often simultaneously.

It is generally considered that approximately 50-60% of individuals with epilepsy will achieve either good or a clinically acceptable level of seizure control on the first and most appropriate ASM. There is reasonable evidence that an additional 5-10% of individuals will gain seizure control on two appropriate ASMs. There is no convincing scientific evidence that seizure control is significantly improved with three ASMs, other than in Dravet syndrome. In this epilepsy syndrome, optimal, although not necessarily full, seizure control seems to be achieved with a combination of sodium valproate, clobazam and stiripentol, and, more recently, a combination of sodium

valproate or clobazam with stiripentol and fenfluramine [Lagae 2021]. Predictably, the higher the number of ASMs being used together, the greater the risk and the incidence of adverse side effects. Consequently, the general principle should be to try and use no more than two maintenance ASMs simultaneously. Three ASMs will usually be required for a few weeks during medication substitution. If a child is already receiving three ASMs, the aim should be to withdraw the one ASM that has been the least effective before then introducing another. There is a specific combination of ASMs that requires particular caution, and that is the simultaneous use of sodium valproate and lamotrigine. It is important to prevent or at least minimise the risk of an acute ADR (specifically a rash) and to maximise anti-seizure activity when lamotrigine is added or withdrawn from a child already taking sodium valproate. The rate of titration will also depend on the dose of sodium valproate the child is receiving. Advice should be sought from the local tertiary epilepsy service to ensure that this specific ASM change is as safe and as smooth as possible. Further information on the principle, 'Monotherapy or polytherapy' and 'Rational polytherapy' can be found in a number of relatively recent publications [French and Faught, 2009; Anderson et al, 2015; Egunsola et al, 2016].

Some neurologists recommend that the withdrawal and discontinuation of the first AED is undertaken before starting another one. This is reasonable in adults and when the seizure frequency is low, for example, a few times a year. However, in paediatric practice many children have a relatively high seizure frequency compared with adults. It may be daily, as in childhood-onset absence epilepsy, myoclonic astatic epilepsy (now known as epilepsy with myoclonic atonic seizures) or a number of the DEEs, so such an approach would not be appropriate.

Serum or plasma levels should, ideally, be measured in every child that experiences a marked and sustained (for more than five days) increase in seizures without any obvious cause, and also in every child that attends the ED in status epilepticus. In adults, poor or no compliance with ASMs is the most common cause of them presenting in convulsive SE to the ED. The levels must be measured on admission to the ED and not many hours later or on the following day.

In adult practice when the seizure frequency is low, that is, a few a year, serum or plasma levels can help when introducing drugs with a narrow therapeutic range (e.g. phenytoin), to titrate up to a reasonable maintenance dose. In this situation levels are often checked after approximately five half-lives (e.g. for phenytoin this would be after 5-10 days) when levels should be at 'steady-state'. However, this advice is not relevant when there has been a loading dose to achieve a 'steady-state' immediately. In paediatric practice, this is not usually necessary because seizure frequency in many epilepsy syndromes is generally high. In these situations, the dose can be titrated against seizure frequency with blood levels only having to be measured if a high dose is reached without any benefit and no adverse side effects. In addition, phenytoin is now rarely used as a maintenance ASM.

Levels may also be of some clinical use on PICU in the management of CSE when the child has received loading doses of a second-line, long-acting ASM, specifically, phenytoin, levetiracetam, sodium valproate, lacosamide or phenobarbital. However, it must be acknowledged that the blood levels of levetiracetam and lacosamide, and to a lesser extent, sodium valproate, may have little or no correlation with anti-seizure activity and therefore seizure control.

Before agreeing a treatment plan with the child and their family (or guardian or carers), it is important to consider the potential outcomes of the plan. At the outset it will be important to justify it and also outline these outcomes. This will help to reassure the child and family if the outcome is not successful. In most situations, once an ASM has been tried using the appropriate titration and maintenance dose and with an unsuccessful outcome and then withdrawn, it would not be appropriate to re-use it in the following six to 12 months. This emphasises that whenever an ASM is prescribed, it should be used in the maximally-tolerated dose, possibly with blood levels at the upper end of the target reference range, and over an appropriate time to determine its efficacy, before abandoning its continued use. It is a common pitfall for the inexperienced doctor to use an ASM in too low a dose and for too short a time before deciding that it was ineffective or poorly tolerated. In real life, the best made plans don't always work and there will need to be a logical therapeutic compromise between the doctor and the child and their family.

It is clearly important to document the treatment plan, including its goals. This may be done through copying the patient letter to the child's GP and other involved healthcare professionals (such as the tertiary consultant paediatric neurologist and local community paediatrician) and school nurse. Alternatively, if the initial letter is addressed to the GP, a copy should be sent to the family and other involved professionals, with the family's consent. At each clinic visit or telephone consultation (with the epilepsy nurse or doctor), always check the following:

- The actual dose being given. It is well-recognised that the dose(s) written in the medical notes or correspondence may be out of date or just incorrect [Whitehouse and Morris, 1997]. This is particularly likely to occur if there have been numerous telephone calls for advice or ED attendances between formal clinic reviews, either by telephone or face-to-face meetings.
- Ask the family or carers to bring all current medications (or at least a list of them) when they come

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for a clinic review. There are many reasons for this. One is because it allows a non-challenging and non-threatening way to assess compliance with the treatment plan (and the ASM regimen.) A useful question might be: "How many doses do you think you may have missed in the last week or month?" Another is to ensure that the same dose of an ASM is being given. This is particularly important for some liquid formulations where there may be different concentrations of the ASM. With clobazam there are at least two commonly available and prescribed formulations, one containing 5mg per ml and one containing 10mg per ml. Switching formulations could obviously result in a halving or doubling of the prescribed dose respectively, with significant clinical consequences.

- How does the child remember to take or family remember to give the medication? This may be with a daily 'Dosette' box, a reminder on their mobile phone or a 'post-it' note on the fridge or microwave door, or a combination of any of these.
- It may be helpful to ask the patient to give the clinic team a photograph of themselves to put in the notes; this will probably allow a quicker recall of the case when reading the notes or having telephone calls between clinic reviews.

Starting and changing (particularly substituting) an ASM may be complicated and is generally either poorly addressed in teaching about epilepsy or its management, or not at all. It is a task that can only be done safely and optimally with a good understanding of the common epilepsy syndromes or epilepsies of childhood, and relevant basic physiology and pharmacology of the medications used in their treatment. The process needs to be undertaken in a rational and appropriately timed manner that will also depend on the child's epilepsy syndrome/epilepsy and specific clinical situation. It also requires an acknowledgement of the child's and family's understanding and perception, and demands a clear communication between the epilepsy clinic team, the child, their family and the GP. Finally, it also requires a close relationship with the local tertiary epilepsy centre when the child's epilepsy is complex, or where parental anxiety is high.

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The Epilepsy Space

The mobile friendly website is a helping hand for 16-25 year olds to live their best life with epilepsy

The Epilepsy Space will help young people to:

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- Feel less alone
- Increase their confidence
- Get the support they need

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It's been created with young people and reviewed by epilepsy nurses.

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Recently published papers

This section highlights recently published papers. Hopefully this will be very useful to all, helping to keep everyone up to date with the latest developments. It will certainly save you research and reading time, not having to search so many journals.

There are many (often over 300) epilepsy papers published every three months, so what follows has been edited. All animal papers have been excluded and as many review papers as possible have been included. We hope you find the papers of interest in your pursuit to keep abreast of the very latest knowledge.

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